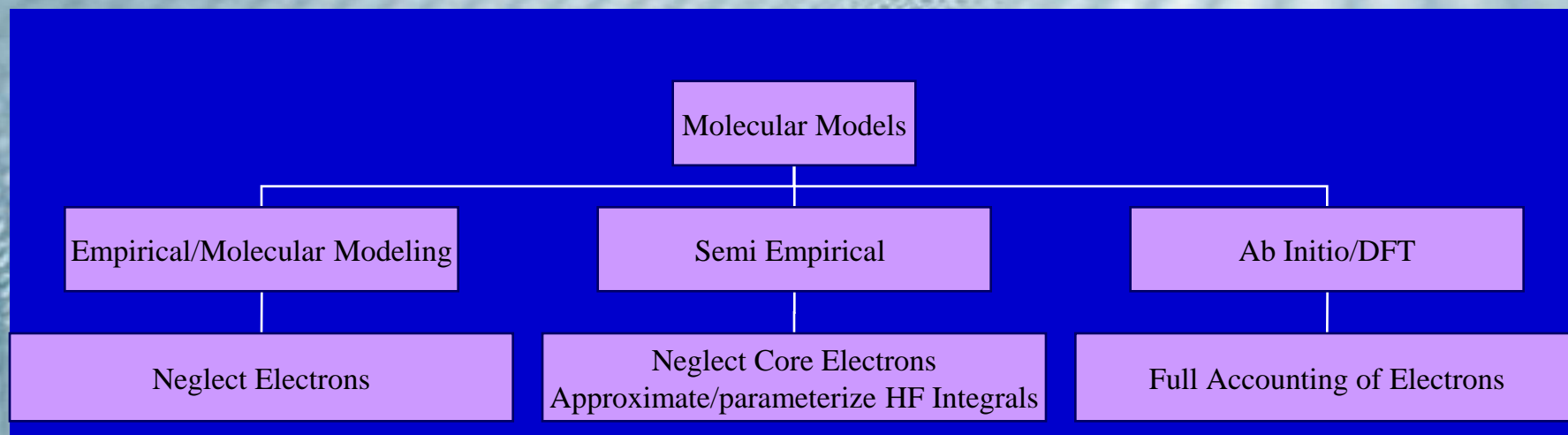# Molecular Modeling: Semi-Empirical Methods

C372

Introduction to Cheminformatics II

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Recall

Huckel Theory

- **Assumptions**
  - Atomic basis set - parallel 2p orbitals
  - No overlap between orbitals, $(S_{ij} = \delta_{ij})$
  - 2p Orbital energy equal to ionization potential of methyl radical (singly occupied 2p orbital)
  - The π stabilization energy is the difference between the 2p-parallel configuration and the 2p perpendicular configuration

  $$\Delta E \equiv stabilization = 2E_p - E_\pi = 2\alpha - E_\pi$$

  - Non-nearest interactions are zero $\quad \beta = \dfrac{\Delta E}{2} = H_{ij}$

Ex. Benzene (C3H6)

- One p-orbital per carbon atom -$\rightarrow$ asis size = 6

- Huckel determinant is

$$\begin{vmatrix} \alpha - E & \beta & 0 & 0 & 0 & \beta \\ \beta & \alpha - E & \beta & 0 & 0 & 0 \\ 0 & \beta & \alpha - E & \beta & 0 & 0 \\ 0 & 0 & \beta & \alpha - E & 0 & 0 \\ 0 & 0 & 0 & \beta & \alpha - E & \beta \\ \beta & 0 & 0 & 0 & \beta & \alpha - E \end{vmatrix} = 0, \beta < 0$$

Ex. Allyl (C3H5)

- One p-orbital per carbon atom -$\rightarrow$ basis size = 3
- Huckel matrix is

$$\begin{vmatrix} \alpha - E & \beta & 0 \\ \beta & \alpha - E & \beta \\ 0 & \beta & \alpha - E \end{vmatrix} = 0, \beta < 0$$

$$E = \alpha + \sqrt{2}\beta, \alpha, \alpha - \sqrt{2}\beta$$

- Resonance stabilization same for allyl cation, radical and anion (NOT found experimentally)

Huckel Theory

- Molecular Orbitals?
  - # MO = #AO
    - 3 methylene radical orbitals as AO basis set
- Procedure to find coefficients in LCAO expansion
  - Substitute energy into matrix equation
  - Matrix multiply
  - Solve resulting N-equations in N-unknowns

Huckel Theory

- Substitute energy into matrix equation:

$$\begin{pmatrix} \alpha - E_1 & \beta & 0 \\ \beta & \alpha - E_1 & \beta \\ 0 & \beta & \alpha - E_1 \end{pmatrix}\begin{pmatrix} a1 \\ a2 \\ a3 \end{pmatrix} = 0$$

$$E_1 = \alpha + \sqrt{2}\beta$$

$$\begin{pmatrix} \alpha - (\alpha + \sqrt{2}\beta) & \beta & 0 \\ \beta & \alpha - (\alpha + \sqrt{2}\beta) & \beta \\ 0 & \beta & \alpha - (\alpha + \sqrt{2}\beta) \end{pmatrix}\begin{pmatrix} a1 \\ a2 \\ a3 \end{pmatrix} = 0$$

Huckel Theory

- Matrix multiply :

$$\begin{pmatrix} \alpha - (\alpha + \sqrt{2}\beta) & \beta & 0 \\ \beta & \alpha - (\alpha + \sqrt{2}\beta) & \beta \\ 0 & \beta & \alpha - (\alpha + \sqrt{2}\beta) \end{pmatrix} \begin{pmatrix} a1 \\ a2 \\ a3 \end{pmatrix} = 0$$

Doing the math!

$$(\alpha - (\alpha + \sqrt{2}\beta)) * a1 \ + \ \beta * a2 \ + 0 * a3 \ = \ 0$$

$$\beta * a1 \ + \ (\alpha - (\alpha + \sqrt{2}\beta)) * a2 \ + \ \beta * a3 = 0$$

$$0 * a1 \ + \ \beta * a2 \ + (\alpha - (\alpha + \sqrt{2}\beta)) * a3 = 0$$

$$3 - equations, 3 - unknowns - NOT$$

Huckel Theory

- Matrix multiply :

$$\sqrt{2}\beta * a1 \ + \ \beta * a2 \ = \ 0 \rightarrow a2 = -\sqrt{2}a1 \quad (1)$$

$$\beta * a1 \ + \ \sqrt{2}\beta * a2 \ + \ \beta * a3 = 0 \qquad\qquad (2)$$

$$\beta * a2 \ + \sqrt{2}\beta * a3 = 0 \rightarrow a2 = -\sqrt{2}a3 \qquad (3)$$

- (1) and (3) reduce problem to 2 equations, 3 unknowns

$$(1) - (3) \rightarrow a1 = -a3$$

$$a2 = -\sqrt{2}a1$$

- Need additional constraint!

Huckel Theory

- Normalization of MO:

$$\int \Psi^* \Psi dr = 1$$

$$\int \left(a1 * \phi_1^* + a2 * \phi_2^* + a3 * \phi_3^* \right) * \left(a1 * \phi_1 + a2 * \phi_2 + a3 * \phi_3 \right) dr = 1$$

$$\text{If } \int \phi_i^* * \phi_j = \delta_{ij}$$

$$(a1)^2 + (a2)^2 + (a3)^2 = 1$$

- Gives third equation, NOW have 3 equations, 3 unknowns.

$$\left. \begin{array}{l} a1 = a3 \\ a2 = \sqrt{2}a1 \\ (a1)^2 + (a2)^2 + (a3)^2 = 1 \end{array} \right\} (a1)^2 + 2(a1)^2 + (a1)^2 = 1$$

$$a1 = \pm\frac{1}{2} = \frac{1}{2} \qquad \therefore \quad a3 = \frac{1}{2}, a2 = \frac{\sqrt{2}}{2}$$

Huckel Theory

- Have 3 equations, 3 unknowns.

$$(a1)^2 + (a2)^2 + (a3)^3 = 1$$

$$\left. \begin{array}{l} a1 = a3 \\ a2 = \sqrt{2}a1 \\ (a1)^2 + (a2)^2 + (a3)^2 = 1 \end{array} \right\} (a1)^2 + 2(a1)^2 + (a1)^2 = 1$$

$$a1 = \pm\frac{1}{2} = \frac{1}{2} \qquad \therefore \quad a3 = \frac{1}{2}, a2 = \frac{\sqrt{2}}{2}$$
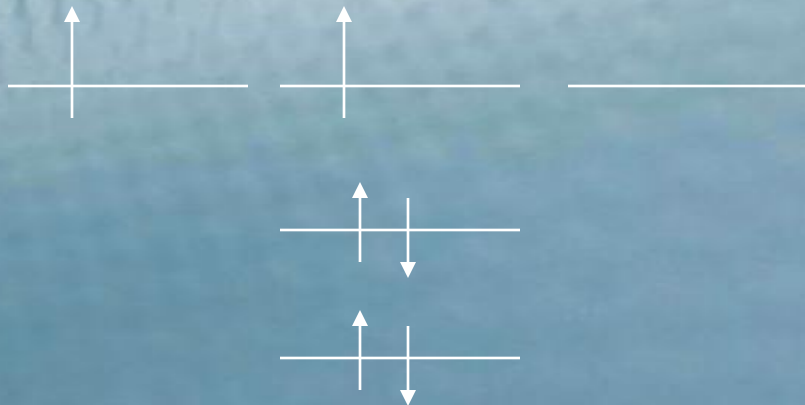
Huckel Theory

$$\Psi_1 = \frac{1}{2} * \phi_1 + \frac{\sqrt{2}}{2} * \phi_2 + \frac{1}{2}\phi_3$$

2p orbitals

Aufbau Principal

- Fill lowest energy orbitals first
  - Follow Pauli-exclusion principle

Carbon

Aufbau Principal

- Fill lowest energy orbitals first
  - Follow Pauli-exclusion principle

$$\alpha - \sqrt{2}\beta$$

$$\alpha \qquad \text{Allyl}$$

$$\alpha + \sqrt{2}\beta$$
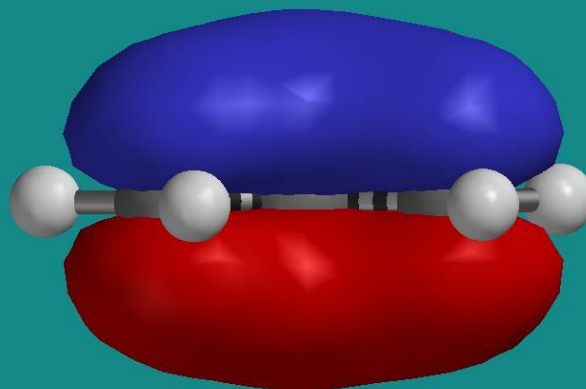
Huckel Theory

- **For lowest energy Huckel MO**

$$a1 = \frac{1}{2}, a2 = \frac{\sqrt{2}}{2}, a3 = \frac{1}{2}$$
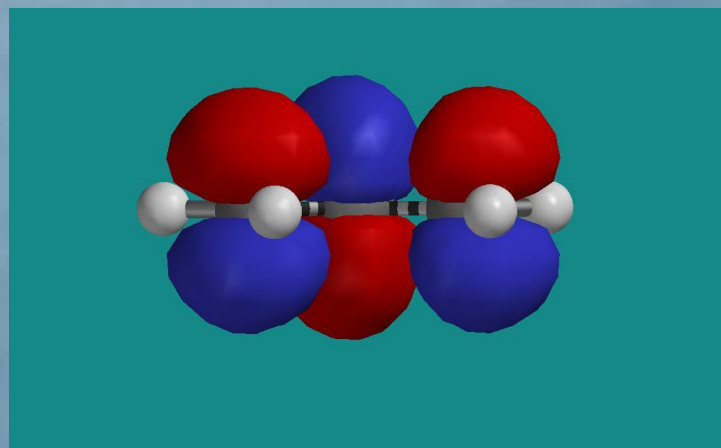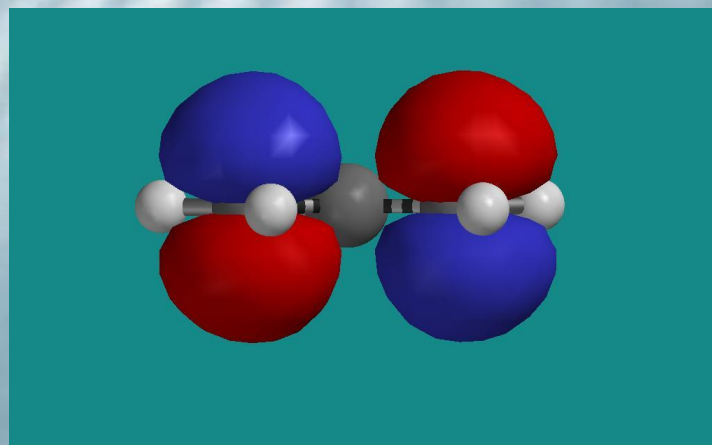
- **Bonding orbital**

Huckel Theory

- **Next two MO**
  - Non-Bonding orbital

$$a1 = \frac{\sqrt{2}}{2}, a2 = 0, a3 = -\frac{\sqrt{2}}{2}$$

  - Anti-bonding orbital

$$a1 = \frac{1}{2}, a2 = -\frac{\sqrt{2}}{2}, a3 = \frac{1}{2}$$

Huckel Theory

- **Electron Density**

$$q_r = \sum_j n_j * a_{jr}^2 \longrightarrow \quad j=1$$

  - The rth atom's electron density equal to product of # electrons in filled orbitals and square of coefficients of ao on that atom

  - Ex. Allyl

    - Electron density on c1 corresponding to the occupied MO is

$$q_1 = 2 * \left(\frac{1}{2}\right)^2$$

$$q_1 = 2 * \left(\frac{1}{2}\right)^2 = .5, \quad q_{c2} = 1 \quad q_{c3} = .5$$

$$Total = 2$$

Central carbon is neutra with partial positive charges on end carbons

Huckel Theory

- Bond Order

$$p_{rs} = \sum_j n_j * a_{jr} * a_{js}$$

Ex. Allyl
    Bond order between c1-
    c2 corresponding to
    the occupied MO is

$$n_1 = 2$$

$$a_{11} \equiv \text{coefficient of AO for HOMO on c1} = \frac{\sqrt{2}}{2}$$

$$a_{12} \equiv \text{coefficient of AO for HOMO on c2} = \frac{1}{2}$$

$$p_{12} = 2 * \frac{\sqrt{2}}{2} * \frac{1}{2} = .707$$

Corresponds to partial pi bond
due to delocalization over three
carbons (Gilbert)

Beyond One-Electron Formalism

- **HF method**
  - Ignores electron correlation
  - Effective interaction potential

  - Hartree Product-
    $$H = \sum_i h_i \quad \text{separabili ty}$$
    $$\Psi = \prod_i^N \psi_i$$

$h_i = \text{hartree hamiltonia n}$

$$= -\frac{1}{2}\nabla_i^2 - \sum_{k=1}^{M} \frac{Z_k}{r_{ik}} + V_i\{j\}$$

$$V_i\{j\} = \sum_{j \neq i} \int \frac{\rho_j}{r_{ij}} dr = \sum_{j \neq i} \int \frac{|\psi_j|^2}{r_{ij}} dr$$

Fock introduced exchange – (relativistic quantum mechanics)

HF-Exchange

- **For a two electron system**

$$\Psi = \psi_a(1)\alpha(1) * \psi_b(2)\alpha(2)$$

$$\hat{P} \equiv Permutivity\ operator$$

$$\hat{P}\psi_a(1)\alpha(1) * \psi_b(2)\alpha(2) = \psi_a(2)\alpha(2) * \psi_b(1)\alpha(1) \quad \text{NO CHANGE IN SIGN}$$

- **Fock modified wavefunction**

$$\Psi = \psi_a(1)\alpha(1) * \psi_b(2)\alpha(2) - \psi_a(2)\alpha(2) * \psi_b(1)\alpha(1)$$

$$\hat{P}\Psi = \psi_a(2)\alpha(2) * \psi_b(1)\alpha(1) - \psi_a(1)\alpha(1) * \psi_b(2)\alpha(2)$$

$$= -\Psi$$

Slater Determinants

- Ex. Hydrogen molecule

$$\Psi = \psi_a(1)\alpha(1) * \psi_b(2)\beta(2)$$

$$\Psi = \psi_a(1)\alpha(1) * \psi_b(2)\beta(2) - \psi_a(2)\alpha(2) * \psi_b(1)\beta(1)$$

$$\hat{P}\Psi = \psi_a(2)\alpha(2) * \psi_b(1)\beta(1) - \psi_a(1)\alpha(1) * \psi_b(2)\beta(2)$$

$$= -\Psi$$

$$\Psi = \left.\begin{vmatrix} \psi_a(1)\alpha(1) & \psi_b(1)\beta(1) \\ \psi_a(2)\alpha(2) & \psi_b(2)\beta(2) \end{vmatrix}\right\} Slater \text{ Determinant}$$

Neglect of Differential Overlap (NDO)

- CNDO (1965, Pople et al)

- MINDO (1975, Dewar)

- MNDO (1977, Thiel)

- INDO (1967, Pople et al)

- ZINDO

- SINDO1

- STO-basis (/S-spectra,/2 d-orbitals)

- /1/2/3, organics

- /d, organics, transition metals

- Organics

- Electronic spectra, transition metals

- 1-3 row binding energies, photochemistry and transition metals

Semi-Empirical Methods

- SAM1
  - Closer to # of *ab initio* basis functions (e.g. d orbitals)
  - Increased CPU time
- G1,G2 and G3
  - Extrapolated *ab initio* results for organics
  - "slightly empirical theory"(Gilbert-more ab initio than semi-empirical in nature)

Semi-Empirical Methods

- AM1
  - Modified nuclear repulsion terms model to account for H-bonding (1985, Dewar et al)
  - Widely used today (transition metals, inorganics)
- PM3 (1989, Stewart)
  - Larger data set for parameterization compared to AM1
  - Widely used today (transition metals, inorganics)

What is Differential Overlap?

- When solving HF equations we integrate/average the potential energy over all other electrons

$$h_i = \text{hartree hamiltonia n}$$

$$= -\frac{1}{2}\nabla_i^2 - \sum_{k=1}^{M}\frac{Z_k}{r_{ik}} + V_i\{j\}$$

$$V_i\{j\} = \sum_{j\neq i}\int\frac{\rho_j}{r_{ij}}dr = \sum_{j\neq i}\int\frac{|\psi_j|^2}{r_{ij}}dr$$

- Computing HF-matrix introduces 1 and 2 electron integrals

Estimating Energy

$$\Psi(r) = \sum_m^F c_m * \Phi_m(r)$$

- **Want to find c's so that** $\dfrac{d < E >}{dc} = 0$

$$\sum_i c_m \left(\int \underbrace{\Phi_m^*(r)\hat{H}\Phi_j(r)dr}_{H_{mj}} - E \int \underbrace{\Phi_{mi}^*(r)\Phi_j(r)dr}_{S_{mj}} \right) = 0 \quad \forall \mathrm{m}$$

$$M \bullet c = 0 \ \} M_{ij} = \int \Phi_i^*(r)\hat{H}\Phi_j(r) - E \int \Phi_i^*(r)\Phi_j(r)$$

$$M_{ij} = H_{ij} - E\ S_{ij}$$

Non - trivial solutions for $\det(M) = 0$

Estimating Energy

$$\sum_i c_m (\int \Phi_m^*(r)\hat{H}\Phi_j(r)dr - E \int \Phi_{mi}^*(r)\Phi_j(r)dr) = 0 \quad \forall m$$

$$\underbrace{\phantom{\int \Phi_m^*(r)\hat{H}\Phi_j(r)dr}}_{H_{mj}} \qquad \underbrace{\phantom{\int \Phi_{mi}^*(r)\Phi_j(r)dr}}_{S_{mj}}$$

$$1-electron \propto \sum_{k=1}^{M} \int \phi_\mu^* \frac{Z_k}{r_{ik}} \phi_\upsilon dr$$

$$2-\text{electron} \propto \int \phi_\mu^* V_i\{j\}\phi_\nu dr \propto \sum_{j \neq i} \int \int \phi_\mu^*(1)\phi_\nu^*(1)\frac{1}{r_{ij}}\phi_\lambda(2)\phi_\sigma(2)dr$$

Differential Overlap

Complete Neglect of Differential Overlap (CNDO)

- Basis set from valence STOs
- Neighbor AO overlap integrals, S, are assumed zero or $S_{\mu\nu} = \delta_{\mu\nu}$
- Two-electron terms constrain atomic/basis orbitals (But atoms may be different!)

$$(\mu\nu|\lambda\sigma) = \delta_{\mu\nu}\delta_{\lambda\sigma}(\mu\mu|\lambda\lambda)$$

  - Reduces from N^4 to N^2 number of 2-electron integrals
  - Integration replaced by algebra

- IP from experiment to represent 1, 2-electron orbitals

Complete Neglect of Differential Overlap (CNDO)

- **Overlap**

$$\left(\mu\nu|\lambda\sigma\right) = \delta_{\mu\nu}\delta_{\lambda\sigma}\left(\mu\mu|\lambda\lambda\right)$$

  - Methylene radical (CH_2*)
    - Interaction same in singlet (spin paired) and triplet state (spin parallel)

$Paired$:

$$\left(\mu\mu|\lambda\lambda\right) \equiv \text{Overlap of electrons paired in } sp^2$$

$$= \gamma$$

$Parallel$:

$$\left(\mu\mu|\lambda\lambda\right) \equiv \text{Overlap of electrons parallel, one in } sp^2$$

$$1 \text{ in p - orbital}$$

$$= \gamma$$

Intermediate Neglect of Differential Overlap (INDO)

- **Pople et al (1967)**
  - Use different values for interaction of different orbitals on same atom s.t.
    - Methylene

$Paired:$

$$(\mu\mu|\lambda\lambda) \equiv \text{Overlap of electrons paired in } sp^2$$

$$= \gamma_{sp^2, sp^2}$$

$Parallel:$

$$(\mu\mu|\lambda\lambda) \equiv \text{Overlap of electrons parallel, one in } sp^2$$

$$1 \text{ in p - orbital}$$

$$= \gamma_{sp^2, p} \neq \gamma_{sp^2, sp^2}$$

Neglect of Diatomic Differential Overlap (NDDO)

- Most modern methods (MNDO, AM1, PM3)
- All two-center, two-electron integrals allowed iff:

$$\mu \text{ and } \nu \text{ are on same atomic center}$$

$$\lambda \text{ and } \sigma \text{ are on same atomic center}$$

$$\mu \neq \nu \text{ and } \lambda \neq \sigma$$

- Recall, CINDO- $\mu = \nu \text{ and } \lambda = \sigma$
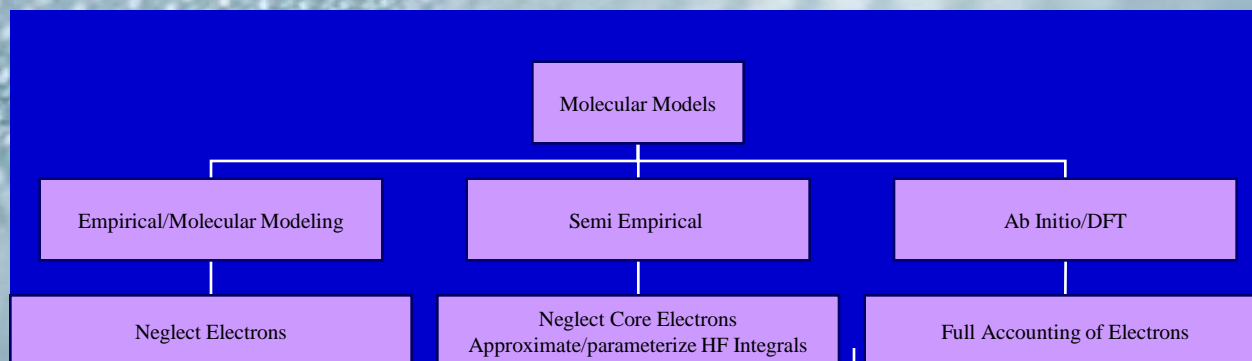- Allow for different values of γ depending on orbitals involved (INDO-like)

Neglect of Diatomic Differential Overlap (NDDO)

- MNDO – Modified NDDO
- AM1 – modified MNDO
- PM3 – larger parameter space used than in AM1

Performance of Popular Methods (c. Cramer)

- Sterics - MNDO overestimates steric crowding, AM1 and PM3 better suited but predict planar structures for puckered 4-, 5- atom rings

- Transition States- MNDO overestimates (see above)

- Hydrogen Bonding - Both PM3 and AM1 better suited

- Aromatics - too high in energy (~4kcal/mol)

- Radicals - overly stable

- Charged species - AO's not diffuse (only valence type)