I. Electron Densities

- Visualization of the electron density gives a better indication of molecular size
  Example: Methane

  - Electron probability density of 0.01e/Å³ similar to conventional (CPK) space filling models

II. Electrostatic Potentials

III. Reactivity Predictions
**Electron Density Function**

- Also called the *electron probability distribution function*: $\rho(r)$
- A 3-D function defined such that $\rho(r)\,dr$ is the probability of finding an electron in a small volume element $(dr)$ at some point in space $(r)$

$$\int \rho(r)\,dr = N$$
- Integration of the function over all space must equal the number of electrons $(N)$:

**Calculation of Electron Density**

- The square of the wavefunction at point $(r)$ is interpreted as a probability
  - For a molecule with $n$ electrons and $n/2$ occupied orbitals, the electron density at point $(r)$ is given by:

$$\rho(r) = 2 \sum_{i=1}^{n/2} |\psi_i(r)|^2$$

  - Recall that M.O.’s ($\Psi_i$) are expressed as linear combinations of a set of basis functions

**Population Analysis**

- Mathematical method of partitioning a wave function or electron density into charges on each atom
  - Condenses nuclear charge and e⁻ density into an atomic partial charge
  - Can help understand reactivity, bond orders, etc.
  - Corresponds to chemist’s view of bond type (ionic, covalent, polar covalent)
  - Since atomic charge is not a quantum mechanical observable, arbitrary methods used to compute
### Mulliken Population Analysis

- Electrons shared between basis functions are **split evenly** between the two atoms involved
  - Relative electronegativity is ignored
- Method is entrenched in software packages due to its ease of implementation
- For small basis sets:
  - Provides an approximate representation of the 3D charge distribution in a molecule
- For larger basis sets:
  - Can produce unreasonable results
    - (e.g. Orbitals with > 2 electrons)

### Löwdin Population Analysis

- Löwdin Method
  - Atomic orbitals are first transformed into an orthogonal set of basis functions
  - MO coefficients are then transformed to give a representation of $\Psi$ using the new basis set
  - Requires more computation
  - No longer have orbitals with > 2 electrons
- Still have basis set dependent results

### Results of Population Analyses

1. Total number of e$^-$’s ($q_A$) “associated” with each atom can be found. Thus, the **total atomic charge** on that atom is calculated via: $A = Z_A - q_A$ (where $Z_A$ is atomic number).

2. The **total overlap population** between two atoms can be determined.
   - Large (+) values reflect strong bonding
   - Large (-) values reflect antibonding
### Caveats

1. Total atomic charges and total overlap populations are strongly dependent on the basis set used.

2. The equal partitioning of electrons between basis sets on different atoms (Mulliken method) is arbitrary, and (often) goes against chemical intuition.

→ More complex methods are available
   - NBO, NPA, AIM, etc.

### II. Electrostatic Potential

- The electrostatic potential surface represents the distance from the molecule at which a (+) test charge experiences a set attraction or repulsion (Not all programs calculate this)
  - Default value (CAChE) = ± 0.03 a.u. (=18 kcal/mol; ± 75 kJ/mol)

- The test charge interacts with both the nuclei and the fixed electron cloud (with zero polarizability)

### Uses of Electrostatic Potential

- What charge distribution does a reactant “see” as it approaches a molecule
- Can rationalize intermolecular interactions (between polar species)
- Helps identify regions of local (-) and (+) potential in a molecule
- Can assist in predicting paths of (charged) reagent approach
  - Potential sites of protonation
  - e.g., electrophiles are attracted to regions of (-) potential
Calculation of Electrostatic Potential

• Usually calculated point-by-point on a set of grid points starting at the van der Waals surface and extending outwards from this surface some distance \( x \)
  
  \(~100\) grid point per atom typically used

  – The calculation sums the positive charges of nuclei and the amount of electronic charge density
  – Results are color coded for charge

Electrostatic Potential: Examples

• Acetaldehyde
  
  Red = (+)
  Blue = (-)

  Where is the oxygen?
  Where is the \(-\text{CH}_3\)?

• Phenylacetylene: Blue = (-); Red = (+)
Electron Density + Electrostatic Potential

- The electrostatic potential can be mapped onto the electron density surface (0.01e-/Å³) using color

Electron Density + Electrostatic Potential

- 1,1-difluoroethylene

III. Reactivity Predictions

- Various approaches can be used:
  1. Partial charges – Usually found via Mulliken population analysis, so the results can sometimes be misleading
     - Could be helpful in charge-controlled reactions
       - “Hard” electrophiles/nucleophiles
       - Protonations/Deprotonations, for example
  2. Electrostatic Potential – Will reveal possible trajectory for the approach of charged reagents
     - Partial charges more important (“Soft” electrophiles and nucleophiles)
Reactivity Predictions - continued

3. HOMO/LUMO: Largest lobes—These can sometimes change using different model chemistries, so try several methods
   • FMO (Frontier Molecular Orbital) approach is well-documented
   • Works best when the HOMO and LUMO are well separated in energy from the other orbitals

4. Reactivity Indices: Electrophilic, Nucleophilic, and Radical Susceptibilities
   – Similar to FMO, but additional orbitals near the HOMO and LUMO are also used for a more comprehensive indicator

Reactivity Prediction: Examples
Where is the site of protonation in formamide?
1. Partial charges (B88-LYP/DZVP)
   ![Formamide partial charges]

2. Electrostatic potential (B88-LYP/DVZP)
   At O atom
   ![Formamide electrostatic potential]
Reactivity Prediction: Examples

Where is the site of protonation in formamide?

3. Position of HOMO (B88-LYP/DZVP)

![](image1)

4. Electrophilic Susceptibility (B88-LYP/DZVP)

“Bullseye”

![](image2)

Frontier Orbital Theory

- HOMO/LUMO overlap between molecules is the governing factor
  - Predict stereochemistry with “soft” nucleophiles and electrophiles (charge less important)
  - Example:

![Image of chemical reaction]

- What is the structure of the product?
**Frontier Orbital Theory**

- Look at HOMO of the phenylbutadiene and the LUMO of the ethylene:
  - Largest lobe of the HOMO is on the terminal C
  - Largest lobe of the LUMO is on the terminal C
  - These two interact

**Frontier Orbital Theory**

- Sterically unfavorable product forms:
  - Phenylbutadiene + Phenylethylene → [4+2]

**Susceptibilities**

- Most useful for larger molecules where the HOMO and LUMO are not well separated in energy from the other orbitals – these other orbitals contribute to the reactivity
  - Can calculate electrophilic, nucleophilic, and radical susceptibilities, and map these onto the electron density surface
  - WebMO: Electrophilic (HOMO), Nucleophilic (LUMO), or Radical Frontier Density
  - Each of these is a function of a weighted sum of the squares of the molecular orbital coefficients
**Electrophilic Susceptibility**

- **Orbital Interactions:**
  - HOMO → Reactant → Reagent (Electrophile)

Mathematically:

\[
\text{EFonD}(x) = \sum_{j=1}^{N} \nu_j \phi_j(x)^2 e^{-\lambda(e_{\text{HOMO}} - e_j)}
\]

\[
\text{EFonD}(x) = \sum_{j=1}^{N} \nu_j (x)^2 e^{-\lambda(e_{\text{HOMO}} - e_j)}
\]

- \(N\) = # of orbitals
- \(\nu_j\) = # e⁻ in orbital
- \(e_j\) = orbital energy
- \(\lambda\) = scaling factor

**Nucleophilic Susceptibility**

- **Orbital Interactions:**
  - LUMO → Reactant → Reagent (Nucleophile)

Mathematically:

\[
\text{NFonD}(x) = \sum_{j=1}^{N} (2 - \nu_j) \phi_j(x)^2 e^{-\lambda(e_{\text{LUMO}} - e_j)}
\]

\[
\text{NFonD}(x) = \sum_{j=1}^{N} (2 - \nu_j) (x)^2 e^{-\lambda(e_{\text{LUMO}} - e_j)}
\]

- \(N\) = # of orbitals
- \(\nu_j\) = # e⁻ in orbital
- \(e_j\) = orbital energy
- \(\lambda\) = scaling factor

**Radical Susceptibility**

- **Orbital Interactions:**
  - LUMO → Reactant → Reagent (Radical)

Mathematically:

- An average of electrophilic and nucleophilic susceptibilities

\[
\text{RFonD}(x) = \left( \frac{1}{2} \right) \text{EFonD}(x) + \left( \frac{1}{2} \right) \text{NFonD}(x)
\]

- \(N\) = # of orbitals
- \(\nu_j\) = # e⁻ in orbital
- \(e_j\) = orbital energy
- \(\lambda\) = scaling factor
**Reactivity Indices: Which To Use?**

- Susceptibilities more widely applicable  
  - Should be used in most cases
- As always, try a variety of computational methods, and determine the common thread
- Use known compounds of similar structure whose *reactivity is known* to verify the results of calculations on unknown compounds
- Use your (or a colleagues) chemical intuition  
  - Be skeptical: Don’t believe the results of all calculations!