

Structural Bioinformatics (C3210)

Molecular Mechanics



INVESTMENTS IN EDUCATION DEVELOPMENT

How to Calculate Energies

- ♦ Calculation of molecular energies is of key importance in protein folding, molecular modelling etc.
- ♦ There are two main computational methods for calculating the energy of a molecule or a set of molecules: **quantum mechanics** and **molecular mechanics** methods.
- ♦ **Quantum mechanics** treats molecules as a systems of nuclei and electrons. Quantum mechanical calculations are time demanding and their computational requirements growth rapidly with the size of system
- ♦ **Molecular mechanics** is based on the idea that the atoms of the molecule feel forces and the energy of a conformation is related to these forces
- ♦ In molecular mechanics **electrons are not explicitly included** in calculation, the energy of a system is calculated as a function of nuclear position only
- ♦ **Molecular mechanics methods are much faster then quantum mechanics** and their computational requirements do not grow fast with size of a system

Force Fields

- ♦ Molecular mechanics uses force fields for calculation of potential energy between atoms
- ♦ **Force field** is an empirical set of energy functions that describe energy related to interaction between atoms
- ♦ A typical force field consists of **bond stretching**, **angle bending**, **torsional rotation**, **van der Waals interaction** and **electrostatic interaction** energy functions
- ♦ **Hydrogen bonding** energy term is also used in some force fields
- ♦ The energy of a conformer is the total sum of all those contributions

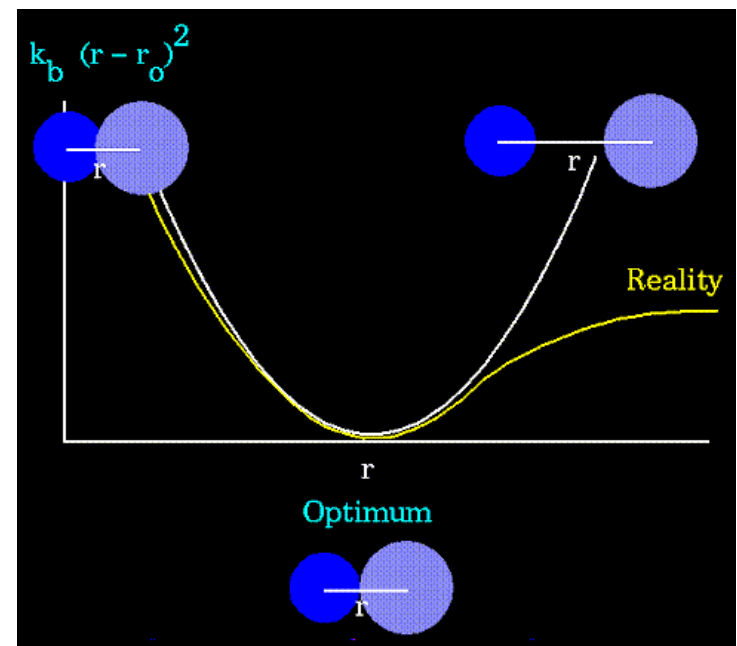
$$E_{\text{total}} = E_{\text{stretching}} + E_{\text{bending}} + E_{\text{torsion}} + E_{\text{VdW}} + E_{\text{elstat}} (+ E_{\text{hbond}})$$

←—————→ ←—————→
covalent energy non-covalent interactions

Bond Stretching

- ♦ Bond stretching describes deformation energies of the bond lengths with respect to their equilibrium values
- ♦ Energetic curve near equilibrium distance can be approximated by **harmonic potential** (Hooke's law)
- ♦ The stretching force constants k_b are determined experimentally from vibration spectroscopy
- ♦ This harmonic approximation can be used if atom bonding distances are near to their equilibrium positions
- ♦ This restricts modeling chemical reactions, as it does not allow for the breaking of bonds

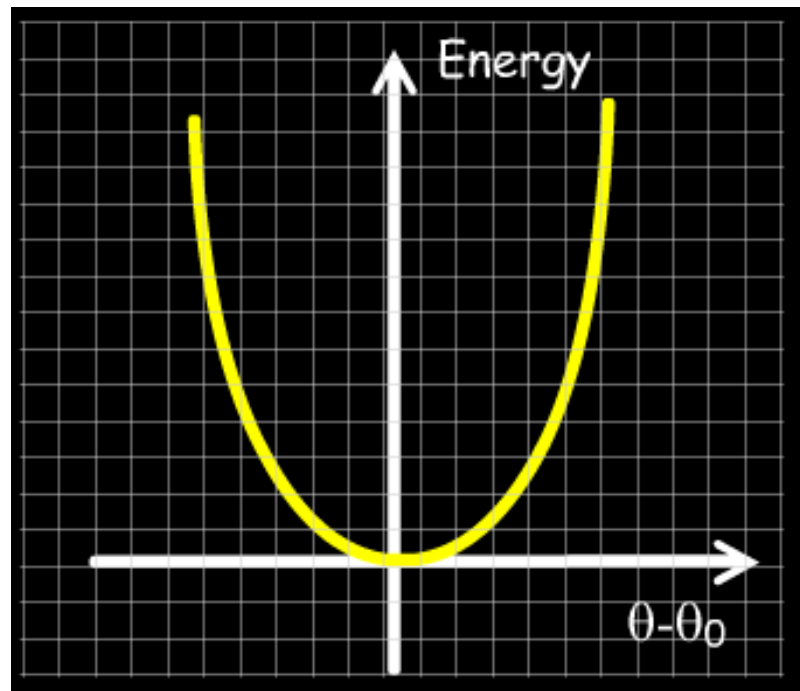
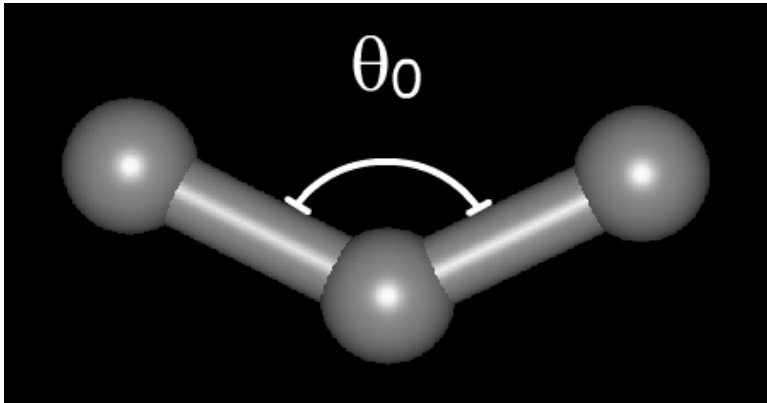
$$E = k_b * (r - r_0)^2$$



Angle Bending

- ♦ Angle bending term describes deformation energies of the bond angles with respect to their equilibrium values
- ♦ Energetic curve near equilibrium angle can be approximated by **harmonic potential**. This approximation can be used if atom bonding angles are near to their equilibrium positions
- ♦ The bending force constants k_a are determined experimentally from vibration spectroscopy

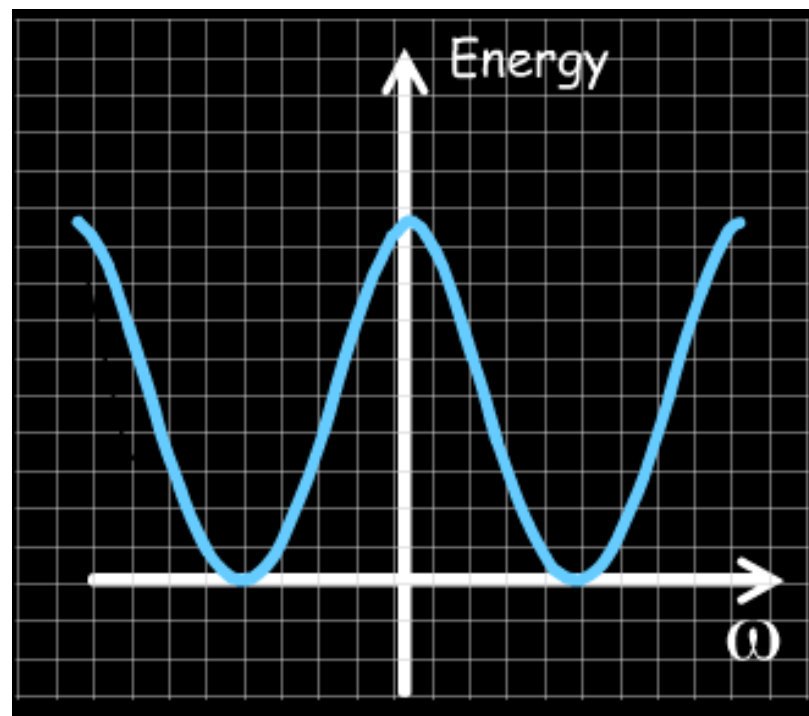
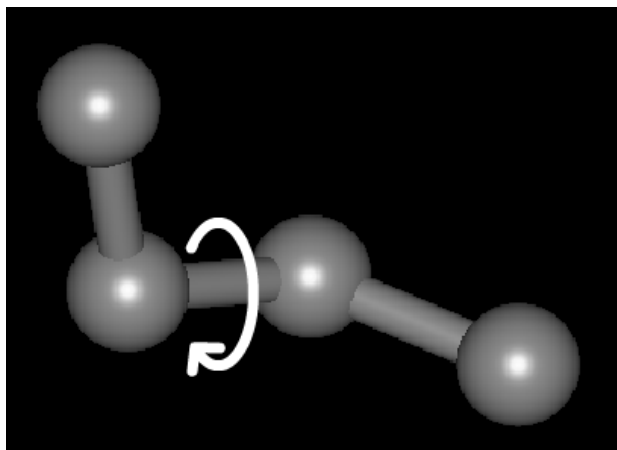
$$E = k_a (\theta - \theta_0)^2$$



Torsional Term

- ♦ Torsional term describes **rotation around covalent bond**
- ♦ The origin of this energy is through-space steric and electronic interactions between non-bonded atoms
- ♦ The energy curve corresponding to torsional energy is periodical and can be approximated using series of goniometric functions
- ♦ The barriers (V_n) are usually obtained from quantum mechanical calculations

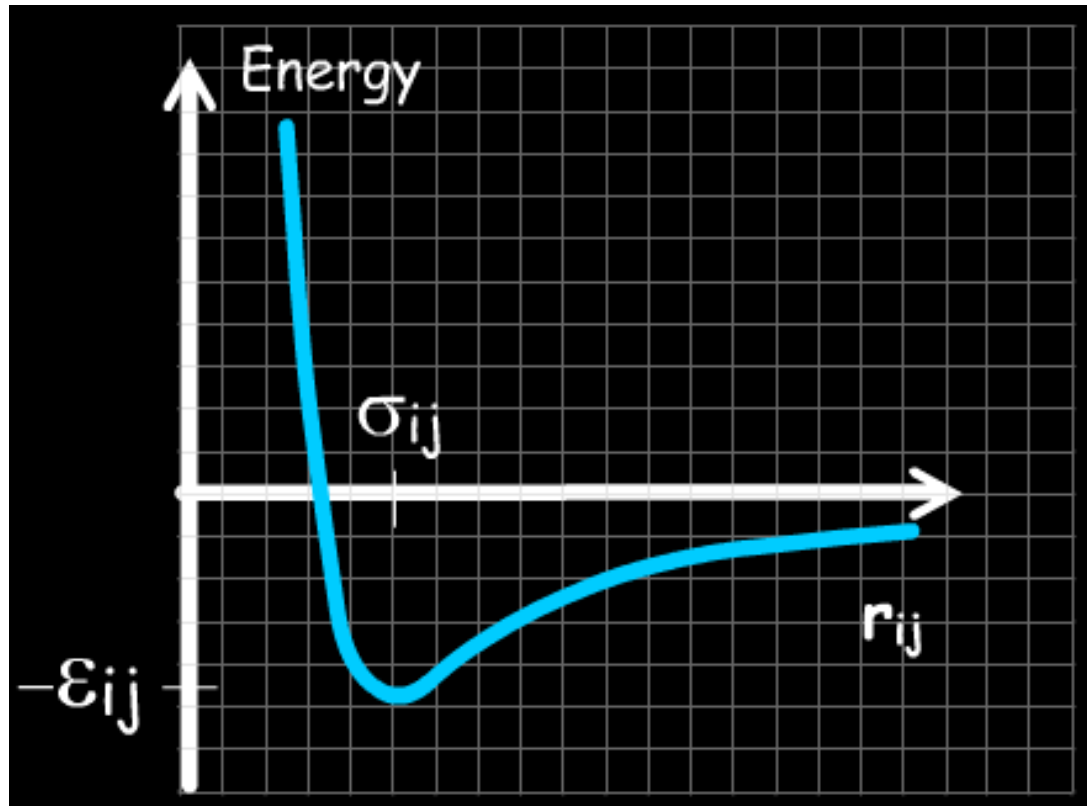
$$E = \sum^n V_n [1 + \cos(n\omega - \gamma)]$$



Van der Waals Term

- ♦ Van der Waals term describes the Van der Waals repulsive and attractive (dispersion) interatomic forces
- ♦ This term is usually approximated by the Lennard-Jones 12-6 potential, although other functions also has been proposed

$$E = 4\epsilon [(\sigma/r)^{12} - (\sigma/r)^6]$$



Hydrogen Bonds Term

- ♦ Hydrogen bond term describes the energy related to hydrogen bond between atoms that can form hydrogen bonds
- ♦ This term is usually approximated by the **12-10 potential** which resembles Lennard-Jones potential, but attractive interaction disappears faster
- ♦ Because the strength of hydrogen bond **depends on D–H····A angle**, the 12-10 potential is sometimes multiplied by cosine of the angle (usually exponentiated to 2 or 4)
- ♦ **Only some force fields include this term**, others describe the effect of hydrogen bonds via electrostatic and vdW terms

$$E = [(A/r)^{12} - (C/r)^{10}] \cos^n \theta$$

Electrostatic Term

- ♦ Electrostatic interaction energy is calculated from **Coulomb's law**, where q_1 and q_2 are atomic partial charges:

$$U_{21} = \frac{1}{4\pi\epsilon} \frac{q_1 q_2}{r}$$

- ♦ Appropriate **relative electrostatic permittivity** can be used to include effects of solvent environment or protein environment (typically 80 for water, 2 - 4 for protein interior)
- ♦ **Partial charges** are usually precalculated using quantum mechanical methods
- ♦ **Static partial charges** are usually used, i.e. the same values for individual atoms are used for all molecular mechanics calculations
- ♦ For more accurate calculations, **polarizable charges** can be used – equilibrium value of partial charge is corrected for each conformation using function with empirical parameters

Total Energy in a Force Field Calculation

- ♦ Force field calculations are based on 3D coordinates and calculate the energy of the corresponding conformation
- ♦ The figure shows a typical result of a force field calculation

Stretching:	1.070	kJ/mol
Bending:	5.654	kJ/mol
Torsion:	1.017	kJ/mol
Van der Waals:	9.406	kJ/mol
Electrostatic:	-6.084	kJ/mol
Hydrogen bonding:	-0.121	kJ/mol
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Total energy:	10.943	kJ/mol

Limitations of Molecular Mechanics

- ♦ Molecular mechanics is fast method but it has some important limitations
- ♦ Molecular mechanics cannot be used to study processes that include **cleavage of covalent bonds** such as chemical reactions, protonation states etc.
- ♦ It cannot be used to study **properties dependent on electron distribution** – NMR shielding constants, spectroscopic data, etc.
- ♦ Problems with **metal atoms** that can form donor-acceptor bonds as well as vdW/electrostatic non-bonding interactions
- ♦ **Stacking interactions** are usually not well described by force fields
- ♦ The method has **limited precision**, significantly lower than QM calculations
- ♦ Empirical parameters must be obtained before the method can be used => **requires parametrization**
- ♦ Some force fields can solve some of these problems although usually for specific types of molecules only

Remarks

- ♦ Different programs may use different functional forms of the force field (e.g. the Van der Waals parameters may be described by other potential than Lennard-Jones, some force fields may include explicit charge polarization terms etc.).
- ♦ Moreover, the final choice of parameters typically results from fitting to different experimental or computational data. Therefore, individual parameters, such as partial charges, are in general not transferable between different force fields. Due to specific parametrization, some force fields may be better suited for studying specific problems (e.g. kinetic vs. thermodynamic aspects) or molecules (nucleic acids vs. lipids, etc.).

Remarks

Relative energies

- ♦ The energies obtained by different force field methods have **absolute values that are meaningless**
- ♦ They are useful only when **comparing the values obtained for different geometries of the same system**
- ♦ Not only should one not compare the numbers obtained for the energies from one program to another, but for a given program, the energy calculated for a molecule must not be compared to the energy calculated for another molecule (except in closely related systems, such as isomers).

Applications of Molecular Mechanics

- ♦ Molecular mechanics (resp. force field) is used within the following computational methods:
- ♦ **Molecular dynamics** – simulates dynamic behaviour of molecules (programs Amber, CHARMM, MM3, Gromos, etc.)
- ♦ **Protein folding** – methods for prediction of protein 3D structure from sequence
- ♦ **Protein-ligand docking** – methods for prediction of protein-ligand binding energy (AuttoDock, DOCK, Glide, ICM, etc.)
- ♦ **Protein-protein or protein-DNA/RNA docking** – methods for prediction of protein-protein or protein-DNA/RNA binding energy