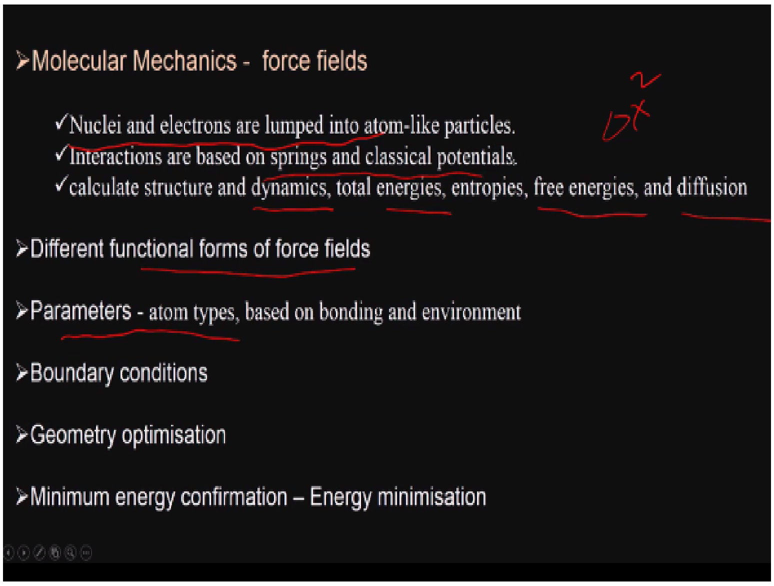
Computer Aided Drug Design
Prof. Mukesh Doble
Department of Biotechnology
Indian Institute of Technology - Madras

Lecture – 23
Quantum Mechanics

Hello everyone, welcome to the course on computer aided drug design, today we are going to talk about quantum mechanics okay. So, we have been talking about molecular mechanics quite a lot, molecular mechanics also known as force fields. So, what does it do?

(Refer Slide Time: 00:33)



- Molecular Mechanics - force fields
  - ✓Nuclei and electrons are lumped into atom-like particles.
  - ✓Interactions are based on springs and classical potentials.
  - ✓calculate structure and dynamics, total energies, entropies, free energies, and diffusion
- Different functional forms of force fields
- Parameters - atom types, based on bonding and environment
- Boundary conditions
- Geometry optimisation
- Minimum energy confirmation – Energy minimisation

Δx^2

Molecular mechanics; just to recap nuclei and electrons are lumped into atom like particles, so you do not differentiate between the electrons and the nucleus, so we do not see electron, electron repulsion, nucleus electron attraction and so on. So, they are based on the springs and classical potentials, Hooke's law come into picture. So, if the bond length is extended delta X, then the bond energy associated will be proportional to delta x square okay and so on actually delta X square.

So, we can use it for calculating these structure, we can do some diffusion properties, dynamics, we can look at total energy okay, we can look at free energies, diffusion, coefficient and so on so, we cannot do those which are related to the electronic property. Then, we looked at a different functional form of force field okay; different function forms. I showed you MM 2, I showed you so many different MMFF and so on.

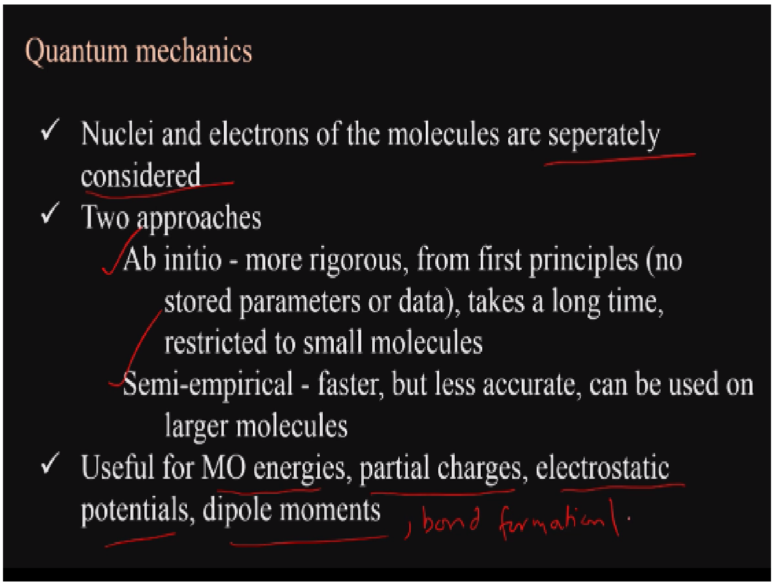
So, there were force field with delta X square, delta X raised to the power 4, E raised to the power delta X and so on and then there are a lot of parameters in this force field, so they all depend upon the atom types, okay. Atom types means a carbon can have different environment and different bonding right, you can have carbon single bond, carbon SP3, carbon double bond carbon SP2, carbon triple bond carbon SP okay.

And then carbon in the aromatic, carbon in a 5 membered ring form and so on, so different types of carbon. Similarly, carbon, oxygen different types of carbon oxygen, you can have ketonic, you can have ether type, ester type inside a 5 membered aliphatic and aromatic form, so many things, so we had parameters for all of them, then the boundary conditions, what type of boundary conditions?

Is it vacuum, is it surrounded by solvents, is it in a periodic box then came the geometric optimization this is very, very important, so you want to find out the minimum energy conformation of the molecule okay, so that is energy minimization, we use lot of numerical techniques to calculate the minimum energy okay, so, because mostly thermodynamically they occupied the minimum energy.

And of course, I also mentioned that it is not that all the molecules will be at that stage, it will be get distributed based on the Boltzmann equation, so you may have some molecules at slightly higher energy and so on actually depend upon the difference in the energy levels from one state to another, so this is called the molecular mechanics, so everything is lumped as atoms. Atoms connected by springs and so on.

(Refer Slide Time: 03:53)



Quantum mechanics

- ✓ Nuclei and electrons of the molecules are seperately considered
- ✓ Two approaches
  - Ab initio - more rigorous, from first principles (no stored parameters or data), takes a long time, restricted to small molecules
  - Semi-empirical - faster, but less accurate, can be used on larger molecules
- ✓ Useful for MO energies, partial charges, electrostatic potentials, dipole moments , bond formation|.

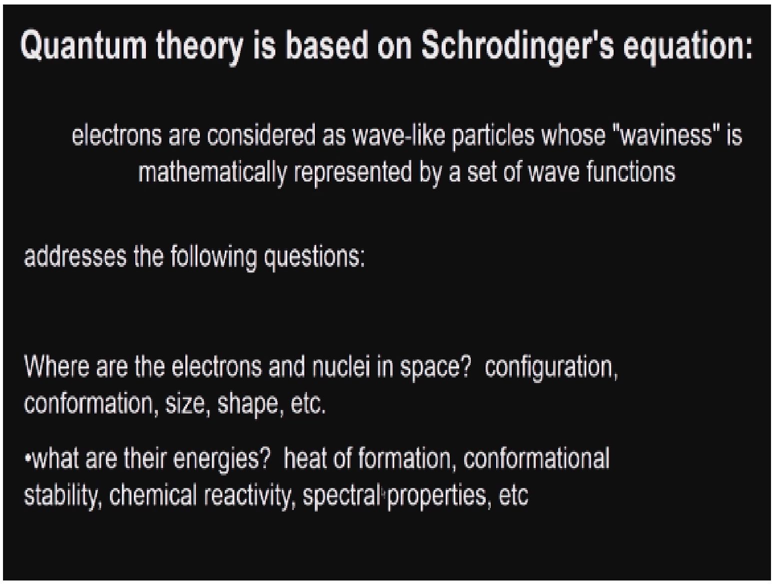
Now, let us go to something different that is called the quantum mechanics. Here nuclei and electrons of the molecules are separately considered okay, so that is very, very important, they are separately considered. There are 2 different approaches; one is called the Ab initio, other one is called the semi empirical. Ab initio is very, very rigorous, it is based on first principles okay, there are no stored parameters or data, so it takes much longer time.

So, Ab initio calculations are done only for few atoms whereas, semi empirical contains lot of stored parameters, it has got some empirical equations relationship, it is less accurate and it can be used for larger molecule, so it is much more practical for drug discovery like our area, so it is more approximate than Ab initio but we can go to hundreds of atoms okay. So, what are the uses of this quantum mechanics?

We can use molecular orbital energies, we can look at partial charges, we can look at electrostatic potential, we can look at dipole moments, we can look at bond formation, energy required for bond formation, energy required for bond breakage okay, so all these can be done; bond formation, breakage, so all these calculations can be done using molecular quantum mechanic theory okay.

So, we can look at the molecules at different oxidation states, so all these can be done in quantum mechanics and we will look at the semi empirical okay which is faster but less accurate Ab initio, which is very rigorous based on first principles okay.

(Refer Slide Time: 05:38)



Quantum theory is based on Schrodinger's equation:

electrons are considered as wave-like particles whose "waviness" is mathematically represented by a set of wave functions

addresses the following questions:

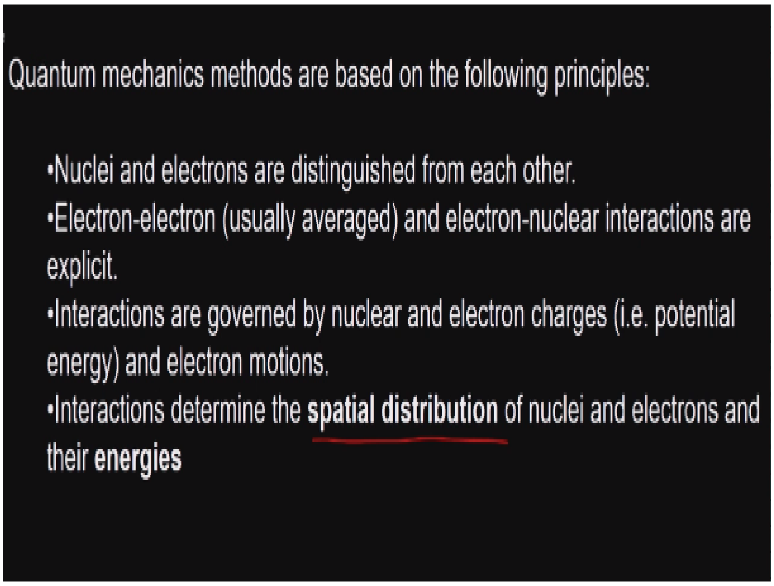
Where are the electrons and nuclei in space? configuration, conformation, size, shape, etc.

- what are their energies? heat of formation, conformational stability, chemical reactivity, spectral properties, etc

So, they are all based on Schrodinger's equation, electrons are considered as wave like particles whose waviness is mathematically represented by a set of wave functions okay. So, it addresses based on the Schrodinger's equation, so where are the electrons and nuclei in space? So, that you can find out from the configuration, confirmation, size, shape and so on actually and the energies; we can do heat of formation, conformational stability, chemical reactivity, spectral properties etc.

So, we can even simulate different types of spectra using a quantum mechanics calculation that is advantage we can simulate different types of spectra okay.

(Refer Slide Time: 06:27)



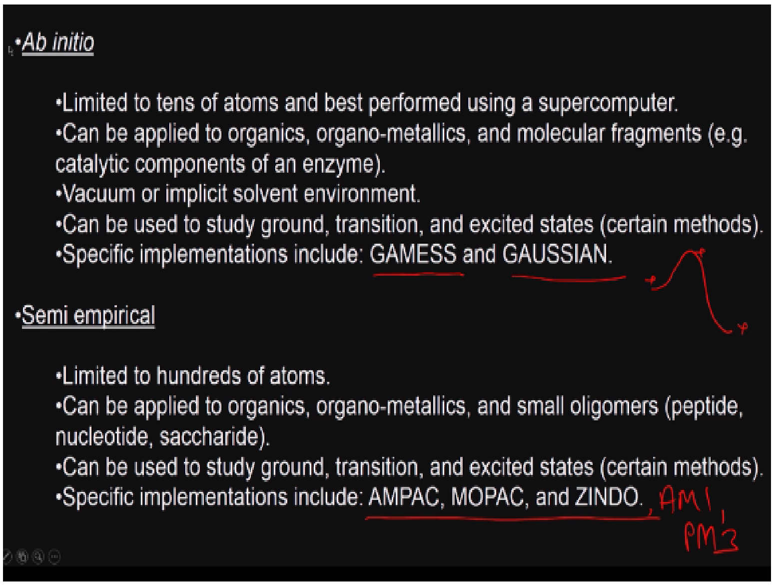
Quantum mechanics methods are based on the following principles:

- Nuclei and electrons are distinguished from each other.
- Electron-electron (usually averaged) and electron-nuclear interactions are explicit.
- Interactions are governed by nuclear and electron charges (i.e. potential energy) and electron motions.
- Interactions determine the **spatial distribution** of nuclei and electrons and their **energies**

So, quantum mechanic methods are based on following principles; nuclear and electrons are distinguished from each other, so you have electron - electron, electron nuclear interaction, so you may have here attractions, here repulsions, so you do not consider all the electrons because that will be too much I will tell about how they are sort of averaged of. Interactions are governed by nuclear and electron charges okay that is the potential energy and then electron motions.

So, the interactions determine the spatial distribution, so we can if you want to find out the size, shape of the molecule these are all determined based on nucleus and electrons and their energy, so nuclear-nuclear repulsions, electron-electron repulsion, the nuclear electron attractions and so on, so that is what quantum mechanics methods are based on okay.

(Refer Slide Time: 07:16)



- *Ab initio*
  - Limited to tens of atoms and best performed using a supercomputer.
  - Can be applied to organics, organo-metallics, and molecular fragments (e.g. catalytic components of an enzyme).
  - Vacuum or implicit solvent environment.
  - Can be used to study ground, transition, and excited states (certain methods).
  - Specific implementations include: GAMESS and GAUSSIAN.
- Semi empirical
  - Limited to hundreds of atoms.
  - Can be applied to organics, organo-metallics, and small oligomers (peptide, nucleotide, saccharide).
  - Can be used to study ground, transition, and excited states (certain methods).
  - Specific implementations include: AMPAC, MOPAC, and ZINDO, AM1, PM3

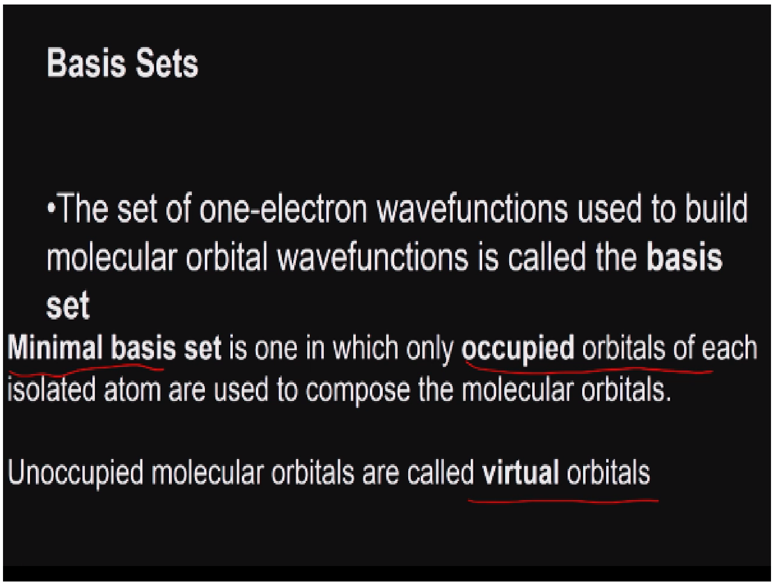
So, like I said we have the Ab initio, we have the semi empirical; Ab initio is limited to tens of atoms okay, so you need to have very good computational resource, so we can apply it for organics, organometallics, molecular fragments, catalytic components of an enzyme, we can also do vacuum, we can do implicit solvent, can be used to study ground state, transition state, excited state okay, there are methods.

So, there are softwares called GAMMES, Gaussian, so all these names will come across if you are interested in looking at Ab initio type of method. So, if I want to really calculate what are the energies like this, so we can calculate energies at these various states very accurately using Ab initio methods? Semi empirical methods Ab initio tens of atoms, we can go to hundreds of atoms or even larger.

So, as I said before if you are looking at thousands of atoms, we will not go for quantum mechanics we have to go for molecular mechanics okay, so limited to hundreds of atoms can be applied to organics, organometallics, oligomers, small peptide, nucleotide, saccharide, so we can do some empirical method. We can look at again ground state transition like this, excited states but of course this will be less accurate unlike the Ab initio.

If you really want to look at the small changes, if you have different enantiomers, I would not recommend this, I would recommend Ab initio method, so many software; many semi empirical methods you will come across; AMPAC, MOPAC, ZINDO, AM1, PM 3, all these are semi empirical methods which you will use as you go long okay. So, 2 basic methods like this generally for drug discovery, this is good enough.

(Refer Slide Time: 09:27)



Basis Sets

- The set of one-electron wavefunctions used to build molecular orbital wavefunctions is called the **basis set**

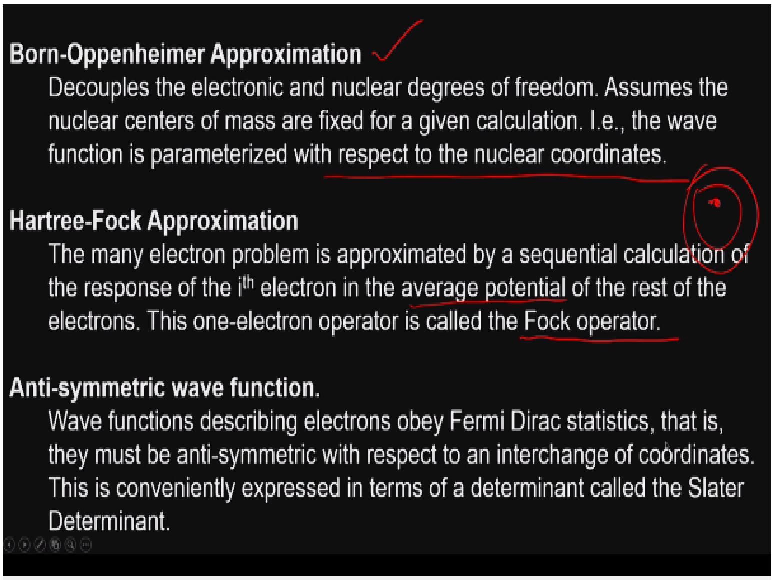
Minimal basis set is one in which only **occupied** orbitals of each isolated atom are used to compose the molecular orbitals.

Unoccupied molecular orbitals are called **virtual** orbitals

If you are a theoretical chemist okay then you may go into Ab initio methods okay, so you need to understand certain terminologies. The most important in Ab initio is called basis sets, this is a set of one electron wave functions used to build the molecular orbital wave functions okay. Basis set means is a one electron wave function used to build a molecular orbital wave function, you also have minimal basis set that is which only occupied orbitals of each isolated atoms are used to compose okay.

So, unoccupied orbitals are called virtual orbitals, so only minimal basis set is only the occupied orbitals are considered okay, we do not consider the unoccupied orbitals okay that is called the minimal basis set okay. So, generally if you want to go into Ab initio is good enough to go with minimal basis set because it does not consider the unoccupied orbitals then the calculations are too much to do.

(Refer Slide Time: 10:42)



Born-Oppenheimer Approximation

Decouples the electronic and nuclear degrees of freedom. Assumes the nuclear centers of mass are fixed for a given calculation. I.e., the wave function is parameterized with respect to the nuclear coordinates.

Hartree-Fock Approximation

The many electron problem is approximated by a sequential calculation of the response of the i^{th} electron in the average potential of the rest of the electrons. This one-electron operator is called the Fock operator.

Anti-symmetric wave function.

Wave functions describing electrons obey Fermi Dirac statistics, that is, they must be anti-symmetric with respect to an interchange of coordinates. This is conveniently expressed in terms of a determinant called the Slater Determinant.

There are many approximations when we consider the quantum mechanics, the most important one we will talk about some of those approximations, the most important one is called the Born-Oppenheimer approximation. So, what it does is it decouples the electronic and nuclear degrees of freedom okay, so it assumes the nuclear centers of mass are fixed okay and the electrons move around this nucleus okay.

So, you reduce the number of degrees of freedom that is the advantage of Born Oppenheimer approximation. So, the wave function is parameterized with respect to the nuclear coordinates, so remember that. So, it assumes that the nucleus is fixed like we assume that Sun is fixed and all the planets revolve around the Sun that is the easiest approximation okay although, you know that Sun also moves then all the planets also move, so the calculations becomes more difficult to do.

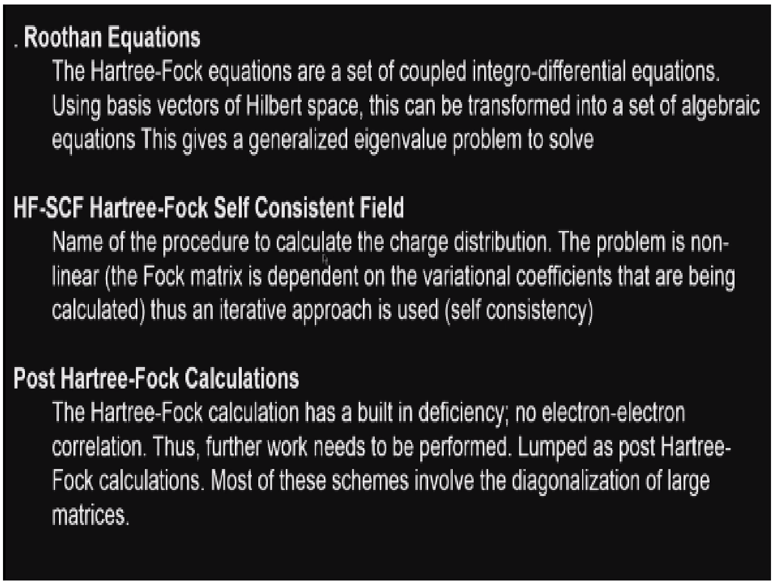
But you have the first approximation we can always assume Sun is fixed, all the planets are going around okay that is the advantage okay like that we can do that that is called the Born-Oppenheimer approximation, then comes Hartree-Fock approximation. So, as you know there are many, many electrons in each atom, so you approximated by a sequential calculation of the response of the ith electron in the average potential of rest of the electrons.

This one electron operator is called the Fock operator that means suppose, there are many electrons; 20 electrons and you are looking at the ith electron interaction with all the 20, it is going to be very, very difficult right, ith with, 1 ith with, 2 ith with, 4 and so on, too many calculations. So, what you do is; we take the average potential of remaining 19 electrons and then we look at the interaction of the ith electron with the remaining 19 electrons.

So, the calculations come down dramatically okay, number of interactions you look at comes down dramatically and that is called the Hartree-Fock approximation okay, so it makes life much simpler, then comes anti-symmetric wave function. Wave functions described in electrons obey Fermi Dirac statistics that is they must be anti-symmetric with respect to an interchange of coordinates, so this is called a term of determined is called the Slater determinant.

So, we have the Born Oppenheim approximation which fixes the nucleus degrees of freedom, only the electron degrees of freedom are considered, then you have the Hartree-Fock approximation where you look at the interaction of the ith electron with an average potential of rest of the electrons, then anti symmetric wave functions describing the obey the Fermi Dirac statistics that is they must be anti-symmetric with respect to an interchange of coordinates okay.

(Refer Slide Time: 13:41)



. Roothan Equations

The Hartree-Fock equations are a set of coupled integro-differential equations. Using basis vectors of Hilbert space, this can be transformed into a set of algebraic equations This gives a generalized eigenvalue problem to solve

HF-SCF Hartree-Fock Self Consistent Field

Name of the procedure to calculate the charge distribution. The problem is non-linear (the Fock matrix is dependent on the variational coefficients that are being calculated) thus an iterative approach is used (self consistency)

Post Hartree-Fock Calculations

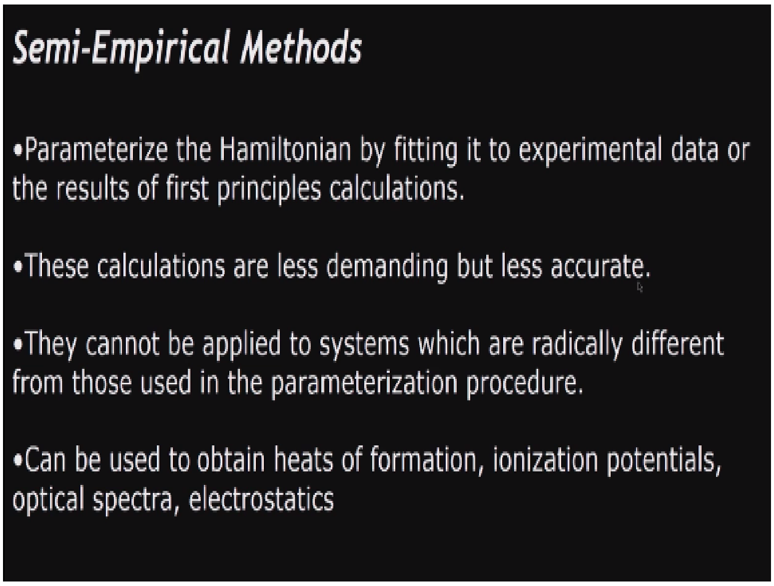
The Hartree-Fock calculation has a built in deficiency; no electron-electron correlation. Thus, further work needs to be performed. Lumped as post Hartree-Fock calculations. Most of these schemes involve the diagonalization of large matrices.

Then we have the Roothan equations that is the Hartree-Fock equations are a set of coupled integro differential equations okay so that is called the Roothan equation using basis vectors of Hilbert space, so this can be transformed into a set of algebraic equations, so this gives a generalized eigenvalue problem to solve because once you have an algebraic set of equations, it becomes much easier for you to calculate okay.

So, Hartree-Fock equation and so we have the Hartree-Fock; SCF Hartree-Fock self-consistent field that is the self-consistent field, this is the name of the procedure to calculate the charge distribution, the problem is nonlinear, the Fock matrix is dependent on the variational coefficients that are being calculated, so we need to have an iterative approach for self-consistency.

Then we have the post Hartree-Fock calculations, so the Hartree-Fock calculation has a built in deficiency, no electron- electron correlation, thus further work needs to be performed, so lumped as post Hartree-Fock calculations. Most of the schemes involve the diagonalization of large matrix. So, so many different types of approximations are done to make it more easier for you.

(Refer Slide Time: 15:01)



Semi-Empirical Methods

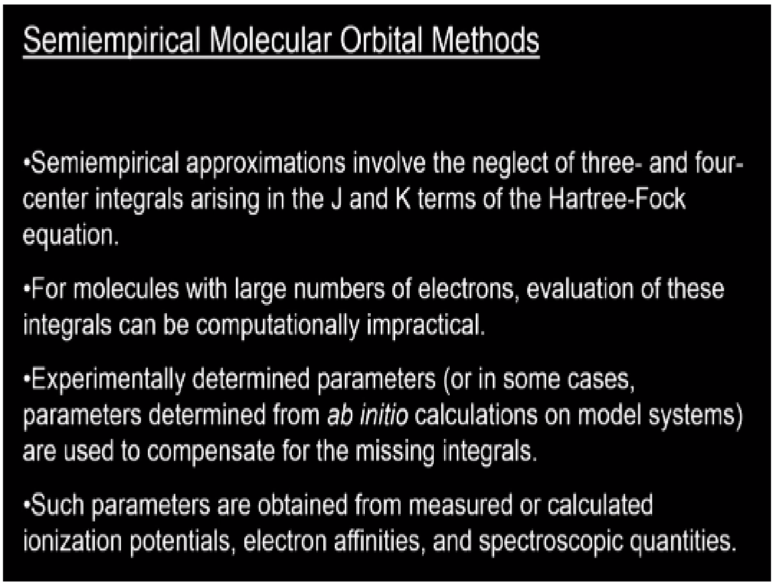
- Parameterize the Hamiltonian by fitting it to experimental data or the results of first principles calculations.
- These calculations are less demanding but less accurate.
- They cannot be applied to systems which are radically different from those used in the parameterization procedure.
- Can be used to obtain heats of formation, ionization potentials, optical spectra, electrostatics

So, the Ab initio methods; GAMESS is one software, another one is called Gaussian, so if you are planning to use Ab initio, these are the 2 software's you will come across; the GAMESS and the Gaussian. So, semi empirical; you have a lot of parameters just like in our force field molecular mechanics, we parameterize many things, so semi empirical methods parameterize the Hamiltonian by fitting it to the experimental data or the results of the first principle that means Ab initio methods.

So, these calculations are less demanding but less accurate, they cannot be applied to systems which are radically different from those used in the parameterization, just like when molecular mechanics we cannot use although, we can sometimes use it but the accuracy wise they are not really very accurate okay but it can be used for different systems but too many too much different then it is not correct.

So, we can use semi empirical methods for calculating heat of formation, ionization potentials; okay so if you ionize the molecule, what is energy required; optical spectra, electrostatic, so lot of these simulations can be done using semi empirical methods that is the advantage of these type of methods. So, many things are parameterized that is the; that is how the method becomes simpler, less computationally intensive faster and we can go up to hundreds of atoms.

(Refer Slide Time: 16:39)



Semiempirical Molecular Orbital Methods

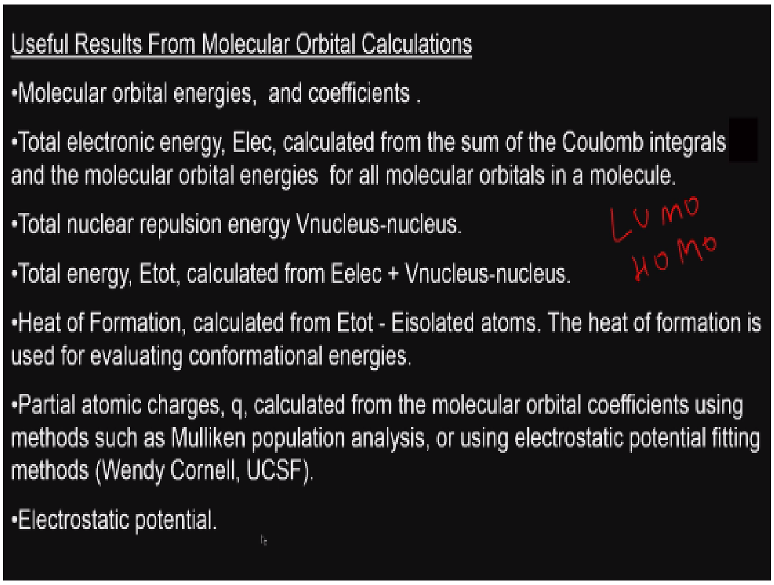
- Semiempirical approximations involve the neglect of three- and four-center integrals arising in the J and K terms of the Hartree-Fock equation.
- For molecules with large numbers of electrons, evaluation of these integrals can be computationally impractical.
- Experimentally determined parameters (or in some cases, parameters determined from *ab initio* calculations on model systems) are used to compensate for the missing integrals.
- Such parameters are obtained from measured or calculated ionization potentials, electron affinities, and spectroscopic quantities.

Because many systems here or parameterised, let us call the semi empirical method. So, we have the semi empirical molecular orbital methods, there are many semi empirical molecular orbital methods. Approximations which involve the neglect of 3 and 4 center integrals arising in the J and K terms of Hartree-Fock equations, so we neglect 3 and 4 center integrals okay.

For molecules with large number of electrons, evaluation of these integrals can be computationally impractical, so we neglect okay, we take only one and 2, so many of them are experimentally determined parameters or sometimes from Ab initio calculations are used to compensate for the missing integral. So, if you neglect higher order integrals, you can approximated from the parameter okay which are calculated experimentally or through Ab initio calculations.

So, these are molecular orbital methods, semi empirical molecular orbital methods, such parameters are obtained from measured or calculated ionization potentials, electron affinities, spectroscopic equations and so on actually okay. So, what are the useful results from we can calculate molecular orbital energies and coefficient.

(Refer Slide Time: 18:01)



Useful Results From Molecular Orbital Calculations

- Molecular orbital energies, and coefficients .
- Total electronic energy, Elec, calculated from the sum of the Coulomb integrals and the molecular orbital energies for all molecular orbitals in a molecule.
- Total nuclear repulsion energy Vnucleus-nucleus.
- Total energy, Etot, calculated from Eelec + Vnucleus-nucleus.
- Heat of Formation, calculated from Etot - Eisolated atoms. The heat of formation is used for evaluating conformational energies.
- Partial atomic charges, q, calculated from the molecular orbital coefficients using methods such as Mulliken population analysis, or using electrostatic potential fitting methods (Wendy Cornell, UCSF).
- Electrostatic potential.

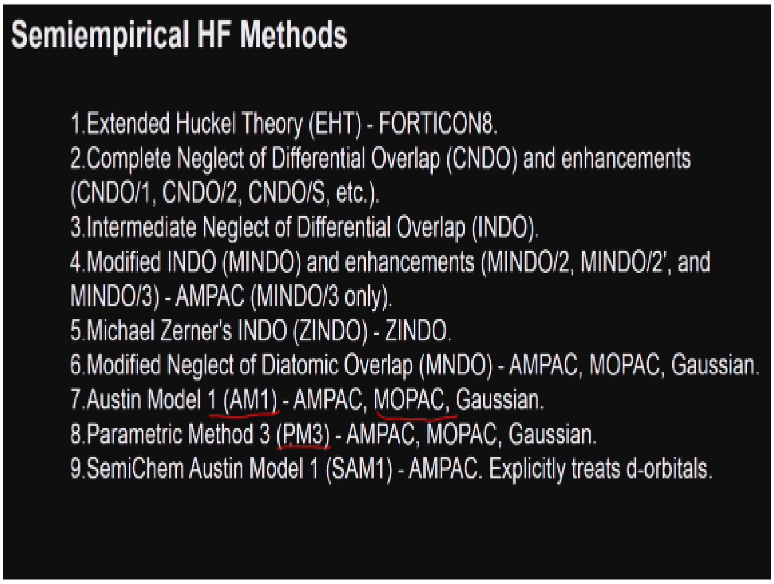
LUMO
HOMO

We can calculate total electronic energy; electronic energy calculated from the sum of coulombs integrals, molecular orbital energies for molecular orbitals in a molecule, so many things can be done if you want to know what is the energy required from moving from one orbital to another orbital okay, we can calculate using semi empirical method and we can look at lowest unoccupied molecular orbital energy.

We can calculate highest occupied molecular orbital energy, so all these can be done using these methods okay. Total nuclear repulsion that is nucleus nucleus repulsion that energy can be calculated, total energy that is electronic energy, nucleus energy all these can be calculated together and we call it total energy, heat of formation; calculated from heat of total minus heat of the isolated atoms.

We can calculate conformational energies, partial atomic charges calculated from the molecular orbital coefficient using methods such as Mulliken population analysis, electrostatic potential fitting all these okay, we can calculate the potential atomic charges that is Mulliken population analysis. Electrostatic potentials; we can calculate, so from molecular orbital calculations we can do all these calculations.

(Refer Slide Time: 19:39)



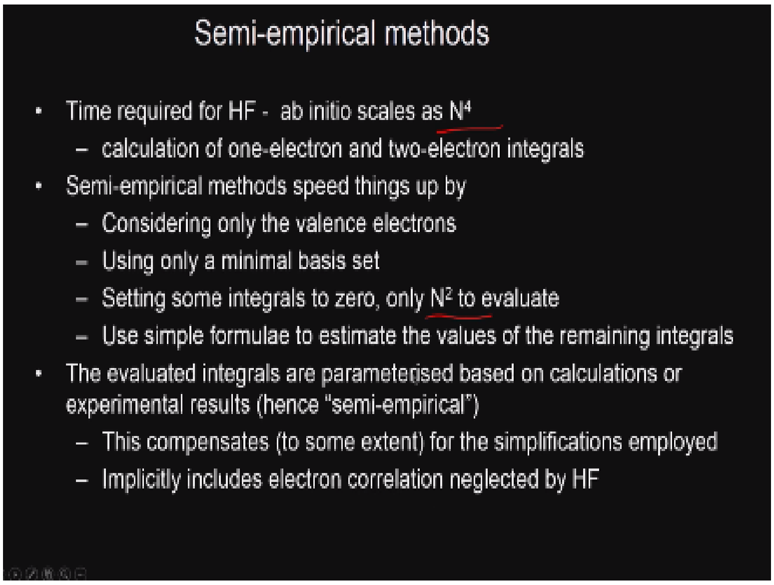
Semiempirical HF Methods

1. Extended Huckel Theory (EHT) - FORTICON8.
2. Complete Neglect of Differential Overlap (CNDO) and enhancements (CNDO/1, CNDO/2, CNDO/S, etc.).
3. Intermediate Neglect of Differential Overlap (INDO).
4. Modified INDO (MINDO) and enhancements (MINDO/2, MINDO/2', and MINDO/3) - AMPAC (MINDO/3 only).
5. Michael Zerner's INDO (ZINDO) - ZINDO.
6. Modified Neglect of Diatomic Overlap (MNDO) - AMPAC, MOPAC, Gaussian.
7. Austin Model 1 (AM1) - AMPAC, MOPAC, Gaussian.
8. Parametric Method 3 (PM3) - AMPAC, MOPAC, Gaussian.
9. SemiChem Austin Model 1 (SAM1) - AMPAC. Explicitly treats d-orbitals.

Dipole moment okay, so what is the dipole moment, we cannot use molecular mechanics, we need to have semi empirical mechanics to calculate dipole moment. So, there are many semi empirical methods, extended Huckel theory, complete neglect of differential overlap, they are called CNDO, CNDO1, CNDO2, CNDOS, intermediate neglect of differential overlap INDO, modified INDO, enhanced INDO; MINDO 2, MINDO 2 dash, 3, AMPAC.

Michael Zerner's INDO that is called ZINDO, okay then modified neglect of diatomic overlapped; AMPAC, MOPAC, Gaussian. Then, Austin model 1; AM1, AMPAC, MOPAC, Gaussian, parametric methods; PM3, AMPAC, MOPAC, Gaussian, SemiChem Austin model 1; AMPAC, explicitly, so many different types of methods and generally I would suggest if you are; you can use these type of methods; the AM methods and PM3 type of methods of course, MOPAC is also used quite a lot okay.

(Refer Slide Time: 20:50)



Semi-empirical methods

- Time required for HF - ab initio scales as N^4
  - calculation of one-electron and two-electron integrals
- Semi-empirical methods speed things up by
  - Considering only the valence electrons
  - Using only a minimal basis set
  - Setting some integrals to zero, only N^2 to evaluate
  - Use simple formulae to estimate the values of the remaining integrals
- The evaluated integrals are parameterised based on calculations or experimental results (hence "semi-empirical")
  - This compensates (to some extent) for the simplifications employed
  - Implicitly includes electron correlation neglected by HF

And so all these methods although are popular generally you can stick to the ones which I have marked here okay. So, let us look at some of these methods, so the time required for Hartree-Fock; Ab initio scale as N raised to the power 4 that is evaluation of one electron and 2 electron integrals okay. Semi-empirical method speed things up; considering only the valence electrons using only a minimal basis set, setting some integrals to 0.

So, it becomes N square to evaluate, whereas time required for Hartree-Fock, Ab initio methods is N raised to the power 4, so in semi empirical method it becomes N square. It also uses simple formulae to estimate the values of the remaining integrals like I mentioned, you can have some that is why it is called semi empirical, so there are certain empirical relation so which can help you to calculate estimate the ones remaining integrals okay.

So, we take only the valence electrons okay, we take minimal basis set and set some integrals to 0, so the evaluated integrals are also parameterize based on calculations or experimental data that is why it is called semi empirical. So, this compound says to some extent from the simplifications, it implicitly includes electron correlation neglected by HF, whatever we neglect we include that okay.

(Refer Slide Time: 22:08)

Semi-empirical methods

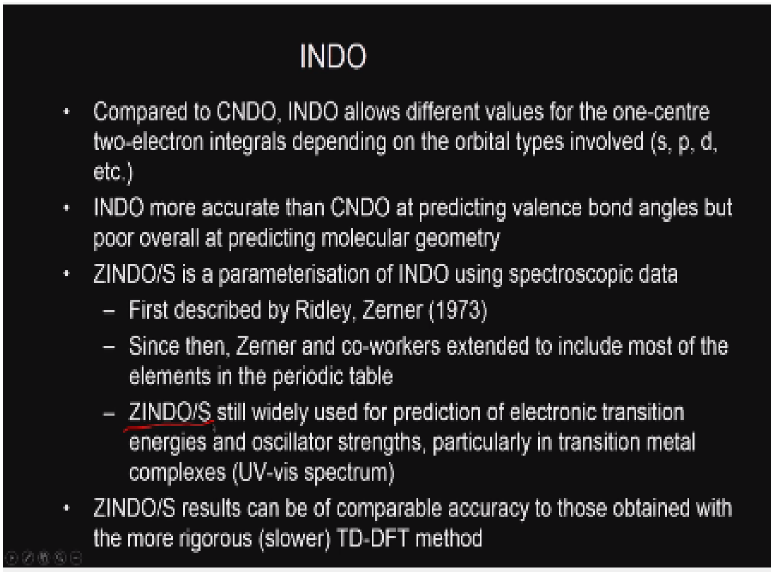
- **CNDO** (Complete Neglect of Differential Overlap)
  - CNDO (Pople, 1965)
- **INDO** (Intermediate Neglect of Differential Overlap)
  - INDO (Pople, Beveridge, Dobosh, 1967)
  - **INDO/S**, "ZINDO/S" (Ridley, Zerner, 1973)
  - MINDO/3 (Bingham, Dewar, Lo, 1973)
  - SINDO1 (Nanda, Jug, 1980)
- **NDDO** (Neglect of Diatomic Differential Overlap)
  - MNDO (Dewar, Thiel, 1977)
  - **AM1** (Dewar, ..., Stewart, 1985)
  - **PM3** (Stewart, 1989)
  - SAM1 (Dewar, Jie, Yu, 1993)
  - MNDO/d (Thiel, Voityuk, 1996)
  - AM1/d (Voityuk, Rosch, 2000)
  - RM1 (Rocha, ..., Stewart, 2006)
  - **PM6** (Stewart, 2007)

So, there are many methods, no MNDO, AM1, RM1, PM6, so many different methods and as you can see the methods is developed over a period of time starting from 1990's going down to 2000's, so CNDO that is complete neglect of differential overlap okay, in 1965, the first CNDO was developed okay, then came INDO; intermediate neglect of differential overlap okay, so slight improvement.

As you can 67, then came 73, 1980, okay so as the time goes improvements on these methods were developed but the earliest is CNDO that is the 65 okay, then came NDDO; neglect of diatomic differential overlap, okay, came MNDO, AM 1, PM 3, SAM 1 okay, so as time goes starting from 65, complete neglect of differential overlap between these electrons and then methods started improvement.

The intermediate neglect, neglect of diatomic differential overlap and so on actually, you can see in 2000's, we have better methods; PM 6 okay which are big improvement but still they are quite fast unlike the Ab initio methods.

(Refer Slide Time: 23:40)



INDO

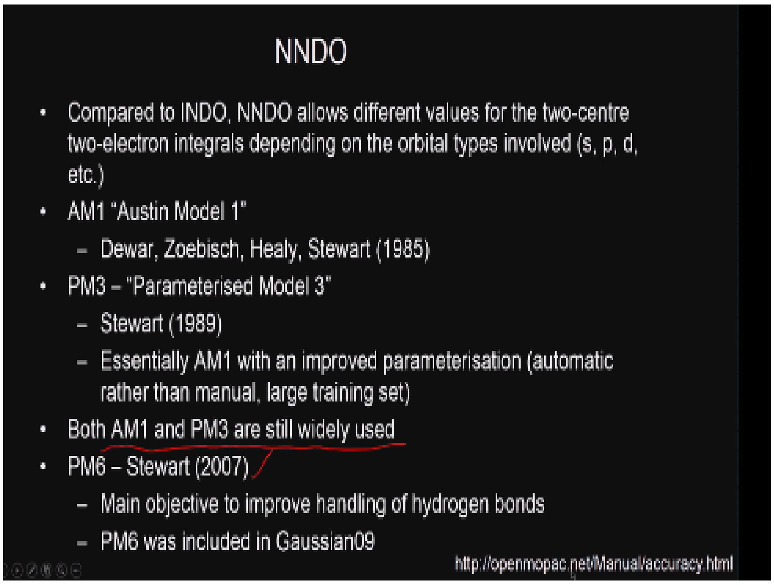
- Compared to CNDO, INDO allows different values for the one-centre two-electron integrals depending on the orbital types involved (s, p, d, etc.)
- INDO more accurate than CNDO at predicting valence bond angles but poor overall at predicting molecular geometry
- ZINDO/S is a parameterisation of INDO using spectroscopic data
  - First described by Ridley, Zerner (1973)
  - Since then, Zerner and co-workers extended to include most of the elements in the periodic table
  - ZINDO/S still widely used for prediction of electronic transition energies and oscillator strengths, particularly in transition metal complexes (UV-vis spectrum)
- ZINDO/S results can be of comparable accuracy to those obtained with the more rigorous (slower) TD-DFT method

Then came INDO, let us look at little bit on each of these methods that is the starting from complete overlap going to INDO that is the intermediate overlap. Compared to CNDO, INDO allows different values for the one center 2 electron integrals depending on the orbital types involved like spd etc okay, so it improves on that it is more accurate than CNDO at predicting valence bond angles but poor overall at predicting molecular geometry okay.

It gives you good idea about the bond angles but molecular geometry, it is not very nice, okay, then, came ZINDOS, this is a parameterization of INDO using spectroscopic data. It was first described in 1973 by Zerner, then they went on extending it to include most of the elements in the periodic table; most of the elements. ZINDOS still widely used for prediction of electronic transition energy, oscillator strengths, transition metal complexes.

So, if some metals, we can think about using ZINDOS okay, ZINDOS results can be of comparable accuracy to those obtained with okay DFT method okay; density function method; DFT are called density function methods which come under the An initio category okay, it can be compared with that so that is the beauty of this type of methods if you have transition methods also into your molecule.

(Refer Slide Time: 25:20)



NNDO

- Compared to INDO, NNDO allows different values for the two-centre two-electron integrals depending on the orbital types involved (s, p, d, etc.)
- AM1 "Austin Model 1"
  - Dewar, Zoebisch, Healy, Stewart (1985)
- PM3 – "Parameterised Model 3"
  - Stewart (1989)
  - Essentially AM1 with an improved parameterisation (automatic rather than manual, large training set)
- Both AM1 and PM3 are still widely used
- PM6 – Stewart (2007)
  - Main objective to improve handling of hydrogen bonds
  - PM6 was included in Gaussian09

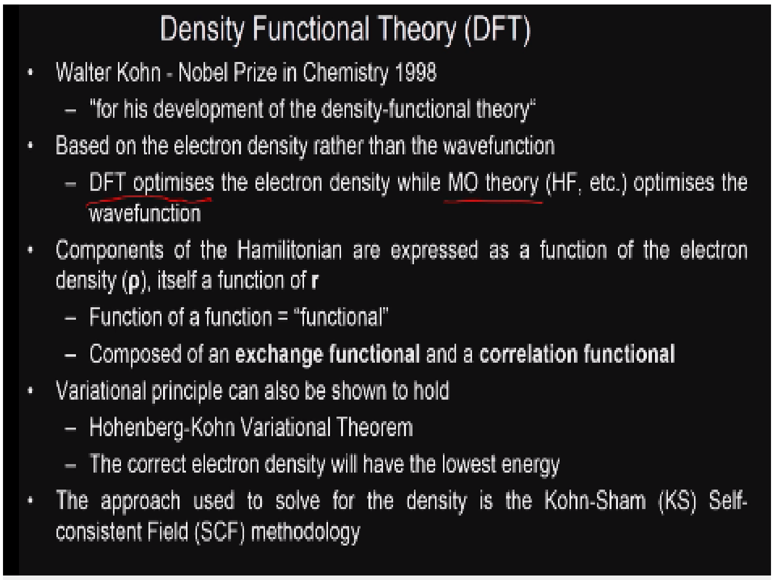
http://openmopac.net/Manual/accuracy.html

Then comes NNDO; NNDO compared to INDO, NNDO allows different values for the 2 center 2 electron integrals depending upon the orbital type spd etc. okay, you have the AM 1, Austin model one which was developed in 1985 by this group and then we have the PM 3 that is a parameterised model against toward 1989, so AM 1 with an improved parameterization automatic rather than manual large transition training set.

So, they used larger training set to get the parameters for this module, so AM 1 like I mentioned AM 1 and PM 3 are still widely used, they are quite popular, I would still recommend that you can use AM 1 PM 3 reasonably well for performing semi empirical calculations with the large number of molecules okay. Then PM 6, this came in the year 2007, as you can see this is meant for improving, handling of hydrogen bonds.

Hydrogen bonds is a big challenge so for in order to do that PM 6 came into so this was included in some softwares; Gaussian 09 and so on, so this information is obtained from this reference.

(Refer Slide Time: 26:46)



Density Functional Theory (DFT)

- Walter Kohn - Nobel Prize in Chemistry 1998
  - "for his development of the density-functional theory"
- Based on the electron density rather than the wavefunction
  - DFT optimises the electron density while MO theory (HF, etc.) optimises the wavefunction
- Components of the Hamiltonian are expressed as a function of the electron density (ρ), itself a function of **r**
  - Function of a function = "functional"
  - Composed of an **exchange functional** and a **correlation functional**
- Variational principle can also be shown to hold
  - Hohenberg-Kohn Variational Theorem
  - The correct electron density will have the lowest energy
- The approach used to solve for the density is the Kohn-Sham (KS) Self-consistent Field (SCF) methodology

Density function methods; these are; it was first developed in 1998, Walter Kohn Nobel Prize in Chemistry for his development of this density functional theory okay. So, based on the electron density rather than the wave form okay, density function theory is based on electron density rather than wave form. So, he did not consider an electron is a wave form, they consider electron spread out, more dense in some areas, less dense in some areas.

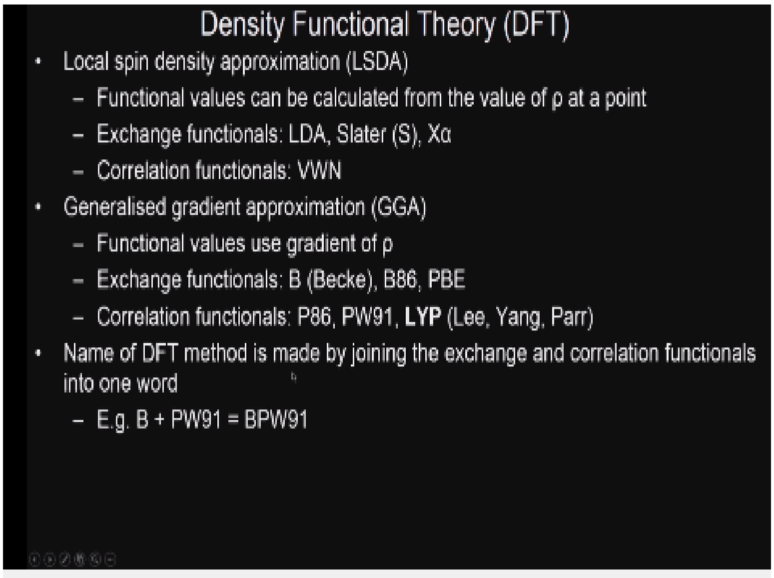
And that is how now it is being; electrons are being thought of that is why he got a Nobel Prize Walter Kohn in the year 1998, so density function theory optimizes the electron density, while molecular orbital theory optimizes the wave function, so that is the big difference between both these methods; DFT optimizes the electron density, MO optimizes the waveform, so molecule orbital thinks of the electrons as a wavy thing.

Whereas a small piece of particle moving in wave form, whereas DFT looks at electrons is a spread out and to big area and in some places it is very dense, in some places it is not so dense okay that is it, components of the Hamiltonian are expressed as a function of the electron density rho itself as a function of R okay. R is as you know is the location, so function of a function.

Composed of an exchange functional and a correlational functional, variational principle can be also be shown to be hold; Hohenberg Kohn variational theorem, the correct electron density will have the lowest energy okay, the approach used to solve for the density is the Kohn Sham self-consistent field methodology, this is our density function works, let us not bother too much about the Ab initio and density function methods.

Because like I said drug discovery; computer aided drug discovery, we do not spend too much time on Ab initio methods because it is not practical to look at large molecules using these methods because they are computationally intensive and very slow, so generally semi empirical methods are followed if you want to look at certain properties of small molecules mainly drugs or inhibitors okay.

(Refer Slide Time: 29:18)



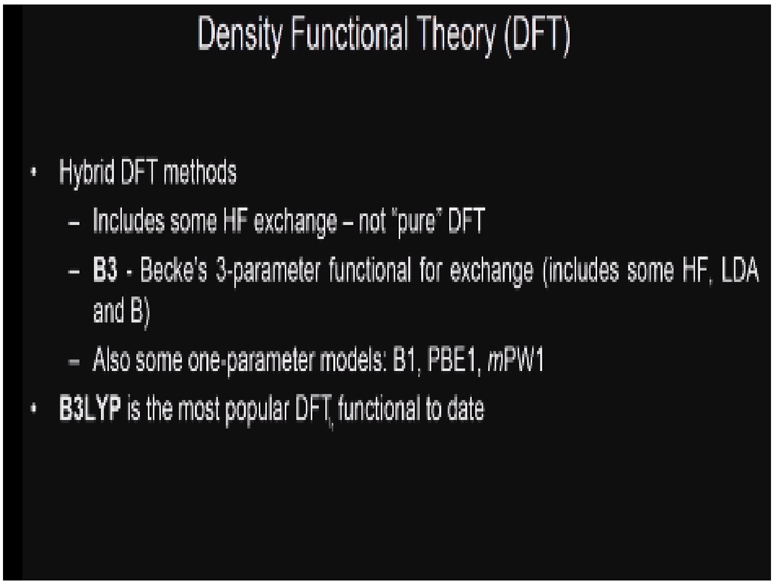
Density Functional Theory (DFT)

- Local spin density approximation (LSDA)
  - Functional values can be calculated from the value of ρ at a point
  - Exchange functionals: LDA, Slater (S), Xα
  - Correlation functionals: VWN
- Generalised gradient approximation (GGA)
  - Functional values use gradient of ρ
  - Exchange functionals: B (Becke), B86, PBE
  - Correlation functionals: P86, PW91, **LYP** (Lee, Yang, Parr)
- Name of DFT method is made by joining the exchange and correlation functionals into one word
  - E.g. B + PW91 = BPW91

So, density function theory, so you have the local spin density approximation, so the function values can be calculated from the value of Rho at any point, exchange functionals okay, local density approximations later, correlation functionals, generalized gradient approximation, functional values use gradient of Rho, exchange functional correlation functions, the name of the density function method is made by joining the exchange and the correlation function into one word okay.

So, we have BPW 91, okay B comes from this okay, PW 91 comes from correlation, so you combine, so different types of density functions, you can have by combining the exchange functions with the correlation functions okay. So, if you really need to have a good knowledge of these type of Ab initio and density function methods, you may start using but generally for very small molecules.

(Refer Slide Time: 30:27)

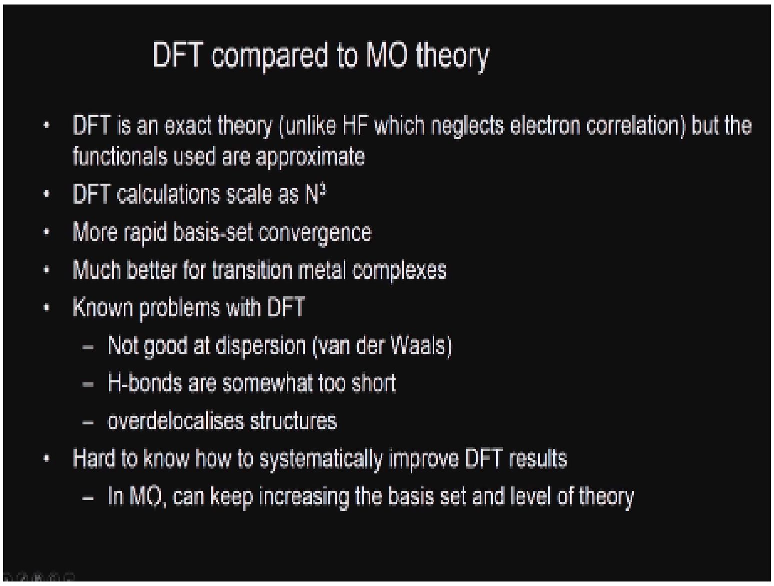


Density Functional Theory (DFT)

- Hybrid DFT methods
  - Includes some HF exchange – not "pure" DFT
  - **B3** - Becke's 3-parameter functional for exchange (includes some HF, LDA and B)
  - Also some one-parameter models: B1, PBE1, *m*PW1
- **B3LYP** is the most popular DFT functional to date

More of this density function okay hybrid density function methods includes they are not pure density but hybrid, Becke's 3 parameter function for exchange one parameter models also are there okay, then you have B3 LYP, most popular density function method.

(Refer Slide Time: 30:43)



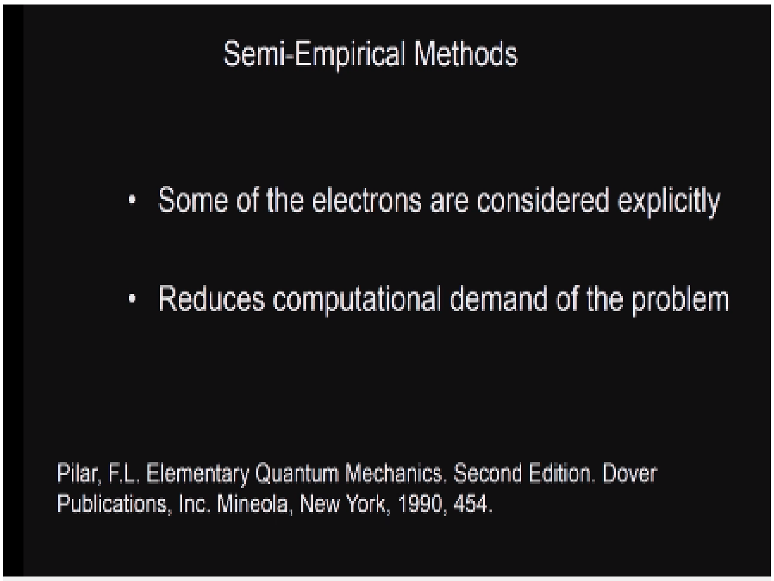
DFT compared to MO theory

- DFT is an exact theory (unlike HF which neglects electron correlation) but the functionals used are approximate
- DFT calculations scale as N^3
- More rapid basis-set convergence
- Much better for transition metal complexes
- Known problems with DFT
  - Not good at dispersion (van der Waals)
  - H-bonds are somewhat too short
  - overdelocalises structures
- Hard to know how to systematically improve DFT results
  - In MO, can keep increasing the basis set and level of theory

So, how do the DFT compares to MO, okay? When DFT is an exact theory unlike Hartree-Fock which neglects electron correlation but the functionals used are approximate. DFT calculates scale as N power 3, Ab initio calculates N power 4, whereas your semi empirical calculates at N power 2, more rapid basis set convergence, much better for transition metal complexes of course, semi empirical are quite approximate.

Known problems with DFT not good at dispersion, hydrogen bonds are somewhat too short, over delocalized structures, hard to know how to systematically improve DFT results. In molecular orbital, we can keep increasing the basis set and level of theory okay, so in DFT you do not know how to improve an improvement further okay.

(Refer Slide Time: 31:38)



Semi-Empirical Methods

- Some of the electrons are considered explicitly
- Reduces computational demand of the problem

Pilar, F.L. Elementary Quantum Mechanics. Second Edition. Dover Publications, Inc. Mineola, New York, 1990, 454.

So, semi empirical methods; some of the electrons like I said are considered explicitly and reduces computational demand of the problem okay, so semi empirical methods are very, very popular and widely used because computationally less intensive and we get reasonably good answers of course it is not exact but reasonably good answers okay. So, we will continue further on these quantum mechanics methods in the next class as well, thank you very much for your time.