# Theory

This section will cover the contents of the drug delivery treatment and the general concept of molecular modeling.

## Cancer cell

The cancer is caused by damage to DNA, resulting in mutations to genes that encode for proteins controlling cell division. Many mutation events may be required to transform a normal cell into a malignant cell. These mutations can be caused by radiation, chemicals or physical agents that cause cancer, which are called carcinogens, or by certain viruses that can insert their DNA into the human genome. Mutations occur spontaneously, and may be passed down from one cell generation to the next as a result of mutations within germ lines. However, some carcinogens also appear to work through non-mutagenic pathways that affect the level of transcription of certain genes without causing genetic mutation.

Carcinogenesis is caused by this mutation of the genetic material of normal cells, which upsets the normal balance between proliferation and cell death. This results in uncontrolled cell division and tumor formation. The uncontrolled and often rapid proliferation of cells can lead to benign tumors; some types of these may turn into malignant tumors (cancer). In the mechanisms of carcinogenesis, Cancer is a disease of genes which regulate cell growth must be damaged. Proto-oncogenes are genes which promote cell growth and mitosis, a process of cell division, and tumor suppressor genes discourage cell growth, or temporarily halt cell division from occurring in order to carry out DNA repair. Typically, a series of several mutations to these genes are required before a normal cell transforms into a cancer cell. Mutations in proto-oncogenes can modify their expression and function, increasing the amount or activity of the product protein. When this happens, they become oncogenes, and thus cells have a higher chance to divide excessively and uncontrollably. The chance of cancer cannot be reduced by removing proto-oncogenes from the genome as they are critical for growth, repair and homeostasis of the body. It is only when they become mutated, that the signals for growth become excessive. However, a mutation can damage the tumor suppressor gene itself, or the signal pathway which activates it, "switching it off". The invariable consequence of this is that

DNA repair is hindered or inhibited: DNA damage accumulates without repair, inevitably leading to cancer.

The cancer cell can be treatment by several methods such as surgery, chemotherapy, immunotherapy, monoclonal antibody therapy, radiation therapy, hormonal suppression, symptom control, treatment trials, cancer vaccines, quackery in the treatment of cancer, and complementary and alternative medicine. At present, the treatment by using drug delivery is very interesting method.

Chemotherapy is the treatment of cancer with drugs ("anticancer drugs") that can destroy cancer cells. It interferes with cell division in various possible ways, e.g. with the duplication of DNA or the separation of newly formed chromosomes. Most forms of chemotherapy target all rapidly dividing cells and are not specific for cancer cells. Hence, chemotherapy has the potential to harm healthy tissue, especially those tissues that have a high replacement rate (e.g. intestinal lining). These cells usually repair themselves after chemotherapy (Wikipedia, 2007).

## Drug delivery treatment

The drug delivery contains the drug, water soluble compound and polypeptide chain. The drug treats a cancer cell such as floxuridine (FUDE), doxorubicin, methotrexate, and cisplatin. The solubilizing compound is a polymer form such as poly(lactic acid), poly(lactic-co-glycolic acid), polyanhydrides, poly(ortho esters), poly(phosphoesters), and poly(ethylene glycol). And the peptide chain is a molecule to cross-linkage with drug. The peptide chain is a polymer molecule such as polychitosan and heparan sulfate. The drug delivery systems have many types such as hydrogel, encapsulation, nanoaggregation, and micelle formation.

For the treatment, the water soluble compound is carried to cancer cell molecule. Next, the proteolytic enzymes or protein molecule in cancer cell attracts with the polypeptide chain molecule. The molecule is separated into two parts. The first part is drug and polypeptide chain. And the second part is the polypeptide chain and water soluble molecule. For the first part, the polypeptide chain is biodegradation and release drug into the cancer cell to block DNA (Woityk, 2005).

## Computational Models and Molecular Modeling

The computational chemistry simulates chemical structures and reactions numerically, based on the full or part of physics fundamental laws. It allows chemists to study chemical phenomena by running theoretical calculations than by examining reactions and compounds experimentally. Some methods can be used to model not only stable molecules, but also short-lived, unstable intermediates and even transition states. In this way, they can provide information about molecules and reactions which is impossible to obtain through observation. Computational chemistry is therefore both an independent research area and a vital adjunct to experimental studies.

The computational chemistry devotes the structure of molecules by molecular mechanics and electronic structure theory. The performance of computational chemistry for calculations:

- Computing the energy of a particular molecular structure (spatial arrangement of atoms or nuclei and electrons). Properties related to the energy may also be predicted by some methods.

- Performing geometry optimizations, which locate the lowest energy molecular structure close proximity to the specified starting structure. Geometry optimizations depend primarily on the gradient of the energy-the first derivative of the energy with respect to atomic positions.

- Computing the vibrational frequencies of molecules resulting from interatomic motion within the molecule. Frequencies depend on the second derivatives of the energy with respect to atomic to atomic structure, and frequency calculations may also predict other properties which depend on second derivatives. Frequency calculations are not possible or practical for all computational chemistry methods (Sonthisawate 2006).

## Molecular Mechanics Method

Molecular mechanics simulations use the laws of classical physics to predict the structures and properties of molecules. Molecular mechanics methods are available in many computer programs, including MM3, HyperChem, Quanta, Sybyl, Alchemy and Gaussian. There are many different molecular mechanics methods. Each electron is characterized by its particular *force field.* A force field has these components:

- A set of equations defining how the potential energy of a molecule varies with the locations of its component atoms.

- A series of *atom types*, defining the characteristics of an element within a specific chemical context. Atom types prescribe different characteristics and behavior for an element. For example, a carbon atom in a carbonyl is treated differently than one bonded to three hydrogens. The atom type depends on hybridization, charge and the types of the other atoms which it is bonded.

- One or more *parameter sets* that fit the equations and atom types to experimental data. Parameter sets define *force constants,* which are values used in the equations to relate atomic characteristics to energy component, and structural data such as bond lengths and angles.

Molecular mechanics calculations don’t explicitly treat the electrons in a molecular system. Instead, they perform computations based upon the interactions among the nuclei. Electronic effects are implicitly included in force fields through parameterization.

This approximation makes molecular mechanics computationally, and allows it to be used for very large systems containing many thousands of atoms. However, it also carries several limitations as well. Among the most important are these:

Each force field achieves good results only for a limited class of molecules, related to those which it was parameterized. No force field can be generally used for all molecular systems of interest

Neglecting of electrons means that molecular mechanics methods cannot treat chemical problems where electronic effects predominate. For example, they cannot describe processes which involve bond formation or bond breaking. Molecular properties which depend on subtitle electronic details are also not reproduced by molecular mechanics methods (Sonthisawate 2006).

### Electronic structure methods (Quantum Mechanics Methods)

Electronic structure methods use the laws of quantum mechanics as the basis for their computations. Quantum mechanics states that the energy and other related properties of a molecule can be obtained by solving the Schrödinger equation:

$$H\Psi = E\Psi \tag{1}$$

For any but the smallest systems, however, exact solutions to the Schrödinger equation are not computationally practical. Electronic structure methods are characterized by their various mathematical approximations for solution. There are two major classes of electronic structure methods:

Semi-empirical method, such as AM1, MINDO/3 and PM3, implemented in programs like MOPAC, AMPAC, HyperChem, and Gaussian, uses parameters which are derived from experimental data to simplify the computation. These methods solve an approximate form of the Schrödinger equation that depends on having appropriate parameters available for the type of chemical system under investigation. The semi-empirical methods are largely characterized by their differing parameter sets, but it gives the good trend in approximation for solution.

Ab initio method uses non experimental parameters in their computations. Instead, their computations are based solely on the laws of quantum mechanics-the first principles referred to in the name ab initio-and on the values of a small number of physical constants such as the speed of light, the masses and charges of electrons and nuclei, and Planck's constant (Sonthisawate 2006).

## Molecular Orbital Theory

Molecular orbital theory which uses one-electron functions or orbitals to approximate the full wave function is an approach to molecular quantum mechanics A molecular orbital, $\psi(x, y, z)$, is a function of the Cartesian coordinates x, y, z of a single electron. The spin coordinates, $\xi$, also has to be included. This coordinate takes one of two possible values $\left(\pm\frac{1}{2}\right)$, and the spin angular momentum component along the z axis in units of $h/2\pi$ (Sonthisawate 2006).

The simplest type of wave function appropriate for the description of an n-electron system would be in the form of a product of spin orbital,

$$\psi_{product} = \chi_1(1)\chi_2(2)\ldots\chi_n(n) \tag{2}$$

Where $\chi_i(i)$ is written for $\chi_i(x_i, y_i, z_i, \xi_i)$, the spin orbital of electron i. The spin orbitals may be arranged in a determinant of wave function.

$$\psi_{\det er \min ant} = \begin{vmatrix} \chi_1(1) & \chi_2(2) & \cdots & \chi_n(1) \\ \chi_1(2) & \chi_2(2) & \cdots & \chi_n(2) \\ \vdots & \vdots & \vdots & \vdots \\ \chi_1(n) & \chi_2(n) & \cdots & \chi_n(n) \end{vmatrix} \tag{3}$$

Here the elements of the first row of the determinant contain assignations of electron 1 to all the spin orbitals $\chi_1, \chi_2, \ldots, \chi_n$, the second row all possible assignations of electron 2, and so forth.

Some further properties of molecular orbital wave functions are worth noting. It is possible to force the orbitals to be orthogonal to each other, that equation is

$$S_{ij} = \int \psi_i^* \psi_j dxdydz \tag{4}$$

This can be accomplished without changing the value of the whole wave function by mixing columns of the determinant. The $\alpha$ and $\beta$ are orthogonal spin functions by integration over spin space (actually summation over the two possible values of $\xi$):

$$\sum_{\xi}\alpha(\xi)\beta(\xi)=\alpha\left(+\frac{1}{2}\right)\beta\left(+\frac{1}{2}\right)+\alpha\left(-\frac{1}{2}\right)\beta\left(-\frac{1}{2}\right)=0 \qquad (5)$$

Molecular orbitals may be normalized, that is

$$S_{ij}=\int\psi_i^*\psi_j\,dxdydz=1 \qquad (6)$$

By multiplication of the individual by a constant, normalization corresponds to the requirement that the probability of finding the electron anywhere in space is unity. Given $S_{ij}=1$, the determinant of wavefunction can be normalized by multiplication by a factor of $(n!)^{-1/2}$, that is

$$\int\cdots\int\Psi^*\Psi d\tau_1\tau_2\cdots d\tau_n=1 \qquad (7)$$

The determinant of wavefunction is normalized by multiplication by a factor of $(n!)^{-1/2}$. This factor can be written down a full many-electron molecular orbital wave function for the closed-shell ground state of a molecule with n(even) electrons, doubly occupying n/2 orbitals:

$$\Psi=(n!)^{-1/2}\begin{vmatrix}\Psi_1(1)\alpha(1) & \Psi_1(1)\beta(1) & \Psi_2(1)\alpha(1) & \cdots & \Psi_{n/2}(1)\beta(1)\\ \Psi_1(2)\alpha(2) & \Psi_1(2)\beta(2) & \Psi_2(2)\alpha(2) & \cdots & \Psi_{n/2}(2)\beta(2)\\ \vdots & \vdots & \vdots & & \vdots\\ \Psi_1(n)\alpha(n) & \Psi_1(n)\beta(n) & \Psi_2(n)\alpha(n) & \cdots & \Psi_{n/2}(n)\beta(n)\end{vmatrix} \qquad (8)$$

The determinant is referred to as a Slater determinant.

This theory starts from the Schrödinger equation. The energies and wavefunctions of stationary states of a system are given by the

Schrödinger equation: $\hat{H}\psi_{e,n} = E\psi_{e,n}$

Hamiltonian: $\hat{H} = \hat{T}_n + \hat{T}_e + \hat{V}_{e,n}$

In this equation, $\hat{H}$ is the Hamiltonian operator which is the kinetic and potential energies operator atomic nuclei and electrons. The Hamiltonian is composed of three parts: the kinetic energy of the nuclei, the kinetic energy of the electrons, and the potential energy of nuclei and electrons. $\psi$ is a wavefunction, one of the solutions of the eigenvalue equation. This wavefunction depends on the coordinates of the electrons and the nuclei.

Four approximations are commonly made (Nix, 2002):

- Time independence; the equations are looking at states that are stationary in time.
- Neglect of relativistic effects; this is warranted unless the velocity of the electrons approaches to the speed of light, which is only in the case of heavy atoms with very high nuclear charge.
- Born-Oppenheimer approximation; separation of the motion of nuclei and electrons.
- Orbital approximation; the electrons are confined to certain regions of space.

The Born-Oppenheimer approximation implies the separation of nuclear and electronic wavefunctions.

Born-Oppenheimer: $\Psi_{e,n} = \chi_n \psi_e$

The theory independence of the experimental values of physical constants, atomic units is introduced:

e = 1 charge of electron

m = 1 mass of the electron

$$\bar{h} = \frac{h}{2\pi}$$

Derived atomic units of length and energy are:

1 bohr = $a_0 = \frac{\bar{h}}{me^2} = 0.529\,\text{Å}$

1 hartree = $\frac{e^2}{a_0} = 4.3598 \times 10^{-18}$ J = 627.51 kcal/mol

With these units the electronic Hamiltonian is:

$$\hat{H}_e = -\frac{1}{2}\sum_{i=1}^{n}\nabla_i^{\,2} - \sum_{i=1}^{n}\sum_{A=1}^{N}\frac{Z_A}{|R_A - r_i|} + \sum_{i<j}^{n}\frac{1}{r_{ij}} \tag{9}$$

The $\nabla_i^{\,2}$ is the Laplace operator $\nabla_i^{\,2} = \frac{\partial^2}{\partial x_i^2} + \frac{\partial^2}{\partial y_i^2} + \frac{\partial^2}{\partial z_i^2}$. The total energy in the Born-Oppenheimer model is obtained by adding the nuclear repulsion energy to the electronic energy:

$$E_{total} = E_e + E_n \tag{10}$$

The nuclear repulsion energy is

$$E_n = \sum_{A<B}^{N}\frac{Z_A Z_B}{|R_A - R_B|} \tag{11}$$

### Hartree-Fock Theory

Hartree-Fock theory is fundamental of electronic structure theory. It is the basis of molecular orbital (MO) theory, which positions of each electron's motion can be described by a single-particle function (orbital) which does not depend explicitly on the instantaneous motions of the other electrons. The Hartree-Fock theory often provides a good starting point for more elaborate theoretical methods which are better approximations to the electronic Schrödinger equation.

Hartree-Fock theory was developed to solve the electronic Schrödinger equation that results from the time-independent Schrödinger equation after invoking the Born-Oppenheimer approximation. In atomic units, and with r denoting electronic and R denoting nuclear degrees of freedom, the electronic Schrödinger equation is

$$\left[-\frac{1}{2}\sum_i \nabla_i^2 - \sum_{A,i}\frac{Z_A}{r_{Ai}} + \sum_{A>B}\frac{Z_A Z_B}{R_{AB}} + \sum_{i>j}\frac{1}{r_{ij}}\right]\Psi(r;R) = E_{el}\Psi(r;R) \tag{12}$$

This approximation starts with a wavefunction of the general form

$$\Psi_{HP}(r_1, r_2, ...., r_N) = \phi_1(r_1)\phi_2(r_2)...\phi_N(r_N) \tag{13}$$

which is known as a Hartree Product

The antisymmetry principle which states that a wavefunction describing fermions should be antisymmetric with respect to the interchange of any set of space-spin coordinates. The General Hartree Fock or Z-Averaged Perturbation Theory changes the notation for orbitals from ∅(r), a spatial orbital, to χ(x), a spin orbital. The Hartree Product becomes

$$\Psi_{HP}(x_1, x_2, ...., x_N) = \chi_1(x_1)\chi_2(x_2)...\chi_N(x_N) \tag{14}$$

The Pauli Exclusion Principle is a consequence of the antisymmetry principle.
The generalization wavefunction to N electrons is

$$\Psi = \frac{1}{\sqrt{N!}} \begin{vmatrix} \chi_1(x_1) & \chi_2(x_1) & \cdots & \chi_N(x_1) \\ \chi_1(x_2) & \chi_2(x_2) & \cdots & \chi_N(x_2) \\ \vdots & \vdots & \ddots & \vdots \\ \chi_1(x_N) & \chi_2(x_N) & \cdots & \chi_N(x_N) \end{vmatrix} \tag{15}$$

In addition, a solution of the electronic Schrödinger equation the wavefunction must be normalized and satisfy the Pauli principle. The normalization condition is connected with the interpretation of the wavefunction as a distribution function which when integrated over entire space should give a value of one:

$$\int \psi^* \psi dx = 1 \tag{16}$$

in "bra-ket" notation: $\langle \psi | \psi \rangle = 1$

An important property of the self consistent field (SCF) method is that its solutions satisfy the Variation Principle, which states that the expectation value of the energy evaluated with an inexact wavefunction is always higher than the exact energy (Sherrill, 2000):

$$E_e = \frac{\langle \psi | H_e | \psi \rangle}{\langle \psi | \psi \rangle} \geq E_{exact} \tag{17}$$

### Energy Expression

The electronic Hamiltonian is simply

$$\hat{H}_{el} = \sum_{i} h(i) + \sum_{i<j} v(i,j) + V_{NN} \tag{18}$$

$V_{NN}$ is just a constant for the fixed set of nuclear coordinates {R}, this term can be ignored (it doesn't change the eigenfunctions, and only shifts the eigenvalues).

The Hartree-Fock wavefunction will have the form of a Slater determinant, and the energy will be given by the usual quantum mechanical expression.

$$E_{el} = \langle \Psi \left| \hat{H}_{el} \right| \Psi \rangle \tag{19}$$

The Hartree-Fock energy $E_{el}$ in terms of integrals of the one- and two-electron operators is

$$E_{HF} = \sum_{i} \left\langle i \middle| h \middle| i \right\rangle + \frac{1}{2} \sum_{ij} [ij|jj] - [ij|ji] \tag{20}$$

where the one electron integral is

$$\left\langle i \middle| h \middle| i \right\rangle = \int dx_1 \chi_i^*(x_1) h(r_1) \chi_j(x_1) \tag{21}$$

and a two-electron integral (Chemists' notation) is

$$[ij|kl] = \int dx_1 dx_2 \chi_i^*(x_1) \chi_j(x_1) \frac{1}{r_{12}} \chi_k^*(x_2) \chi_l(x_2) \tag{22}$$

There are efficient computer algorithms for computing such one- and two-electron integrals (Sherrill, 2000).

### The Hartree-Fock Equations

The Hartree-Fock method seeks to approximately solve the electronic Schrödinger equation, and assumes that the wavefunction can be approximated by a single Slater determinant made up of one spin orbital per electron. The Hartree-Fock method which was used to determine the set of spin orbitals minimize the energy and give the best single determinant. The Hartree-Fock energy can be accomplished by Lagrange's method of undetermined multipliers, where this method is employed a functional L defined as

$$L[\{x\}] = E_{HF}[\{\chi_i\}] - \sum_{ij} \varepsilon_{ij}(\langle i|j\rangle - \delta_{ij}) \tag{23}$$

where $\varepsilon_{ij}$ are the undetermined Lagrange multipliers and < i|j > is the overlap between spin orbitals i and j, i.e.,

$$\langle i|j\rangle = \int \chi_i^*(x)\chi_j(x)dx \tag{24}$$

Setting the first variation δL = 0, and working through some algebra, the Hartree-Fock equations defining the orbitals are arrived:

$$h(x_1)\chi_i(x_i) + \sum_{j\neq i}\left[\int dx_2 \left|\chi_j(x_2)\right|^2 r_{12}^{-1}\right]\chi_i(x_1) - \sum_{j\neq i}\left[\int dx_2 \chi_j^*(x_2)\chi_i(x_2) r_{12}^{-1}\right]\chi_j(x_1) = \varepsilon_i\chi_i(x_i) \tag{25}$$

where $\varepsilon_i$ is the energy eigenvalue associated with orbital $\chi_i$.

The Hartree-Fock equations can be solved numerically (exact Hartree-Fock), in the space spanned by a set of basis functions (Hartree-Fock-Roothaan equations). In either case, note that the solutions depend on the orbitals. Hence, the basis functions need to guess some initial orbitals and then refine our guesses iteratively. For this reason, Hartree-Fock is called a self-consistent-field (SCF) approach. The first term above in square brackets

$$\sum_{j\neq i}[\int dx_2 \left|\chi_j(x_2)\right|^2 r_{12}^{-1}]\chi_i(x_1) \tag{26}$$

gives the Coulomb interaction of an electron in spin orbital $\chi_i$ with the average charge distribution of the other electrons. Here the sense Hartree-Fock is a mean field" theory. This is called the Coulomb term, and it is convenient to define a Coulomb operator as

$$J_j(x_{1)} = \int dx_2 \left|\chi_j(x_2)\right|^2 r_{12}^{-1} \tag{27}$$

This gives the average local potential at point x₁ due to the charge distribution from the electron in orbital $\chi_j$.

The other term in brackets in the Hartree-Fock equations [25] defining the orbitals equation is hard to explain and does not have a simple classical analog. It arises from the antisymmetry requirement of the wavefunction. It looks much like the Coulomb term, except that it switches or exchanges spin orbitals $\chi_i$ and $\chi_j$. Hence, it is called the exchange term:

$$\sum_{j\neq i}[\int dx_2\chi_j^*(x_2)\chi_i(x_2)r_{12}^{-1}]\chi_j(x_1) \tag{28}$$

An exchange operator can define in terms of its action on an arbitrary spin orbital $\chi_j$:

$$K_j(x_1)\chi_i(x_1)=\sum_{j\neq i}\left[\int dx_2\chi_j^*(x_2)\chi_i(x_2)r_{12}^{-1}\right]\chi_j(x_1) \tag{29}$$

In terms of these Coulomb and exchange operators, the Hartree-Fock equations become considerably more compact.

$$[h(x_1)-\sum_{j\neq i}J_j(x_1)-\sum_{j\neq i}K_j(x_1)]\chi_i(x_1)=\varepsilon_i\chi_i(x_1) \tag{30}$$

The Hartree-Fock equations are eigenvalue equations which realize that

$$[J_i(x_1)-K_i](x_1)]\chi_i(x_1)=0 \tag{31}$$

Then, it becomes clear that the restrictions can remove j ≠ i in the summations and introduces a new operator, the Fock operator, as

$$f(x_1)=h(x_1)+\sum_j J_j(x_1)-K_j(x_1) \tag{32}$$

And now the Hartree-Fock equations are just

$$f(x_1)\chi_i(x_1) = \varepsilon_i \chi_i(x_1) \tag{33}$$

Introducing a basis set, the Hartree-Fock equations can be transformed into the Roothaan equations. Denoting the atomic orbital basis functions as $\tilde{\chi}$, the expansion is

$$\chi_i = \sum_{\mu=1}^{K} C_{\mu i}\tilde{\chi}_\mu \tag{34}$$

for each spin orbital i. This leads to

$$f(x_1)\sum C_{\nu i}\tilde{\chi}_\nu(x_i) = \varepsilon_i \sum_\nu C_{\nu i}\tilde{\chi}_\nu(x_1) \tag{35}$$

Left multiplying by $\tilde{\chi}^*_\mu(x_1)$ and integrating yields a matrix equation

$$\sum_\nu C_{\nu i}\int dx_1 \tilde{\chi}^*_\mu(x_1) f(x_1)\tilde{\chi}_\nu(x_1) = \varepsilon_i \sum_\nu C_{\nu i}\int dx_1 \tilde{\chi}^*_\mu(x_1)\tilde{\chi}_\nu(x_1) \tag{36}$$

This can be simplified by introducing the matrix element notation

$$S_{\mu\nu} = \int dx_1 \tilde{\chi}^*_\mu(x_1)\tilde{\chi}_\nu(x_1) \tag{37}$$

$$F_{\mu\nu} = \int dx_1 \tilde{\chi}^*_\mu f(x_1)\tilde{\chi}_\nu(x_1) \tag{38}$$

For two electrons, the Hartree-Fock equation is

$$F_{\mu\nu} = H^{core}_{\mu\nu} + \sum_{\lambda\sigma} P_{\lambda\nu}\left[(\mu\nu/\lambda\sigma) - \frac{1}{2}(\mu\nu/\lambda\sigma)\right] \tag{39}$$

$$F_{\mu\nu} = H^{core}_{\mu\nu} + G_{\mu\nu} \tag{40}$$

where $H^{core}_{\mu\upsilon}$, core-Hamiltonian matrix defined as

$$H^{core}_{\mu\nu} = \int dr_1 \varphi^*_1(1)h(1)\varphi_\nu(1) \tag{41}$$

$$P_{\mu\upsilon} = 2\sum_{a}^{N/2} C_{\mu\upsilon}C^*_{\upsilon a} \tag{42}$$

The matrix S is the overlap matrix, indicating the overlap between orbitals.

$$S_{\mu\upsilon} = \int dr_1 \phi_\mu^*(1)\phi_\upsilon(1) \tag{43}$$

The term $(\mu\upsilon/\lambda\sigma)$ in Equation signified the two-electron repulsion integrals, defined as

$$(\mu\upsilon/\lambda\sigma) = \int dr_1 dr_2 \phi_\mu^*(1)\phi_\upsilon(2) r_{12}^{-1} \phi_\lambda^*(2)\phi_\sigma(2) \tag{44}$$

Now the Hartree-Fock-Roothaan equations can be written in matrix form as

$$\sum_\nu F_{\mu\nu} C_{\nu i} = \varepsilon_i \sum_\nu S_{\mu\nu} C_{\nu i} \tag{45}$$

or even more simply as matrices

$$FC = SC\varepsilon \tag{46}$$

where $\varepsilon$ is a diagonal matrix of the orbital energies $\varepsilon_i$. This is like an eigenvalue equation except for the overlap matrix **S**. One performs a transformation of basis to an orthogonal basis to make **S** vanish. Then it's just a matter of solving an eigenvalue equation (or, equivalently, diagonalizing F!). Well, not quite. Since **F** depends on it is own solution (through the orbitals), the process must be done iteratively (Sherrill, 2000).

Restricted Open-shell Hartree-Fock (ROHF) is a variant of Hartree-Fock theory for open shell doubly occupied molecular orbitals as far as possible and then singly occupied orbitals for the unpaired electrons. But, it is difficult to implement (Wikipedia, 2007).

Restricted Hatree-Fock theory for closed shell molecules, leads to a Roothaan equation written in the form of a generalized eigenvalue problem. The restricted Hartree-Fock equation is $FC = SC\varepsilon$.

Unrestricted Hartree-Fock (UHF) theory is the most common molecular orbital method for open shell molecules where the number of electrons of each spin is not equal. This theory uses different molecular orbitals for the α and β electrons. This has been called *different orbitals for different spins* (DODS) method. The result is pair of coupled Roothaan equations; know as Pople-Nesbet equations. The unrestricted Hartree-Fock equation is

$$F^{\alpha}C^{\alpha} = SC^{\alpha}\varepsilon^{\alpha}\,,\ F^{\beta}C^{\beta} = SC^{\beta}\varepsilon^{\beta} \tag{47}$$

Where $F^{\alpha}$ and $F^{\beta}$ are the Fock matrices for the $\alpha$ and $\beta$ orbitals, $C^{\alpha}$ and $C^{\beta}$ are the matrices of coefficients for the $\alpha$ and $\beta$ orbitals, S is the overlap matrix of the basis functions, the $\varepsilon^{\alpha}$ and $\varepsilon^{\beta}$ are the (diagonal, by convention) matrices of orbital energies for the $\alpha$ and $\beta$ orbitals. The pair of equations is coupled because the Fock matrix elements of one spin contain coefficients of both spin as the orbital has to be optimized in the average field of all other electrons. The final result is a set of molecular orbitals and orbital energies for the $\alpha$ spin electrons and a set of molecular orbitals and orbital energies for the $\beta$ electrons. The unrestricted open-shell Hartree–Fock (UHF) formalism was applied to open-shell systems (Wikipedia, 2007).

### Density Functional Theory

The functional employed by DFT methods partition the electronic energy *E* of a molecule into the terms

$$E(\rho) = E^{T}(\rho) + E^{V}(\rho) + E^{J}(\rho) + E^{XC}(\rho) \tag{48}$$

where $E^{T}$ is the kinetic energy of the electrons, $E^{V}$ is the potential energy of nuclear–electron attraction and nuclear–nuclear repulsion, $E^{J}$ is the electron–electron repulsion of the classical energy of the density ρ, and $E^{XC}$ is the exchange energy (X) arising from the wave function including the dynamical correlation (C) of electron motion.

The major problem with DFT is that the exact functional for exchange and correlation are not known except for the free electron gas. However, approximations exist which permit the calculation of certain physical quantities quite accurately. In physics the most widely used approximation is the local-density approximation (LDA), where the functional depends only on the density at the coordinate where the functional is evaluated:

$$E_{XC}[n] = \int \varepsilon_{XC}(n)n(r)d^3r \tag{49}$$

The local spin-density approximation (LSDA) is a straightforward generalization of the LDA to include electron spin:

$$E_{XC}[n_\uparrow, n_\downarrow] = \int \varepsilon_{XC}(n_\uparrow, n_\downarrow)n(r)d^3r \tag{50}$$

Highly accurate formulae for the exchange-correlation energy density $\varepsilon_{XC}(n_\uparrow, n_\downarrow)$ have been constructed from Quantum Monte Carlo simulations of a free-electron gas.
Generalized gradient approximations (GGA) are still local but also take into account the gradient of the density at the same coordinate:

$$E_{XC}[n_\uparrow, n_\downarrow] = \int \varepsilon_{XC}(n_\uparrow, n_\downarrow, \vec{\nabla} n_\uparrow, \vec{\nabla} n_\downarrow)n(r)d^3r \tag{51}$$

Using the latter (GGA) very good results for molecular geometries and ground state energies have been achieved. Many further incremental improvements have been made to DFT by developing better representations of the functional (Wikipedia, 2007).

The term $E^{XC}$ is divided into two separate functional

$$E^{XC}(\rho) = E^X(\rho) + E^C(\rho) \tag{52}$$

The definition of the $E^X(\rho)$ and $E^C(\rho)$ functional can be found that Becke introduced a gradient-corrected functional $E^X(B)(\rho,\nabla\rho)$ and formulated functional which include a mixture (hybrid) of Hartree–Fock (HF) exchange and DFT exchange (X) plus correlation (C) as

$$E^{XC}(hybrid) = c_{HF}E^X(HF) + c_{DFT}E^C(DFT) \tag{53}$$

where the coefficients c are adjustable parameters. Becke's B3LYP functional, for instance, is a three parameter functionals of the following composition:

$$E^{XC}(B3LYP) = E^{X} + c_{0}\left[E^{X}(HF) - E^{X}(DFT)\right] + c_{X}E^{X}(B) + E^{C}(VWN3) + \\ c_{C}\left[E^{C}(LYP) - E^{C}(VWN3)\right] \tag{54}$$

where VWN is the Vosko, Wilk, Nusair functional, and LYP is the Lee, Yang, Parr functional. The parameters $c_0$, $c_X$, and $c_C$ are determined by fitting to atomization energies, ionization energies, proton affinities, and atomic energies of a set of molecules. Thus, the B3LYP procedure is semi-empirical in this sense. DFT calculations precede in the same way as *ab initio* HF calculations, with the addition of the extra term $E^{\mathrm{XC}}$, which is computed via numerical integration (Janaoschek 2001).

Vosko-Wilk-Nusair correlation energy functional (TCM Group, 2007)

$$E_{C}^{VWN}\left[\rho_{\alpha},\rho_{\beta}\right] = \int dr\rho\varepsilon_{C}^{VWN}\left(\rho_{\alpha},\rho_{\beta}\right) \tag{55}$$

$$\varepsilon_{C}^{VWN}\left(\rho_{\alpha},\rho_{\beta}\right) = \varepsilon_{I}\left(\rho_{\alpha},\rho_{\beta}\right) + \Delta\varepsilon_{C}(r_{S},\zeta) \tag{56}$$

$$\varepsilon_{I}\left(\rho_{\alpha},\rho_{\beta}\right) = A_{i}\left[\ln\frac{x^{2}}{X(x)} + \frac{2b}{Q}\left(\frac{Q}{2x+b}\right) - \frac{bx_{0}}{X(x)}\left(\ln\frac{(x-x_{0})^{2}}{Q}\tan^{-1}\frac{Q}{2x+b}\right)\right]_{x=r_{S}^{1/2}} \tag{57}$$

$$Q = (4c_{i} - b_{i}^{2})^{1/2} \tag{58}$$

$$X(x) = X^{2} + b_{i}x + c_{i} \quad (i = I, II) \tag{59}$$

$$\Delta\varepsilon_{C}(r_{S},\zeta) = \varepsilon_{III}(\rho_{\alpha},\rho_{\beta})\left[\frac{f(\zeta)}{f''(0)}\right]\left[1 + \beta_{1}(r_{S})\zeta^{4}\right] \tag{60}$$

$$\beta_{1}(r_{S}) = \left[\frac{f''(0)}{\varepsilon_{III}\left(\rho_{\alpha},\rho_{\beta}\right)}\right]\Delta\varepsilon(r_{S},1) - 1 \tag{61}$$

$$\Delta\varepsilon(r_{S},1) = \varepsilon_{I}\left(\rho_{\alpha},\rho_{\beta}\right) - \varepsilon_{II}\left(\rho_{\alpha},\rho_{\beta}\right) \tag{62}$$

**Table 2** Constants for the Vosko-Wilk-Nusair parameterizations

| **Parameter** | **I** | **II** | **III** |
|---|---|---|---|
| $A_{\mathrm{i}}$ | 0.062184 | 0.031091 | –0.033774 |
| $b_{\mathrm{i}}$ | 3.72744 | 7.06042 | 1.131071 |
| $c_{\mathrm{i}}$ | 12.9352 | 18.0578 | 13.0045 |
| $x_{0\mathrm{i}}$ | –0.10498 | –0.32500 | –0.0047584 |

Lee, Yang and Parr correlation energy functional and potential

$$E_C^{LYP}\left[\rho_\alpha,\rho_\beta\right]=-a\int dr\,\frac{\gamma(r)}{1+d\rho^{-1/3}}\left\{\rho+2b\rho^{-5/3}\left[2^{2/3}C_F\rho_\alpha^{8/3}+2^{2/3}C_F\rho_\beta^{8/3}-\rho t_w\right.\right.$$

$$\left.\left.+\frac{1}{9}\left(\rho\alpha t_w^{\alpha}+\rho\beta t_w^{\beta}\right)+\frac{1}{18}\left(\rho_\alpha\nabla^2\rho_\alpha+\rho_\beta\nabla^2\rho_\beta\right)\right]\exp\left(-c\rho^{-1/3}\right)\right\} \tag{63}$$

$$\gamma(r)=2\left(1-\frac{\rho_\alpha^2(r)+\rho_\beta^2(r)}{\rho^2(r)}\right) \tag{64}$$

$$t_w(r)=\frac{1}{8}\frac{\left|\nabla\rho(r)\right|^2}{\rho(r)}-\frac{1}{8}\nabla^2\rho \tag{65}$$

$$C_F=\frac{3}{10}(3\pi^2)^{2/3} \tag{66}$$

a = 0.04918, b = 0.132, c = 0.2533, d = 0.349

$$v_{c\sigma}^{LYP}=-a\left(F_2'\rho+F_2\right)-2^{5/3}abC_F\left[G_2'\left(\rho_\alpha^{8/3}+\rho_\beta^{8/3}\right)+\frac{8}{3}G_2\rho_\alpha^{5/3}\right]$$

$$\frac{-ab}{4}\left[\rho\nabla^2G_2+4\nabla G_2\cdot\nabla\rho+G_2'\left(\rho\nabla^2\rho-\left|\nabla\rho\right|^2\right)\right]$$

$$\frac{-ab}{36}\left[3\rho_\alpha\nabla^2G_2+4\nabla\rho_\alpha\cdot\nabla G_2+4G_2\nabla^2\rho_\alpha+3G_2'\left(\rho_\alpha\nabla^2\rho_\alpha+\rho_\beta\nabla^2\rho_\beta\right)\right]$$

$$\left.+G_2'\left(\left|\nabla\rho_\alpha\right|^2+\left|\nabla\rho_\beta\right|^2\right)\right] \tag{67}$$

$$F_2=\frac{\gamma(r)}{1+d\rho^{-1/3}} \tag{68}$$

$$G_2 = F_2(\rho)\rho^{-5/3}\exp(-c\rho^{-1/3}) \quad (69)$$

$$F_2^{'} = \frac{dF_2}{\partial\rho_\sigma} \quad (70)$$

$$G_2^{'} = \frac{dG_2}{\partial\rho_\sigma} \quad (71)$$

### Basis Functions

The basis functions in the LCAO-MO method are atomic orbitals. Indeed, the basis orbitals used in practical calculations mostly are atom-centered functions that resemble orbitals as they can be found for isolated atoms. The radial part of such orbitals is an exponentially decaying function. Basis orbitals of this type are called Slater-type orbitals (STO). The general expression for a basis function is given as:

Basis Function = N * $e^{(\text{-alpha * r})}$

Where N = normalization constant, alpha = orbital exponent, and r = radius (Å)

This expression given as a Slater Type Orbital (STO) equation is:

$$STO = \frac{\zeta^3}{\pi^{0.5}} e^{(-\zeta r)} \quad (72)$$

Now it is important to remember that STO is a very tedious calculation. S.F. Boys came up with an alternative when he developed the Gaussian Type Orbital (GTO) equation:

$$GTO = \frac{2x}{\pi^{0.75}} e^{(-\chi r^2)} \quad (73)$$

Notice that the difference between the STO and GTO is in the "r." The GTO squares the "r" so that the product of the gaussian "primitives" (original gaussian equations) is another gaussian. By doing this, we have an equation we can work with and so the equation is much easier. However, the price we pay is loss of accuracy. To compensate for this loss, we find that the more gaussian equations we combine, the more accurate our equation.

For practical calculations they have the disadvantage that evaluation of integrals involving such functions is time-consuming. Therefore these orbitals are approximated by a linear combination of gaussian basis functions (GTO) (The Shodor Education Foundation, Inc., 2000):

$$\varphi^{STO} = \sum_{\nu=1}^{n} k_n \varphi_\nu^{GTO} \tag{74}$$

$$\varphi(r) = e^{-\alpha r^2} \tag{75}$$

### Basis Sets

*Ab initio* electronic structure computations are almost always carried out numerically using a *basis set* of orbitals. It is important to choose a basis set large enough to give a good description of the molecular wave function. Typically, the basis functions are centered on the atoms, and so sometimes they are called "atomic orbitals". However, it is important to note that this does *not* imply that they are actually solutions to the electronic Schrödinger equation for the atom. In modern practice, these atom-centered basis functions are usually chosen to be Gaussian-type orbitals (GTO's), which have the form

$$\Psi_{GTO}(x, y, z) = x^l y^m z^n e^{-\zeta r^2} \tag{76}$$

where $x$, $y$, $z$ are the local (atom-centered) Cartesian coordinates, $l$, $m$, $n$ are positive integers which more or less describe the angular momentum of the orbital, and $r$ is the radial distance to the atomic center. Spherical orbitals are usually given by $l = m = n = 0$, a $p_x$ orbital is given by $l = 1$, $m = n = 0$, a $d_{xy}$ orbital is given by $l = m = 1$, $n = 0$, etc. Unlike hydrogen atom orbitals, GTO's do not have radial nodes; however, radial nodes can be obtained by *combining* different GTO's. Quite frequently, an atomic basis function is actually a fixed linear combination of GTO's; this is called a *contracted Gaussian basis function*.

The smallest possible basis set is called the *minimal basis set*, and it contains one orbital (which may be contracted) for every orbital we usually think of for an atom (including unoccupied orbitals). For example, hydrogen has just one orbital, but carbon has 5 (1s, 2s, $2p_x$, $2p_y$, and $2p_z$) even though one of the p orbitals for carbon atom will be unoccupied. The STO-3G basis is a very well-known minimal basis set which contracts 3

Gaussian functions to approximate the more accurate (but more difficult to compute) Slater type orbitals. Although a contracted GTO might give a good approximation to an atomic orbital, it lacks any flexibility to expand or shrink in the presence of other atoms in a molecule. Hence, a minimal basis set such as STO-3G is not capable of giving highly accurate results.

The solution is to add extra basis functions *beyond* the minimum number required to describe each atom. Then, the Hartree-Fock procedure (below) can weight each atomic orbital basis function more or less to get a better description of the wave function. If we have *twice* as many basis functions as in a minimum basis, this is called a "double zeta" basis set (the zeta, $\zeta$, comes from the exponent in the GTO). Hence, a double-zeta basis set for hydrogen would have two functions, and a true double-zeta basis set for carbon would have 10 functions. However, sometimes people "cheat" and use only a single orbital for the core (1s), giving 9 functions for carbon. Such basis sets are said to be "double-zeta *in the valence*" space; they are also called "split-valence" basis sets. Double-zeta basis sets are often denoted DZ. Often additional flexibility is built in by adding higher-angular momentum basis functions. Since the highest angular momentum orbital for carbon is a p orbital, the "polarization" of the atom can be described by adding a set of d functions. A hydrogen atom would use a set of 3 p functions as polarization functions. A double-zeta plus polarization basis set might be designated DZP. The most famous example of a split-valence double-zeta plus polarization basis set is Pople's so-called 6-31G* basis. This obscure notation means that the core orbital is described by a contraction of 6 Gaussian orbitals, while the valence is described by two orbitals, one made of a contraction of 3 Gaussians, and one a single Gaussian function. Just to confuse you, the star (*) indicates polarization functions on non-hydrogen atoms. If polarization was added to hydrogen atoms also, this basis would be called 6-31G**. The confusing nature of this nomenclature has caused some chemists to start switching to slightly improved notation such as 6-31G(d,p), where the polarization functions are listed explicitly (Sherrill, 2001).

A few examples of common split-valence basis sets are 3-21G, 4-31G, and 6-31G such as this term X-YZG,
where
x is the number of gaussian functions summed to describe the inner shell orbital.
Y is the number of gaussian functions that comprise the first STO of the double zeta.

Z is the number of gaussian functions summed in the second STO (The Shodor Education Foundation, Inc., 2000).

### Semi-Empirical Calculations

Due to their greatly increased requirement for central processing unit time and storage space in the computer memory, *ab initio* quantum chemical methods are limited in their practical applicability. The approximate quantum chemical methods require significantly less computational resources. Semi-empirical methods are based on the Roothaan-Hall.

In ab initio calculations all elements of the Fock matrix are calculated, irrespective of whether the basis functions $\phi_\mu$, $\phi_\nu$, $\phi_\sigma$ and $\phi_\lambda$ are on the same atom, on atoms that are bounded or on atoms that are not formally boned. The semi-empirical methods consider the Fock matrix element in three groups: $F_{\mu\mu}$ (the diagonal elements); $F_{\mu\nu}$ (where $\phi_\mu$ and $\phi_\nu$ are on the same atom, and $\phi_\sigma$ and $\phi_\lambda$ are on different atoms).

The greatest proportion of the time required to perform ab initio Hartree-Fock SCF calculation is invariably calculating and manipulating integrals. The most obvious way to reduce the computational effort is to neglect or approximate some of these integrals. Semi-empirical methods achieve this part by explicit considering into the nuclear core. The overlap matrix, S, is set equal to identity matrix, I. So, the main implication is that the Roothaan-Hall equations are simplified: FC = SCF becomes
FC = CE.

The NDDO (neglect of diatomic differential overlap), this theory neglects differential overlap between atomic orbital on different atoms.

The elimination of three- and four-centre integrals greatly reduces the time and storage requirements for an NDDO calculation (which now increase as the square of the number of atoms) relative to that for a full Hartree-Fock treatment.

All semi-empirical methods make use of the "zero-differential overlap approximation" to some extent. This approximation simply says that the overlap between many atomic orbtals will be small and thus the electron repulsion integrals will have negligible values. If the differential overlap is assumed to be zero then the evaluation of the electron repulsion integrals are generally simplified (Cross, 1999): (μν|λσ) = 0 unless μ = ν and λ = σ

Three levels of NDDO theory are included in SPARTAN'S SEMI EMPIRICAL module:

MNDO Modified Neglect of Diatomic Overlap

AM1 Austin Model 1

PM 3 MNDO Parameterization Method 3

In all of these formalisms, only the valence electrons are considered. The one-electron terms are given by,

$$H_{\mu\nu}^{core} = U_{\mu\nu} - Z_A \sum_{B \neq A} Z_B \langle \mu\nu / \delta\delta \rangle \tag{77}$$

Here, μ and ν are located on atom A and B, respectively. The summation is over all other atoms. $U_{\nu\nu}$ is related to the binding energy of an electron in atomic orbital ν, and is determined from spectroscopic data. $U_{\mu\nu}$ is set to be zero for $\nu \neq \mu$. The second term in Equation represents to the attraction of an electron on atom A from the nuclear framework. The two center integral involved only the s function on atom B.ZA is the charge of atom A without its valence electrons.

All one-centre, two-electron integrals $(\upsilon\upsilon / \mu\mu)$ and $(\upsilon\mu / \upsilon\mu)$ are fitted to spectroscopic data. The two-centre, two electron repulsion integrals $(\upsilon\mu / \lambda\sigma)$ are approximated by classical multipole-multipole charge interactions between atoms A and B. The multipole charge separations within an atom are treated as adjustable parameters, i.e. optimized to fit the experimentally derived one-centre integrals.

The $\beta_{\mu\lambda}$ terms appearing in the Fock matrix are the one-electron, two-center core resonance integrals and are approximated as,

$$\beta_{\rho\lambda} = \frac{\beta_\rho + \beta_\lambda}{2} S_{\rho\lambda} \tag{78}$$

Where S is the overlap integral between Slater orbitals and $\rho$, $\lambda$ are adjustable parameters optimized using experimental thermo chemical data for simple molecules. Because all of the adjustable parameters are rooted in experimental data, these methods are known as semi-empirical. As in ab initio Hartree-Fock calculations, an SCF procedure is converged on a density matrix and the electronic energy as well.

The three methods differ only in the core-repulsion terms (they also differ in the detailed parameterization). Core repulsion includes nuclear repulsion and non-valence electron-electron repulsion, which are not explicitly considered in the calculation of the electronic energy. For example in the MNDO model, the core repulsion energy is given by,

$$E^{CR} = \sum_{A \neq B} \sum_{B \neq A} Z_A Z_B \left\langle \delta(A) / \delta(B) \right\rangle \left( e^{-\sigma_a E_{AB}} + e^{-\sigma_B E_{AB}} \right) \tag{79}$$

where δ is the intermolecular distance and $\sigma_A$, $\sigma_B$ are adjustable parameters fit to give the correct empirical behavior. Details are provided in the original papers. MNDO tends to overestimate core repulsion between two atoms at van der Waals distances. For this reason, the AM1 model was developed.

The AM1 and PM3 are based on MNDO (the name derives from the fact that PM3 is the third parameterization of MNDO, AM1 being considered as the second). In AM1, a sum of Gaussians is employed to better represent the core-core repulsion behavior at Van der Waals distances just outside bonding distances. PM3 uses a similar core repulsion function, but differs in the parameterization procedure (Sonthisawate, 2006).