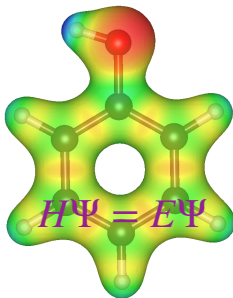


Computational chemistry methods in drug design: Quantum chemical approaches



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MC-610, NIPER Hyderabad: Lecture 4 (May 28, 2021)

Introduction to electronic structure theory II

$$H\Psi = E\Psi$$



$\Psi =$

Single Slater
determinant

HF equations

Additional
approximations



**Semi-empirical
methods**

Addition of more
determinants



**Electron correlation
methods**

Electron correlation methods

Electron correlation energy

- ▶ In the Hartree-Fock approximation, each electron sees the average field arising from all other electrons
- ▶ Two electrons cannot occupy the same point in space
- ▶ Electrons must move to avoid each other, i.e., their motion must be correlated – the “dynamic correlation”
- ▶ Arising from the multi-state character: Single Slater determinant is not enough – the “static correlation”
- ▶ For a given basis set, the difference between the exact energy and the Hartree-Fock energy is the electron correlation energy:
$$E_{\text{corr}} = E_{\text{exact}} - E_{\text{HF}}$$
- ▶ ca 20 kcal/mol correlation energy per electron pair
- ▶ In a sufficiently large basis set, the HF wave function is able to account for $\sim 99\%$ of the total energy, but the remaining $\sim 1\%$ is often very important for describing chemical phenomena

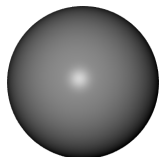
Aims to develop methods for electron correlation

- ▶ Efficient & applicable to all molecules
- ▶ Variational
- ▶ Size-consistent
- ▶ Hierarchical accuracy vs. cost

Electron correlation, how important is this?

The fundamental approximation of the Hartree-Fock method: interactions between electrons are treated in an average way, not an instantaneous way

$$\hat{F}_i = -\frac{1}{2}\nabla_i^2 - \sum_A^{\text{nuclei}} \frac{Z_A}{r_{iA}} + \hat{V}_i^{HF}\{j\}$$

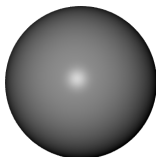


One electron

$$E_{\text{HF}} = -0.5 \text{ a.u.}$$

$$E_{\text{exact}} = -0.5 \text{ a.u.}$$

H atom



Two electrons

$$E_{\text{HF}} = -2.86167 \text{ a.u.}$$

$$E_{\text{exact}} = -2.9037 \text{ a.u.}$$

Error $\sim 26 \text{ kcal/mol}$!

He atom

Shull, H. and Löwdin P., J. Chem. Phys. **25**, 1035 (1956).

Correlated Methods. I. Configuration Interaction (CI)

The HF method determines the energetically best one-determinant trial wave function (within the given basis set). So construct a trial wave function that contains more than one Slater determinant (SD) Φ . A generic multideterminant trial wave function can be written as:

$$\Psi = a_0\Phi_{HF} + a_1\Phi_1 + a_2\Phi_2 + \dots$$

where a_0 is usually close to one; the coefficients a reflect the weight of each determinant in the expansion. Electron correlation methods differ in how they calculate the coefficients in front of the other determinants.

Slater determinants that are singly, doubly, triply, quadruply, etc., excited

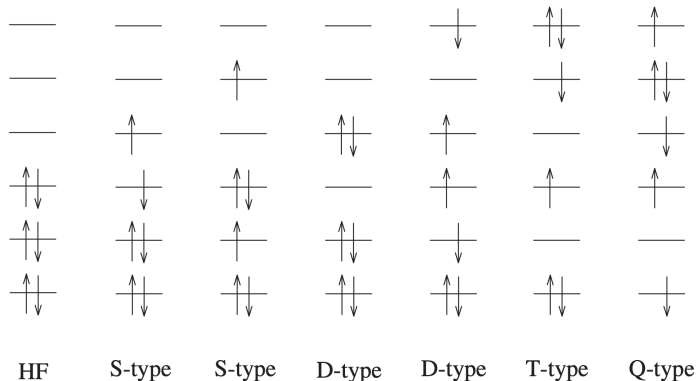
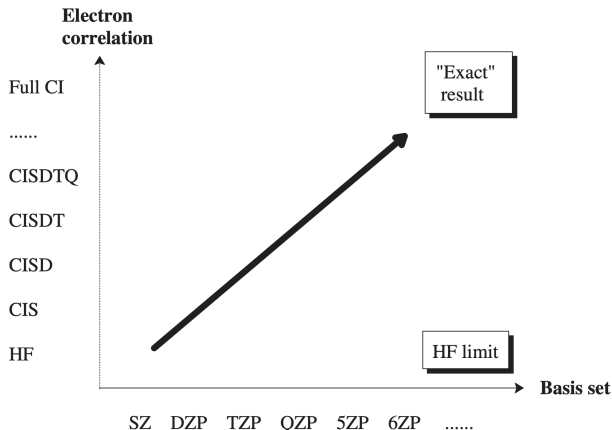


Figure 4.2 Excited Slater determinants generated from an HF reference.

Configuration Interaction methods

- ▶ CIS – include all single excitations – useful for excited states, but not for recovering electron correlations of the ground state
- ▶ CISD – include all single and double excitations – most useful for correlating the ground state
- ▶ CISDT – singles, doubles and triples
- ▶ Full CI – all possible excitations – exact for a given basis set

CI convergence as basis set size grows



Convergence to the exact solution.

Chapter 4 from Jensen, F. (2017). Introduction to Computational Chemistry. John Wiley & Sons.

Correlated Methods. II. Møller-Plesset perturbation theory

- ▶ An energy correction due to electronic correlation, is introduced through a perturbation scheme by Møller and Plesset, the acronym MP n where n is the order at which the perturbation theory is truncated, e.g., MP2, MP3, etc.
- ▶ Unperturbed Hamiltonian $\hat{H}_0 = \sum_i \hat{F}_i$
- ▶ Perturbed Hamiltonian $\hat{H}' = \hat{H}_{\text{ele}} - \hat{H}_0$
- ▶ The Hartree-Fock ground state wavefunction acts as the reference unperturbed wave function Ψ_0
- ▶ $E(\text{MP0}) = \sum_i \epsilon_i$; $E(\text{MP1}) = E(\text{HF})$; $E(\text{MP2}) = E(\text{HF}) + E^{(2)}$
- ▶ MP2 captures a “good” amount of correlation energy at low cost, higher orders available (up to about MP6 in modern codes—becomes expensive rapidly)
- ▶ MP4 order recovers most of the rest of the correlation energy
- ▶ Convergence poor, normally

Correlated Methods. III. The Coupled-Cluster Method

- ▶ An exponential ansatz applied with \hat{T}_n n -particle excitation operators.
- ▶ The Schrödinger equation to be solved is

$$\hat{H}_{\text{ele}} e^{\hat{T}} \psi_0 = E e^{\hat{T}} \psi_0.$$

- ▶ $\hat{T} = 0$ simplifies to HF
- ▶ In coupled-cluster singles, doubles and triples (CCSDT) method,
 $\hat{T} = \hat{T}_1 + \hat{T}_2 + \hat{T}_3$
- ▶ CCSDT is very expensive. A perturbative estimate of the effect of triple excitations defines the CCSD(T) method, sometimes called the “gold standard” of modern single-reference wavefunction theory

Post-HF levels: Accuracy vs. Cost

A rough quality ordering often observed:

HF < MP2 ~ MP3 ~ CCD < CISD
< MP4SDQ ~ QCISD ~ CCSD < MP4
< QCISD(T) ~ CCSD(T)

Table 7.5 Formal scaling behavior, as a function of basis functions N , of various electronic structure methods

Scaling behavior	Method(s)
N^4	HF
N^5	MP2
N^6	MP3, CISD, MP4SDQ, CCSD, QCISD
N^7	MP4, CCSD(T), QCISD(T)
N^8	MP5, CISDT, CCSDT
N^9	MP6
N^{10}	MP7, CISDTQ, CCSDTQ

Chapter 7 from Cramer, C. J. (2013). Essentials of Computational Chemistry: Theories and Models. John Wiley & Sons.

Post-HF levels: Accuracy vs. Cost

Table 4.5 Correlation energies for the beryllium atom in a 4s2p basis set.

Level	ΔE_{corr} (au)	%	Level	ΔE_{corr} (au)	%	Level	ΔE_{corr} (au)	%
MP2	0.05317	67.85						
MP3	0.06795	86.70	CISD	0.07528	96.05	CCSD	0.07818	99.75
MP4	0.07412	94.58				CCSD(T)	0.07836	99.99
MP5	0.07692	98.15	CISDT	0.07547	96.29	CCSDT	0.07836	99.99
MP6	0.07809	99.64						
MP7	0.07849	100.15	CISDTQ	0.07837	100	CCSDTQ	0.07837	100

Results are courtesy of Professor Jeppe Olsen.

Chapter 4 from Jensen, F. (2017). Introduction to Computational Chemistry. John Wiley & Sons.

Semi-empirical methods

Why and how?

- ▶ The high cost of *ab initio* MO calculations is largely due to the many integrals that need to be calculated (esp. two electron integrals)
- ▶ Semi-empirical MO methods start with the general form of *ab initio* Hartree-Fock calculations, but make numerous approximations for the various integrals
- ▶ Many of the integrals are approximated by functions with empirical parameters
- ▶ These parameters are adjusted to improve the agreement with experiment

Examples of semi-empirical methods

- ▶ Developed by Pople and Dewar research groups
- ▶ Few of them are: CNDO, INDO, NDDO, MINDO, MNDO, AM1 etc.
- ▶ Core orbitals are not treated by semi-empirical methods, since they do not change much during chemical reactions
- ▶ Only a minimal set of valence orbitals are considered on each atom (e.g., 2s, 2px, 2py, 2pz on Carbon atom)
- ▶ Acronyms: Zero Differential Overlap (ZDO) and Neglect of Diatomic Differential Overlap (NDDO)

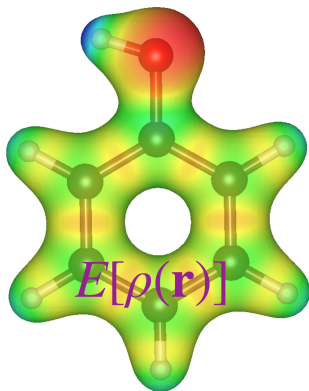
Zero Differential Overlap (ZDO)

- ▶ Two-electron integrals in HF approx. Roothan-Hall formulation:

$$(\mu\nu|\lambda\sigma) = \int \int \phi_\mu(1)\phi_\nu(1) \frac{1}{r_{12}} \phi_\lambda(2)\phi_\sigma(2) dr_1 dr_2$$

- ▶ In this approximation, overlap between two different orbitals (*i.e.*, basis functions are on different atoms) are set to zero;
- ▶ Few more to name... complete neglect of differential overlap (CNDO), intermediate neglect of differential overlap (INDO), modified INDO (MINDO) variations; modified neglect of diatomic overlap (MNDO)
- ▶ Later AM1, and PM3 were developed. All these semi-empirical methods either completely neglect two-electron integrals, and retain fewer integrals, also heavily parameterized

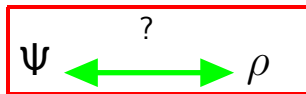
Density Functional Theory



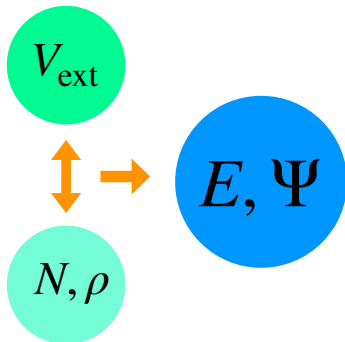
Density Functional Theory

TISE:

$$\underbrace{\left[-\frac{\hbar^2}{2m} \nabla^2 + V(\mathbf{r}) \right]}_H \Psi(\mathbf{r}) = E \Psi(\mathbf{r})$$



Fundamental concept of density functional theory:



Hohenberg-Kohn theorem (1964) establishes an equivalence of wave-function theory; N particle electron density ρ would determine the potential V_{ext}

Density Functional Theory: Hohenberg-Kohn

- ▶ DFT in principle provides an exact solution of the many-electron problem – Hohenberg-Kohn theorem

... An n -electron system has a complex multi-dimensional wavefunction $\Psi(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_n)$ that depends on the coordinates of all of its electrons. From such a wavefunction, we can obtain the familiar electron density

$$\rho(\mathbf{r}_1) = n \int \Psi^*(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_n) \Psi(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_n) d\mathbf{r}_2 d\mathbf{r}_3 \dots d\mathbf{r}_n$$

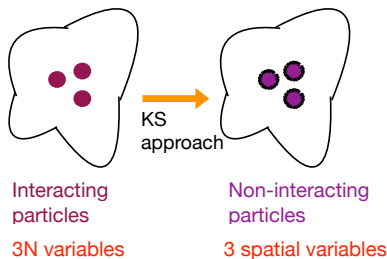
which gives the probability that an electron will be found at the point \mathbf{r}_1 , by integrating over the coordinates of all but one of the electrons. Remarkably, according to the Hohenberg–Kohn proof, no significant information is lost in this integration and, therefore, the electron density is as fundamental a variable as the original wavefunction. This was the breakthrough that allowed Density Functional models to aspire to the status of theories and earned Walter Kohn a share of the 1998 Nobel Prize for chemistry.

– by Peter M.W. Gill, Aust. J. Chem. 2001, **54**, 661–662.

Density Functional Theory: Hohenberg-Kohn

- ▶ The total electronic energy of the system and all its contributions are functionals of the ground-state electron density $E[\rho(\vec{r})]$.
- ▶ Unfortunately, no explicit expression for the total electronic energy in the functional form is known and it can only be formulated by approximate analytic expressions.
- ▶ A variational principle of DFT: The second Hohenberg-Kohn theorem provides a variational principle w.r.t. the density. Variation of the total energy $E[\tilde{\rho}(\vec{r})]$ w.r.t. a positive definite trial density $\tilde{\rho}(\vec{r})$ that integrates to the correct total number of electrons yields the ground state density $\rho(\vec{r})$ at the energy minimum.

Density Functional Theory: Kohn-Sham



KS non-interacting electrons live under an external potential, such that, non-interacting electron-density is same as fully-interacting density

$$\hat{H}_{KS}\psi_i(\mathbf{r}) = \left[-\frac{1}{2}\nabla^2 - \sum_A^{\text{nuclei}} \frac{Z_A}{r_A} + \int \frac{\rho(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} d\mathbf{r}' + V_{xc}(\mathbf{r}) \right] \psi_i(\mathbf{r}) = \epsilon_i \psi_i(\mathbf{r})$$

with the electron density: $\rho(\mathbf{r}) = \sum_i^N |\psi_i(\mathbf{r})|^2$,

$V_{xc}(\mathbf{r})$ is known as exchange-correlation functional

Density Functional Theory

Except the following term,

$$V_{XC}(\mathbf{r}) = \frac{\delta E_{XC}[\rho(\mathbf{r})]}{\delta \rho(\mathbf{r})}$$

in fact, all other terms in Kohn-Sham DFT formulation can be computed

- ▶ $E_{XC}[\rho(\mathbf{r})]$ can be defined as the sum of all non-classical contributions to the electron-electron interaction and the difference between the true kinetic energy and the non-interacting kinetic energy
- ▶ Unfortunately, the exact form of XC-functionals are not known
- ▶ Hence, use approximate XC-functionals, like, LDA, B3LYP etc.

- ▶ The exact form of XC-functional is not known, approximate forms have been defined and developed
- ▶ Most functionals have a separate components for the exchange energy and correlation energy
- ▶ No systematic means for finding the exact functional
- ▶ Parameterized factors incorporated

Various XC-functionals

- ▶ **Local density approximation (LDA):** Functional depends only on the (local) density at a given point. Example: S-VWN
- ▶ **Gradient-corrected approximation (GGA):** Functional depends on local density and its gradient. Examples: PW91 and LYP correlation functionals, B88 exchange functional
- ▶ **Meta-GGA:** Functional depends on density, its gradient, and its second derivative. Example: M06-L
- ▶ **Hybrid DFT:** Mixes in Hartree-Fock exchange. Most popular example: B3LYP (hybrid GGA); also M05-2X and M06-2X hybrid meta-GGAs
- ▶ **Double hybrids:** Hybrid DFT that mixes in some MP2 correlation. Ex. B2-PLYP

Electronic structure theory so far. . .

