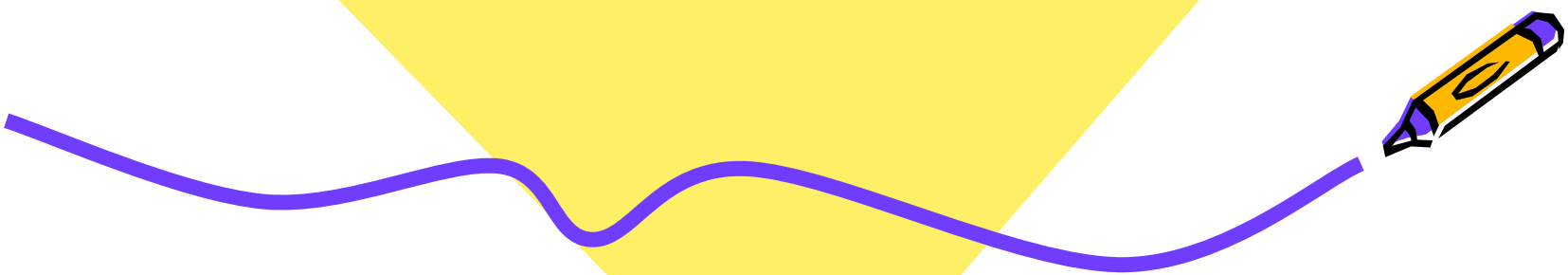
Molecular Mechanics

A Brief Introduction



The range of applicability

- Molecules containing thousands of atoms.
- Organics, oligonucleotides, peptides, and saccharides (metallo-organics and inorganics in some cases).
- Vacuum, implicit, or explicit solvent environments.
- Ground state molecular structure and energy only.
- Thermodynamic and kinetic (via molecular dynamics) properties.

Molecular Modeling

- Nuclei and electrons are lumped into atom-like particles.
- Atom-like particles are spherical (radii obtained from measurements or theory) and have a net charge (obtained from theory).
- Interactions are based on springs and classical potentials – "Newtonian" physics laws.
- Interactions must be preassigned to specific sets of atoms.
- Interactions determine the **spatial distribution** of atom-like particles and their **energies**.

Components of "Steric Energy"

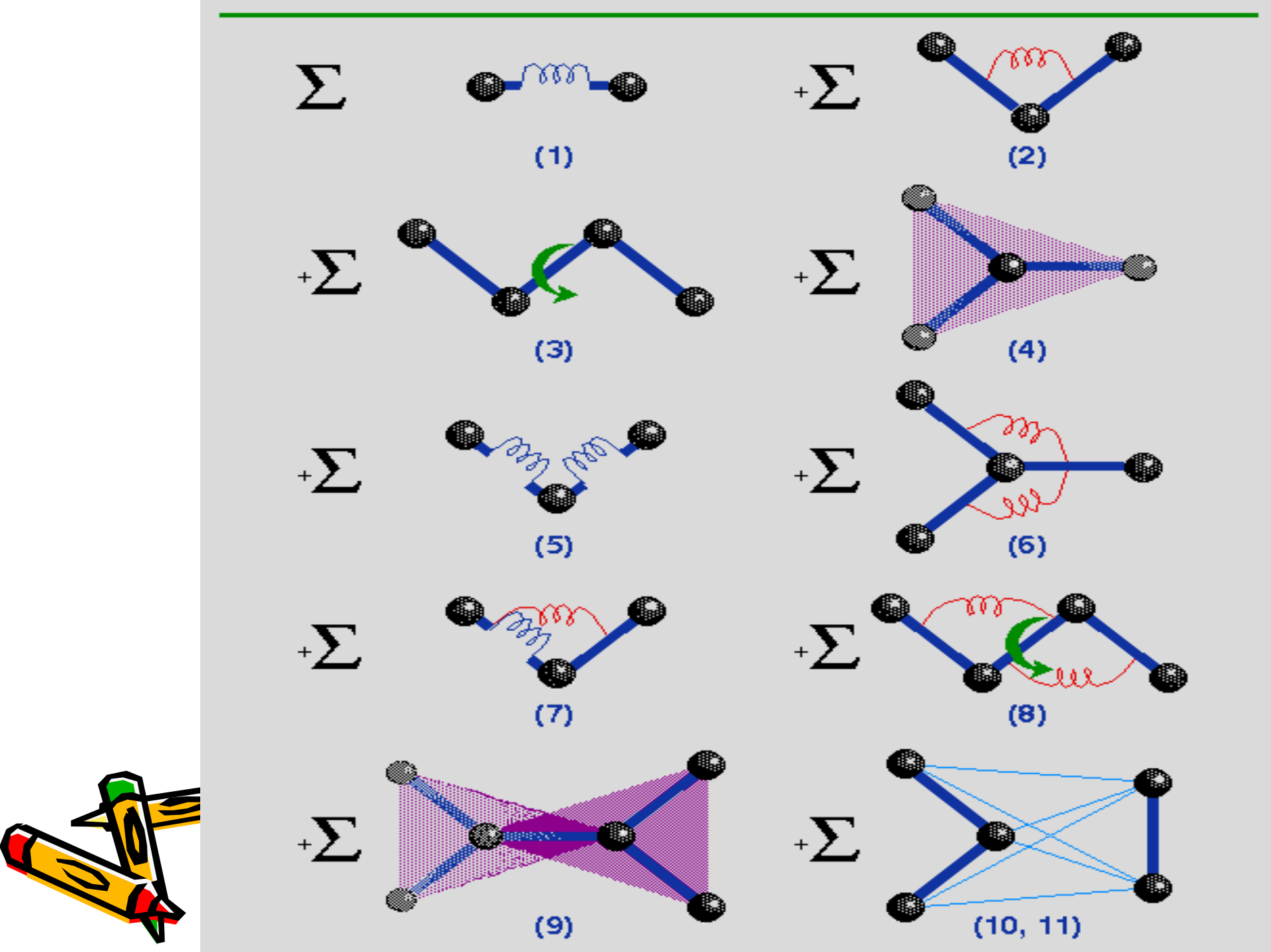
"Steric energy" based on energy increments due to deviation from some "ideal" geometry

$$E_{steric} = E_{stretch} + E_{bend} + E_{torsion}$$

$$+ E_{stretch\text{-}bend} + (E_{other\text{-}cross\text{-}term})$$

$$+ E_{H\text{-}bonding} + E_{vdW}$$

$$+ E_{electrostatic} + E_{dipole\text{-}dipole}$$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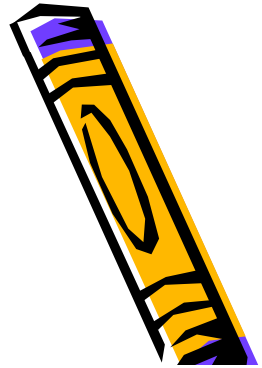
Description of the Classical (Newtonian) Forcefield:



$$E_{\text{pot}} = \sum_{b} D_b \left[1 - e^{-\alpha(b - b_0)}\right] + \sum_{\theta} H_\theta (\theta - \theta_0)^2 + \sum_{\phi} H_\phi [1 + s\cos(n\phi)]$$

(1) (2) (3)

$$+ \sum_{\chi} H_\chi \chi^2 + \sum_{b} \sum_{b'} F_{bb'} (b - b_0)(b' - b_0') + \sum_{\theta} \sum_{\theta'} F_{\theta\theta'} (\theta - \theta_0)(\theta' - \theta_0')$$

(4) (5) (6)

$$+ \sum_{b} \sum_{\theta} F_{b\theta} (b - b_0)(\theta - \theta_0) + \sum_{\phi} F_{\phi\theta\theta'} \cos\phi (\theta - \theta_0)(\theta' - \theta_0') + \sum_{\chi} \sum_{\chi'} F_{\chi\chi'} \chi\chi'$$

(7) (8) (9)

$$+ \sum \varepsilon \left[(r^*/r)^{12} - 2(r^*/r)^6\right] + \sum q_i q_j / \varepsilon r_{ij}$$

(10) (11)

Use of Cut-offs

- Van der Waals forces, hydrogen bonding, electrostatic forces, and dipole-dipole forces have dramatic distance dependencies; beyond a certain distance, the force is negligible, yet it still "costs" the computer to calculate it.
- To economize, "cut-offs" are often employed for these forces, typically somewhere between 10 and 15Å.

Forcefield Parameters

- A parameter should be adjusted so that the simulated system reproduces properties of the real system. It does NOT have to equal a microscopic descriptor.
- As yet, there is no universal forcefield. Parameters for particular forcefields can only be used to study particular molecules.
- Forcefield parameters must be cohesive--- modelers can't just "plug & play" new parameters without testing
- Forcefield parameters must be referenced

Types of Forcefields

- **Diagonal force field**: no cross terms (AMBER, CHARMM)
- **Matrix force field**: with cross terms (MM4, CFF)
- **Class II force field**: parameters derived from quantum mechanics (ESFF)
- **"Fast" force fields**: only torsion & non-bond terms (SCULPT, YETI)

Hyperchem Force Fields

- **MM2 / MM3** (Allinger) best; general purpose
- **MMX** (Gilbert) added TS's, other elements; good
- **MM+** (Ostlund) general; good
- **OPLS** (Jorgenson) proteins and nucleic acids
- **AMBER** (Kollman) proteins and nucleic acids +
- **BIO+** (Karplus) CHARMm; nucleic acids

Properties Calculated

- Optimized geometry (minimum energy conformation)
- Equilibrium bond lengths, bond angles, and dihedral (torsional) angles
- Dipole moment (vector sum of bond dipoles)
- Enthalpy of Formation.

Steps in Performing MM Calculations

- Construct graphical representation of molecule to be modeled ("front end")
- Select forcefield method and termination condition (gradient, # cycles, or time)
- Perform geometry optimization
- Examine output geometry... is it reasonable?
- Search for <u>global</u> minimum.

Energy Minimization

- Local minimum vs global minimum
- Many local minima; only ONE global minimum
- Methods: Newton-Raphson (block diagonal), steepest descent, conjugate gradient, others.