



Computational Biochemistry

Lecture 3 Molecular Mechanics



What is molecular mechanics and why ?

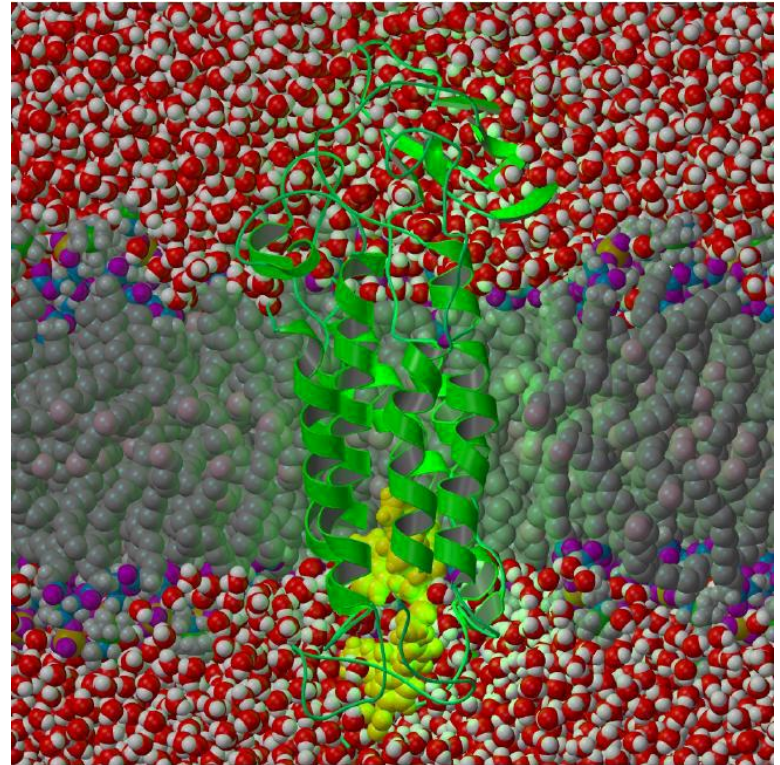
Basic Premise

If we want to study a protein, piece of DNA, biological membranes, polysaccharide, crystal lattice, nano materials, diffusion in liquids,... the number of electrons (i.e. the number of energy calculations) make *quantum mechanical calculations impossible even with present-day computers*.

Instead, we replace the nuclei and electrons, and their interactions, by new potential functions: "classical" atoms.

Based on simple physical concepts

Enables the systems under study to be VERY large (100,000 atoms).





Molecular Mechanics Force Fields

The molecular interactions, also known as the potentials, together form a **force field**,

A force field is a mathematical description of the classical forces or energies between particles (atoms).

Energy = *function of atomic positions* (x,y,z)

- The force field equation consists of **several functions** that describe molecular properties both **within and between** molecules
- The force field also contains **parameters** (numbers) in the potential functions that are tuned to **each type of molecule** (protein, nucleic acid, carbohydrates)
- There are many different force field equations and parameter sets
- A force field must be **simple enough** that it can be evaluated **quickly**, but **sufficiently** detailed that it reproduces the key features of the physical system being modeled.



Force field classification

In general, force fields can be classified as either:

- ***Specific*** (*many parameters, limited applicability, high accuracy*)
 - *Often developed in academic labs for study of specific molecular classes*
- ***Generic*** (*fewer parameters, more generalizations, wide applicability, poor accuracy*)
 - *Easiest to use in point-and click software*



Force field classification

Force Field Parameters can come from:

- *Experimental sources (mainly from x-ray diffraction, evaporation, etc)*
- *Theoretical calculations (mainly from QM)*

Many force fields employ similar mathematical equations but differ in the parameters used in the equations.

It is therefore extremely dangerous mix to parameters between force fields.



Different Force Fields

- **AMBER** (Assisted Model Building with Energy Refinement).
- **CHARMM** (Chemistry at HARvard using Molecular Mechanics).
- **GROMOS** (GROenigen Molecular Simulation)
- **OPLS** (Optimized Parameters for Large-scale Simulations)
- MMFF (the Merck Molecular Force Field)
- DREIDING Generic force field due to Mayo et al. (1990)
- UNIVERSAL (UFF)Generic force field due to Rappeet al. (1992)
- CVFF/PCFF Force fields for fluorinated hydrocarbons
- MM2, MM3, MM4 Developed by Allinger et al. for calculations on small molecules
- COMPASS Commercial force field marketed by Accelrys Inc.

Force Field Potential Functions

The potential functions may be divided into **bonded terms**, which give the energy contained in the internal degrees of freedom, and **non-bonded terms**, which describe interactions between molecules.

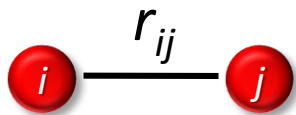
$$E_{pot} = \sum_{bonds} V_r + \sum_{angles} V_{\theta} + \sum_{torsions} V_{\tau} + \sum_{atoms} V_{vanderWaals} + \sum_{atoms} V_{electrostatics}$$

Potentials between bonded atoms

Potentials between non-bonded atoms

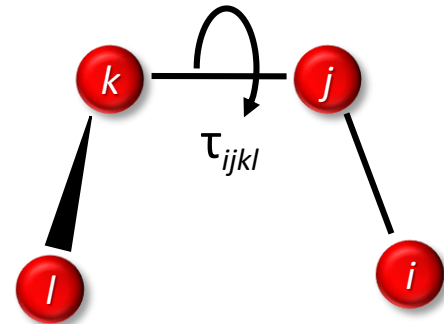
Total potential Energy, E_{pot} or V_{tot}

Force Field Potential Functions



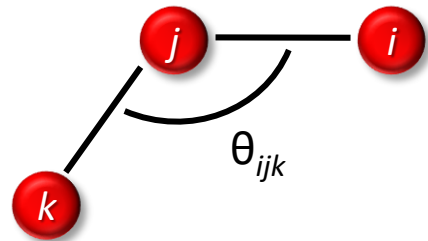
$$V_{bonds} = \frac{1}{2} k_r^{ij} (r_{ij} - r_{ij}^0)^2$$

(Robert Hooke - 1660)

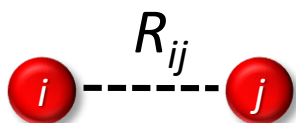


$$V_{torsions} = \frac{1}{2} \sum_n k_n^{ijkl} (1 - \cos(n\tau))$$

(Jean Baptiste Joseph Fourier – 1822)



$$V_{angles} = \frac{1}{2} k_\theta^{ijk} (\theta_{ijk} - \theta_{ijk}^0)^2$$



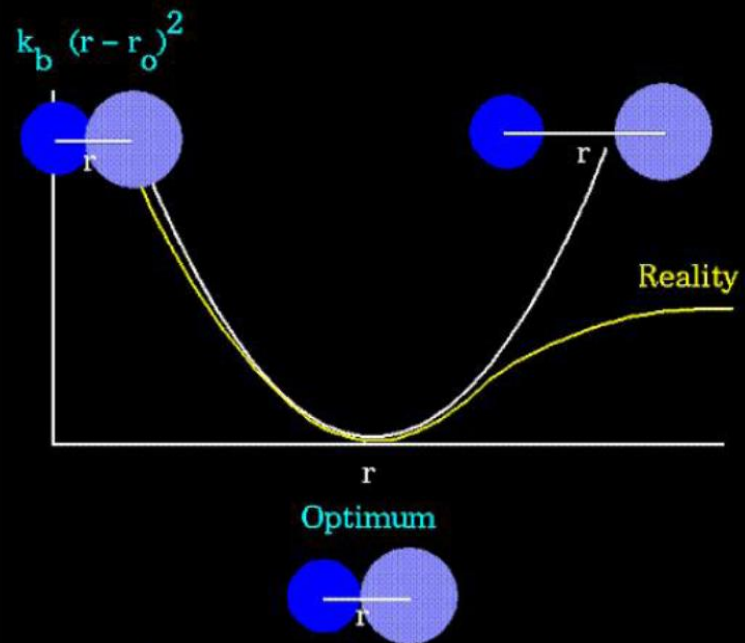
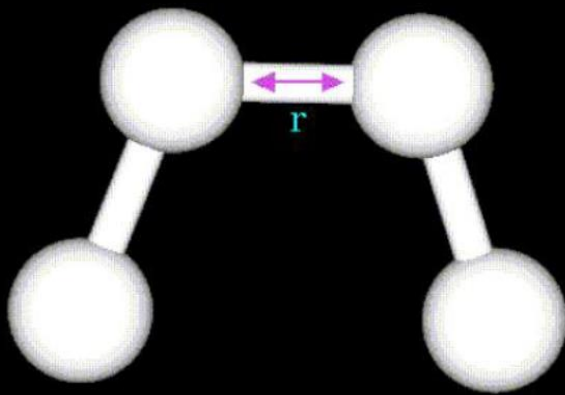
$$V_{vanderWaals} = 4\epsilon \left[\left(\frac{\sigma_{ij}}{R_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{R_{ij}} \right)^6 \right] \quad (\text{John Lennard-Jones – 1931})$$

$$V_{Electrostatic} = \frac{q_i q_j}{4\pi\epsilon R_{ij}}$$

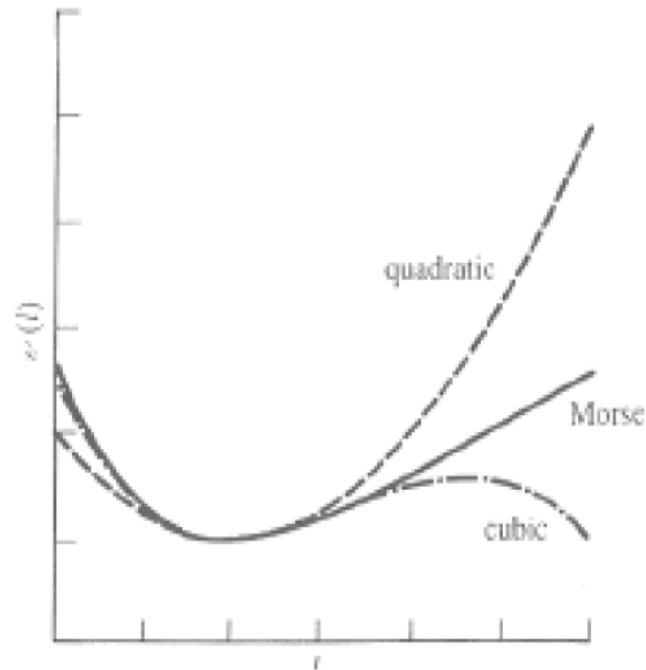
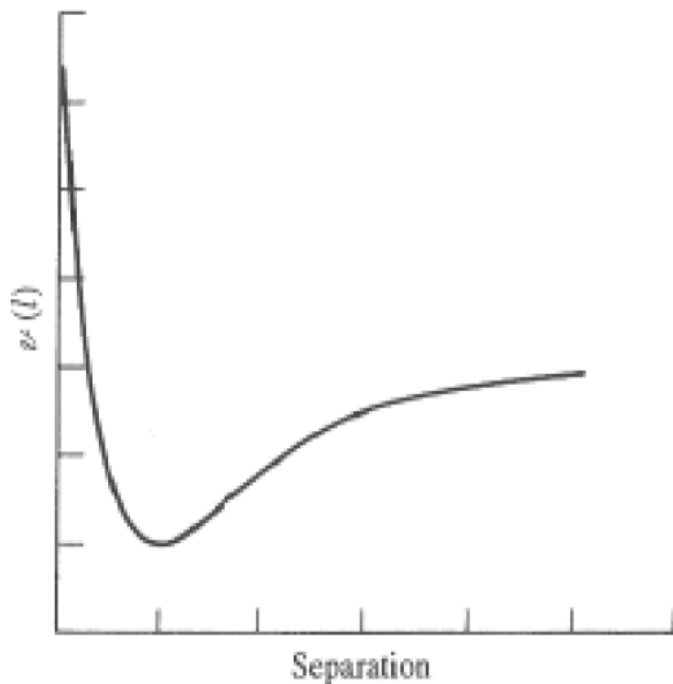
(Charles Augustin de Coulomb -1785)

Bond stretching

Bond-stretching



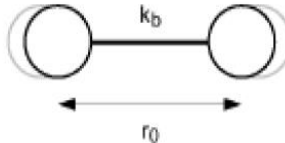
Problem with harmonic approximation



- In reality, bonds can break if stretched, but they cannot break when using a harmonic model.
- This is the essence of Molecular Mechanics; no bonds are broken or formed, therefore molecular mechanics is rarely used for modeling chemical reactions.

Alternatives to Harmonic Bond Stretching

Approximated by a simple harmonic function about an equilibrium bond length r_0 with force constant k_b , which is defined between every pair of bonded atoms.

$$V_b^{\text{harm}}(r_{ij}) = \frac{k_b}{2} (r_{ij} - r_0)^2$$
A diagram illustrating the harmonic bond model. It shows two circles representing atoms connected by a horizontal line. Above the line is the label k_b . Below the line is a double-headed arrow with the label r_0 underneath it, indicating the equilibrium bond length.

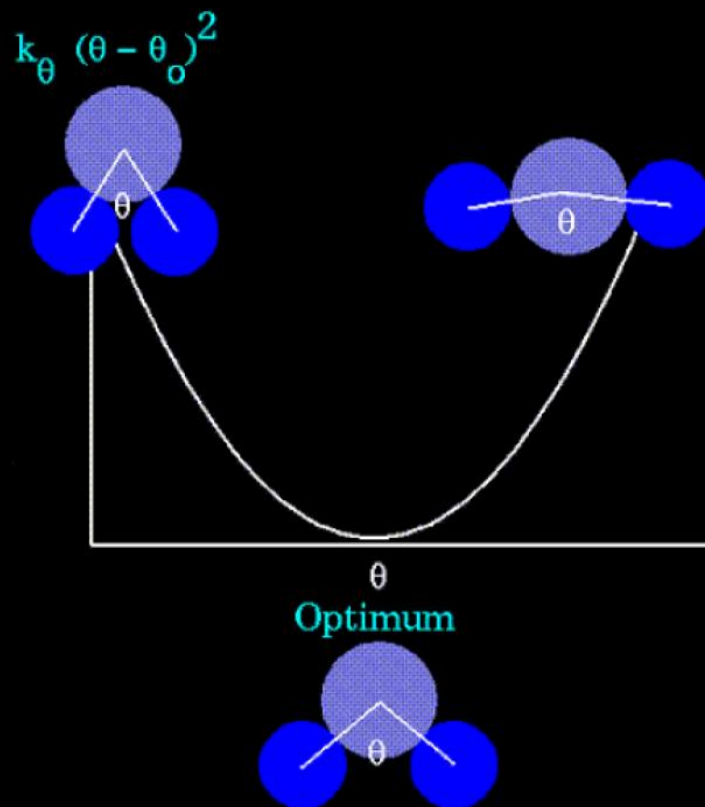
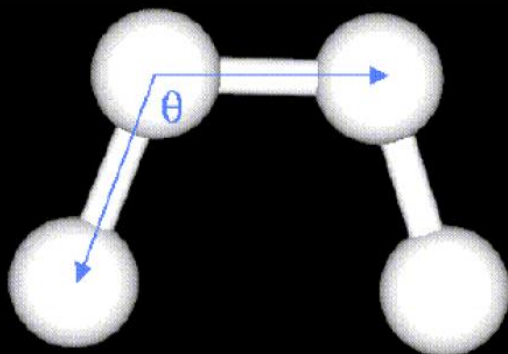
This is fairly poor approximation at extreme values of r , but bonds are usually stiff that it works under moderate temperature.

Accuracy can be improved by using a Morse potential, which is anharmonic, but this is considerably slower.

$$V_b^{\text{Morse}}(r_{ij}) = D_e \left\{ 1 - \exp \left[-a (r_{ij} - r_0) \right] \right\}^2$$

Angle-bending

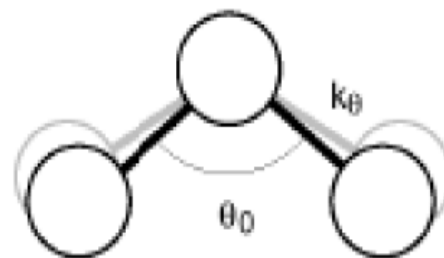
Angle-bending



Angle Bending are Similar to Bond Stretching

The bond angle bending energy is also approximated by a harmonic function, about an equilibrium bond angle θ_0 with a force constant k_θ . It is defined between every triplet of bonded atoms.

$$V_\theta(\theta_{ijk}) = \frac{k_\theta}{2} (\theta_{ijk} - \theta_0)^2$$



The force constants for bending motion tend to be smaller than those for stretching by a factor of 5 to 7.

Also, be aware that there may be other contributions to the bending energy from the non-bonded energies of atoms connected to the bonded pair.



Electrostatics

Differences in electronegativity between atoms generate unequal charge distributions in a molecule.

Electronegativity differences are often represented as fractional atomic charges (q) within the molecule (normally centered at the nuclei).

Electrostatic interaction energy is calculated as a sum of interactions between partial atomic charges, using Coulombs law.

Naturally, this equation is also used for modeling interactions between integral charges, such as between ions.

$$V_{Electrostatic} = \frac{q_i q_j}{4\pi\epsilon R_{ij}}$$

The problem with this approach is that there is no such thing as a fractional electron, therefore there is no perfect method to derive the partial atomic charges



Van der Waals Interactions

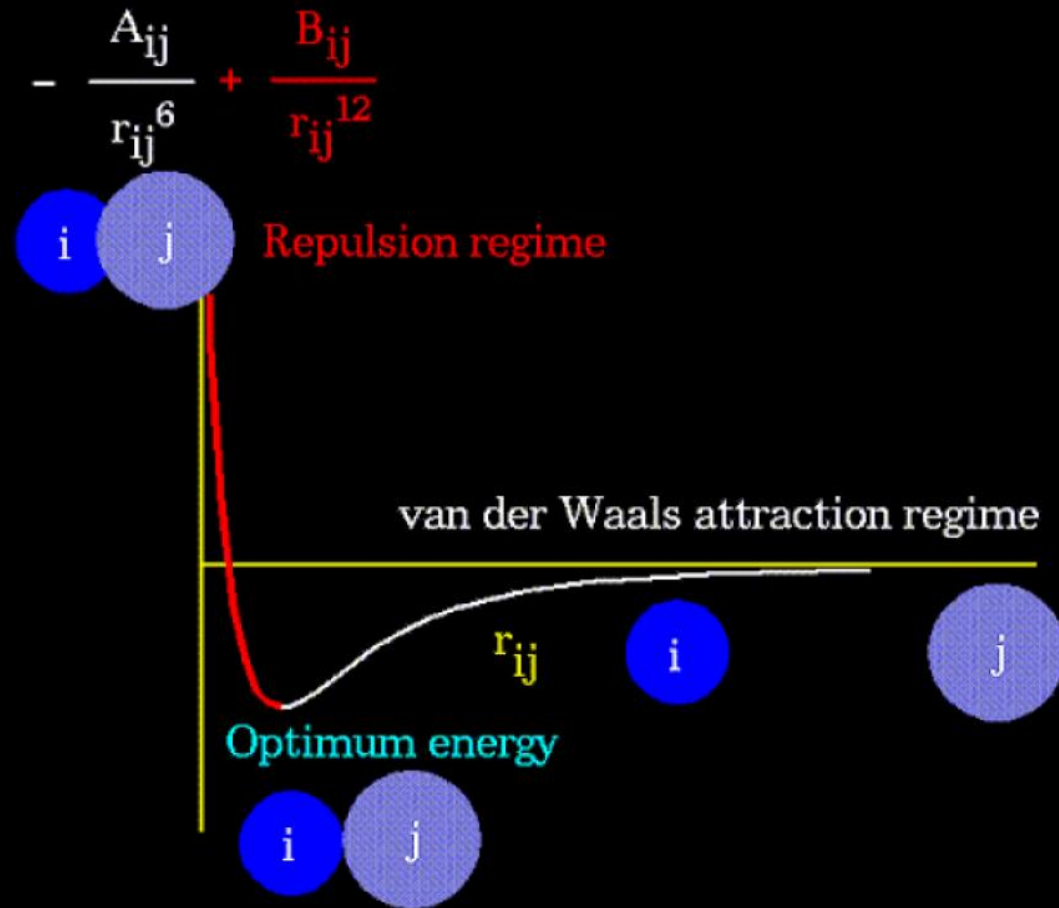
Non-bonded interactions that are not electrostatic (e.g. between atoms in noble gas) are labeled van der Waals interactions

Contains **dispersion and repulsion components**

Dispersion interactions always attractive. Arise from instantaneous dipoles that occur during fluctuations within the molecular electron cloud

Repulsive interactions occur at short-range. Also labeled exchange, or overlap, forces. They occur between electrons with the same spin that must not occupy same region in space (Pauli exclusion principle)

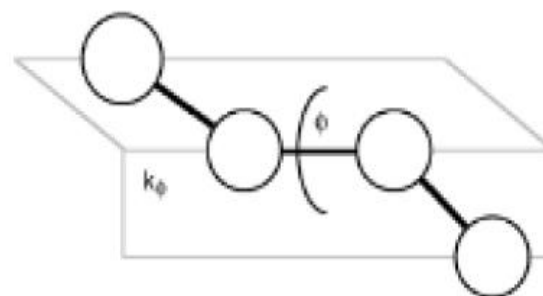
Van der Waals Interactions



Torsion Angle or Dihedral Angle Energy

The torsional energy is defined between every four bonded atoms (1-4 interactions), and depends on the torsion (aka dihedral) angle ϕ made by the two planes incorporating the first and last three atoms involved in the torsion

$$V_{\phi}(\phi_{ijkl}) = \frac{k_{\phi}}{2} (1 + \cos 3\phi_{ijkl})$$



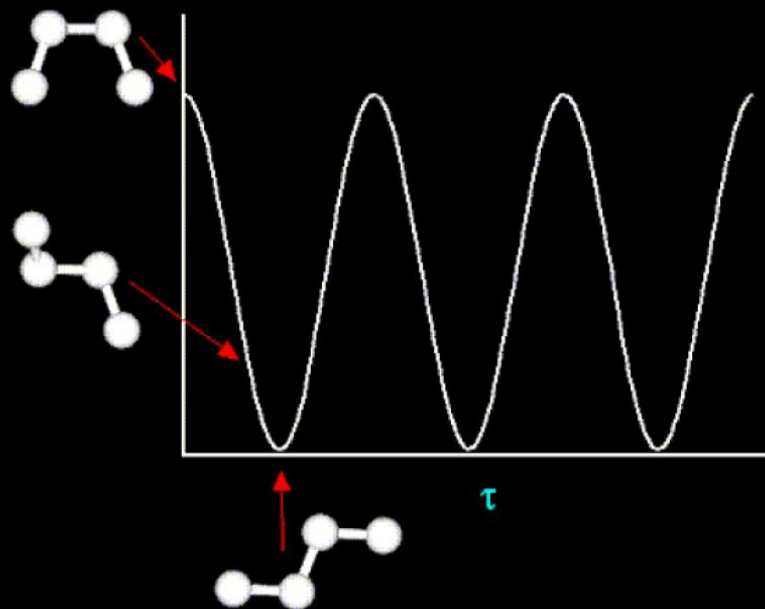
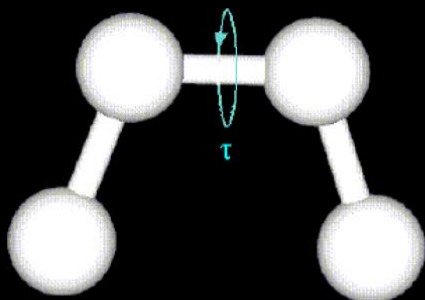
Torsion terms account for any interactions between 1-4 atom pairs that are not already accounted for by non-bonded interactions between these atoms

For example: they could be used to describe barriers to bond rotation from electron delocalization (double bonds or partial double bonds), or stereo-electronic effects

Torsion Angle or Dihedral Angle Energy

Torsion

$$A [1 + \cos(n\tau - \phi)]$$

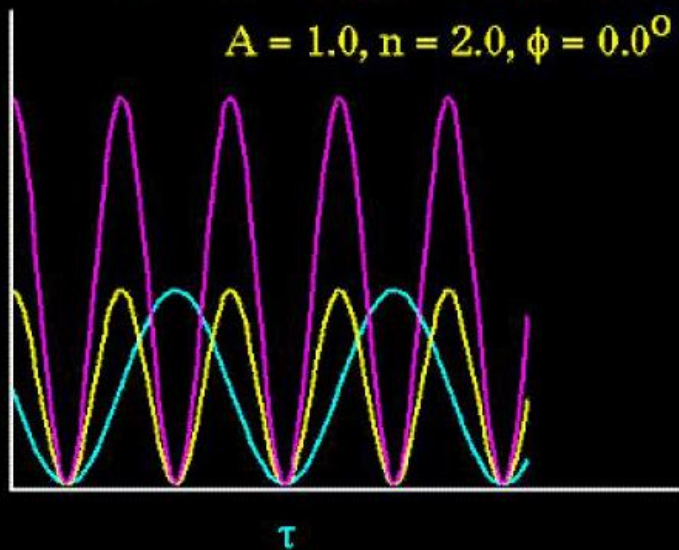


Torsion Angle or Dihedral Angle Energy

Torsions (cont.)

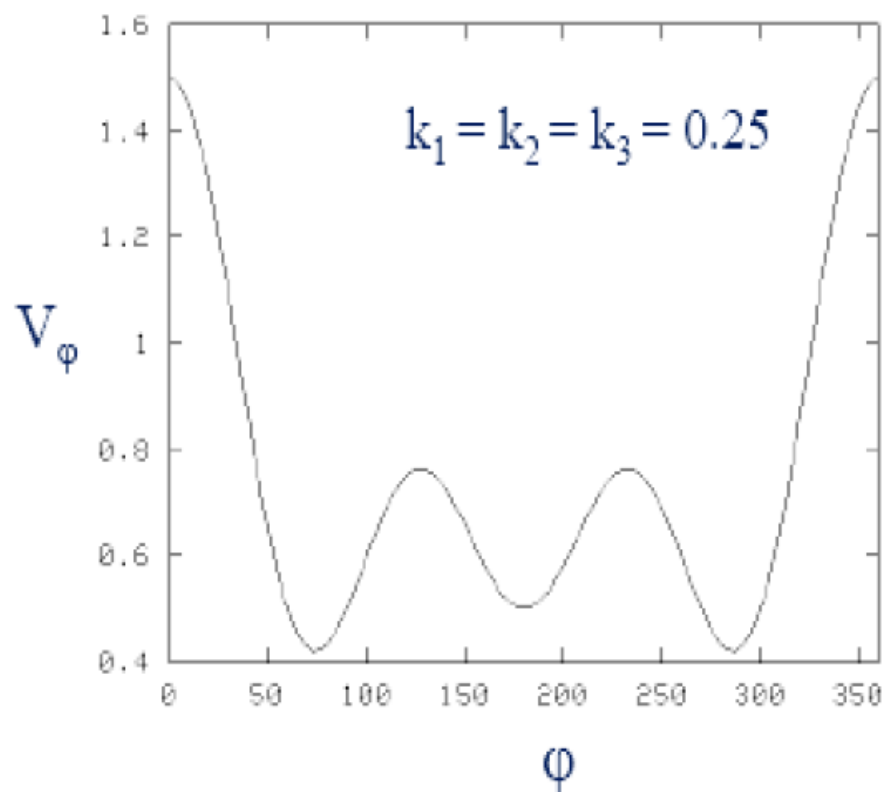
$$A [1 + \cos(n\tau - \phi)]$$

$A = 2.0, n = 2.0, \phi = 0.0^\circ$
 $A = 1.0, n = 1.0, \phi = 90.0^\circ$
 $A = 1.0, n = 2.0, \phi = 0.0^\circ$



Complex torsion contributions can be modeled

$$V_{\varphi}(\varphi) = \frac{k_1}{2}(1 + \cos \varphi) + \frac{k_2}{2}(1 + \cos 2\varphi) + \frac{k_3}{2}(1 + \cos 3\varphi)$$



To introduce a difference between the stabilities of the *gauche*- and *anti*-conformations, the torsion function can be expanded with additional terms, each with its unique contribution to the rotational energy



SUMMARY – Force Field Terms

Electrostatic energy is represented using a set of partial atomic charges.

van der Waals energy has both weakly attractive and strongly repulsive components and arises from represents electron correlation.

The dispersion term is always negative whereas short-range energy is always repulsive.

Torsion terms describe bond rotational properties that arise from non-classical effects, such as electron delocalization.

The remaining **bond length** and **angle terms** describe covalent bonding.

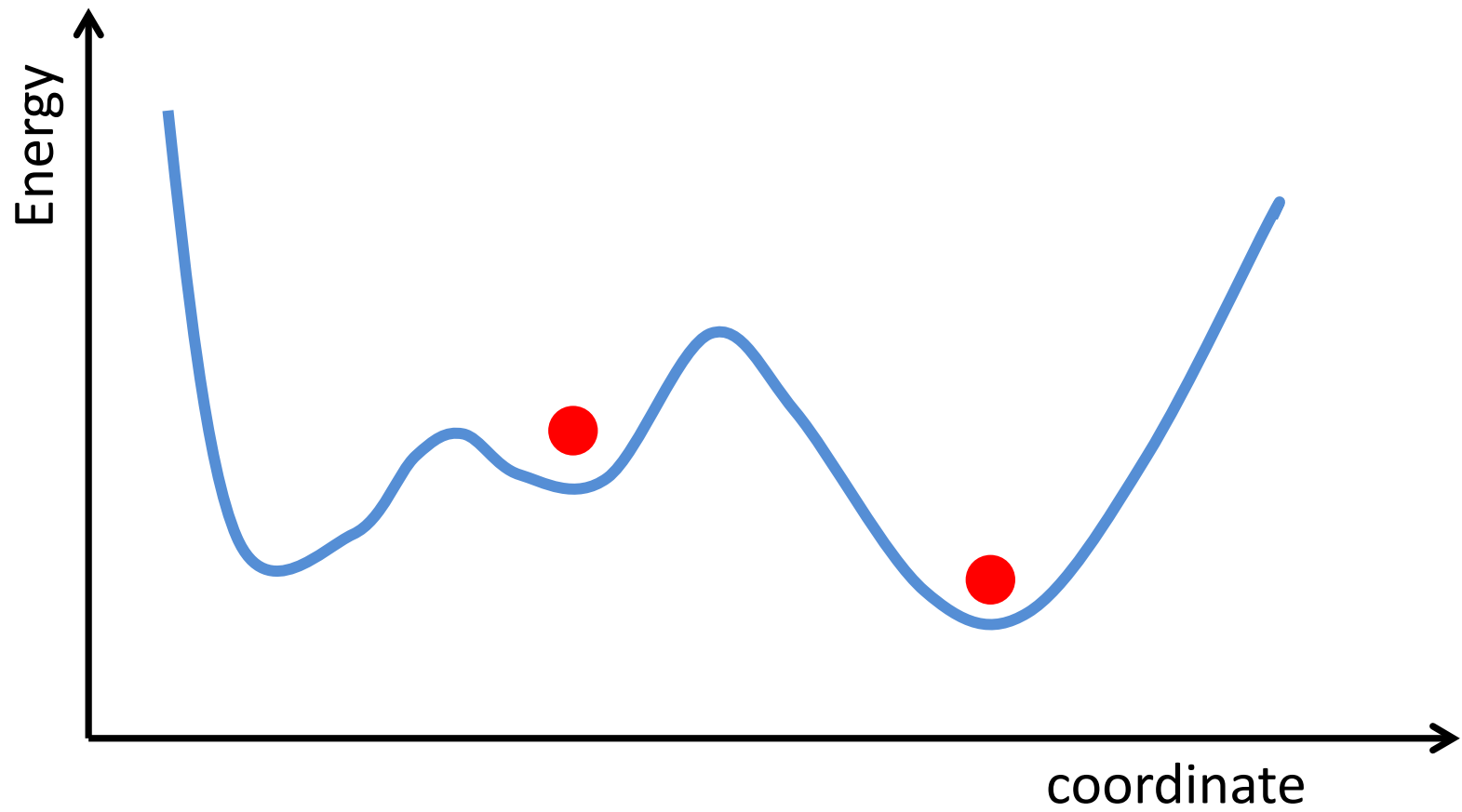
Once we have a force field, what can we do with it?

- Energy minimization
- Molecular Dynamics
- Conformational analysis

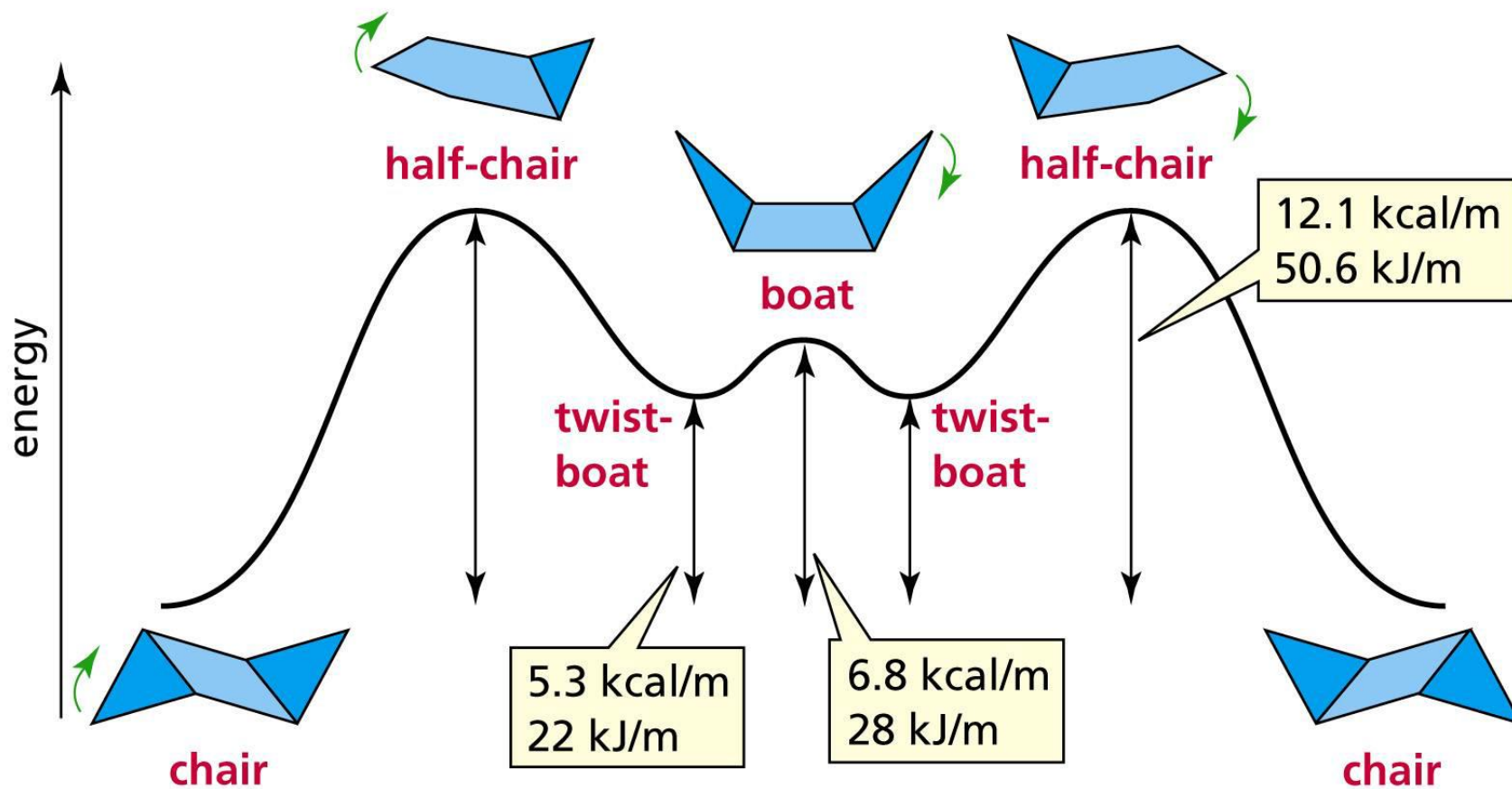
The accuracy of the output from all these techniques will obviously be sensitive to a greater or lesser extent on the parameterization of the force field.



Energy minimization



Relative energies, minima, maxima





Finding the Global Minimum

Energy Minimization Algorithms (aka Geometry Optimization)

- Used to find minima or maxima (transition state search).
- Based on the calculation of energies and energy gradients (1st and 2nd order).
- Ideal for finding stationary points (min or max) for small molecules.
- Can be used to “adjust” high resolution 3D structures of macromolecules before conformational search.

Conformational Search Algorithms (global minimum search)

Ideal for larger systems (20 atoms or more)

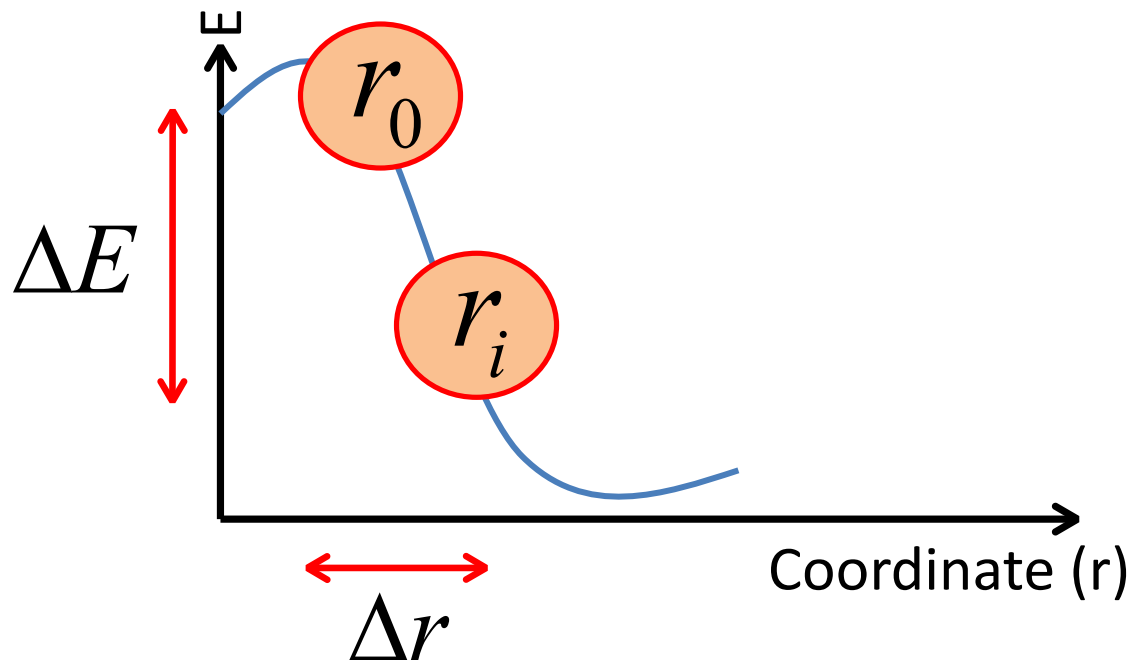
- Grid Search
- Simulated Annealing
- Genetic Algorithms

Mathematics/Physics Background

When we do energy minimization (geometry optimization) we are interested in **how does the energy changes relative to change in the geometry of the molecule** (r).

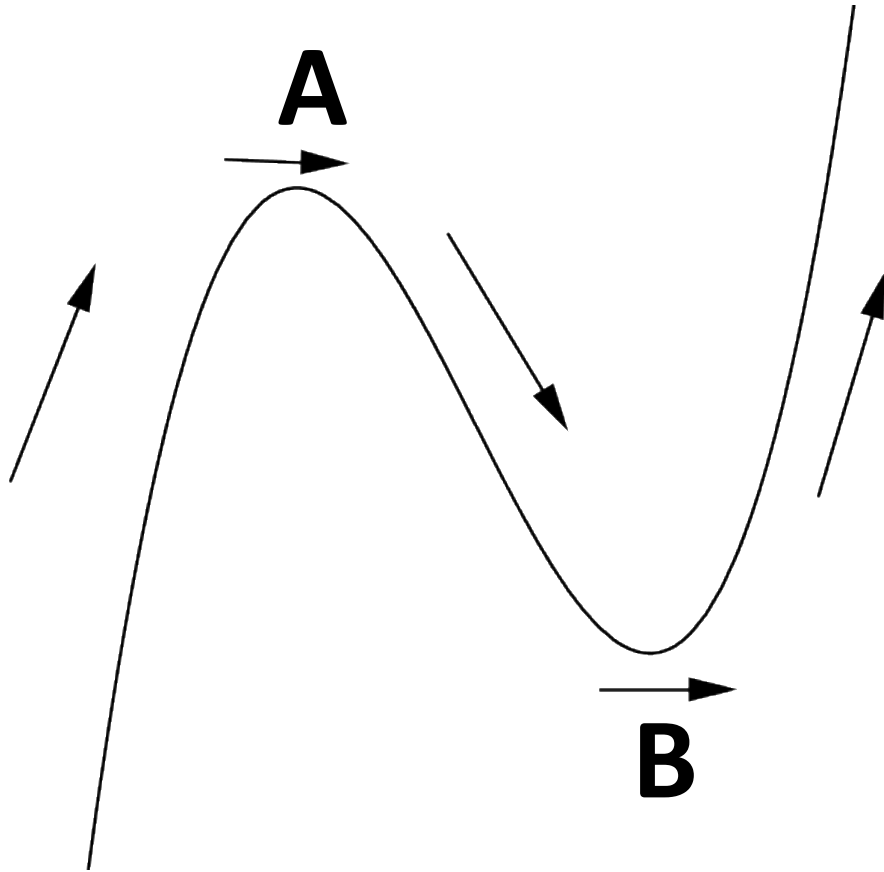
$$\Delta E = E_i - E_0$$

$$\Delta r = r_i - r_0$$



$$gradient = \lim_{r_i \rightarrow r_0} \left(\frac{\Delta E}{\Delta r} \right) = \frac{dE}{dr}$$

Defining Stationary Points (Maxima, Minima)



At a maximum or minimum (turning points) what is the value of the gradient?

$$\frac{dE}{dr} = 0$$

How do I know I reached a maximum?

$$\frac{dE}{dr} = 0 \quad \frac{d^2E}{dr^2} < 0$$

How do I know I reached a minimum?

$$\frac{dE}{dr} = 0 \quad \frac{d^2E}{dr^2} > 0$$

Derivative Minimization Methods

- Following the Path of Least Resistance

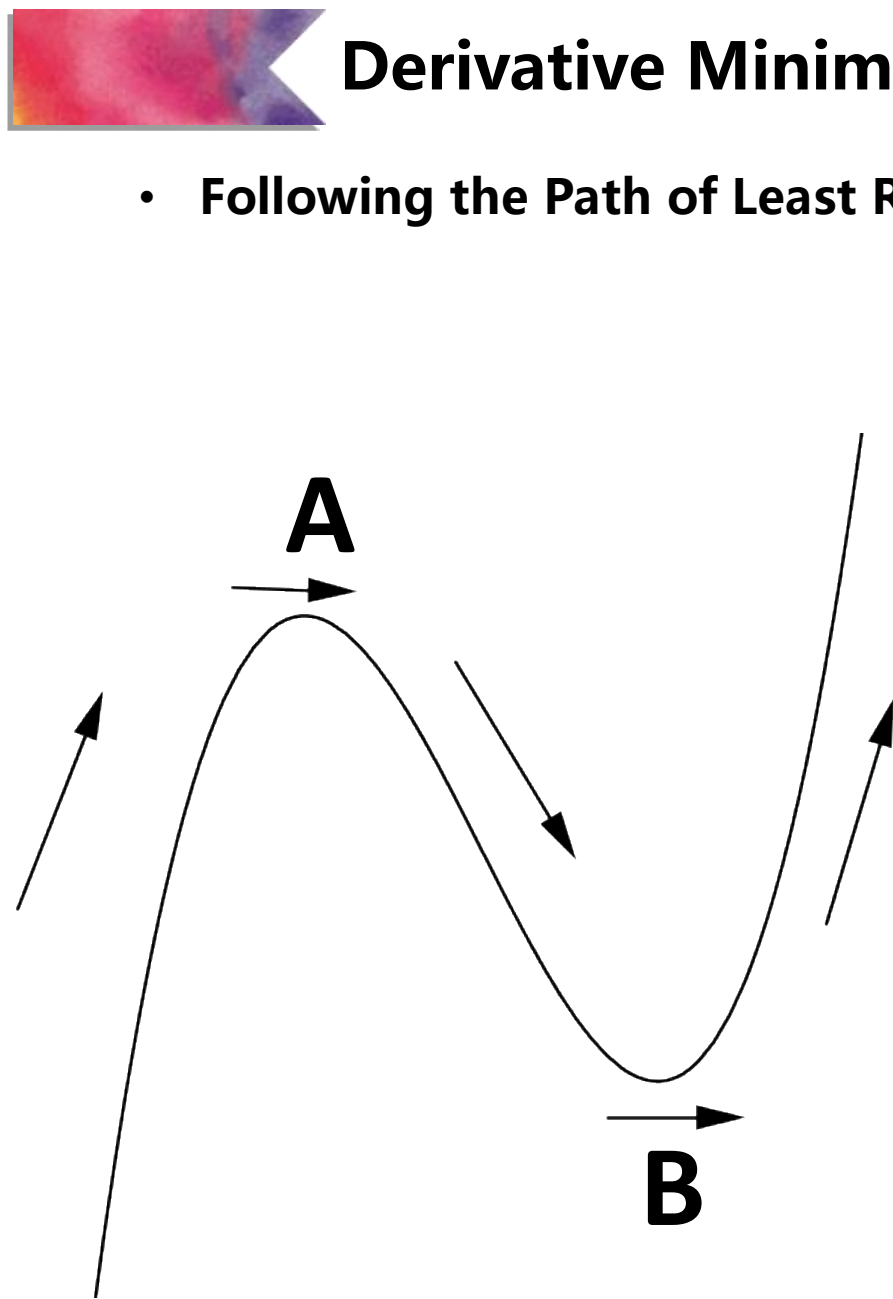
Direction towards the minimum (max) is given by the first derivative

Magnitude of the gradient indicates the steepness of the slope

The curvature of the function is given by the second order derivative

$$F = -\frac{dE}{dr}$$

The minimum energy point can be found by moving each atom in response to the force acting on it.





Summary

- Molecular energy (and the energy of interactions between molecules) can be modeled using non-quantum (classical) mechanics.
- There are no right or wrong force fields, just ones that are more appropriate for the question at hand.
- Classical models do not permit bond breaking or bond formation (no chemistry)!
- Energy minimization is essentially the same as Force minimization.
- Absolute energies are not relevant, but relative energies are.