Molecular Mechanics: Principles, Force Field, Optimization Methods
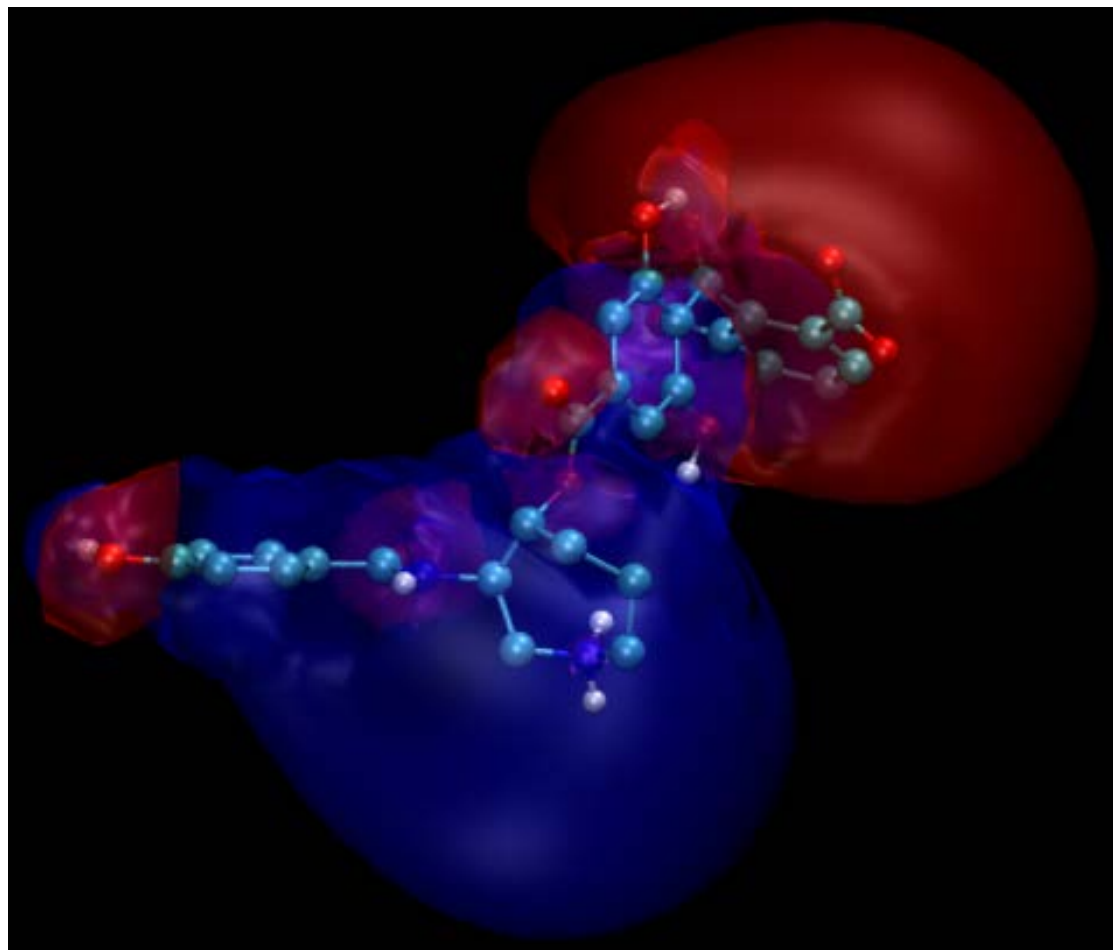
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Quantum *vs.* Classical World

Outline

Molecular Mechanics

Definition of the force field

Bonding terms

Non-bonded terms

Parametrization

Geometry Optimization
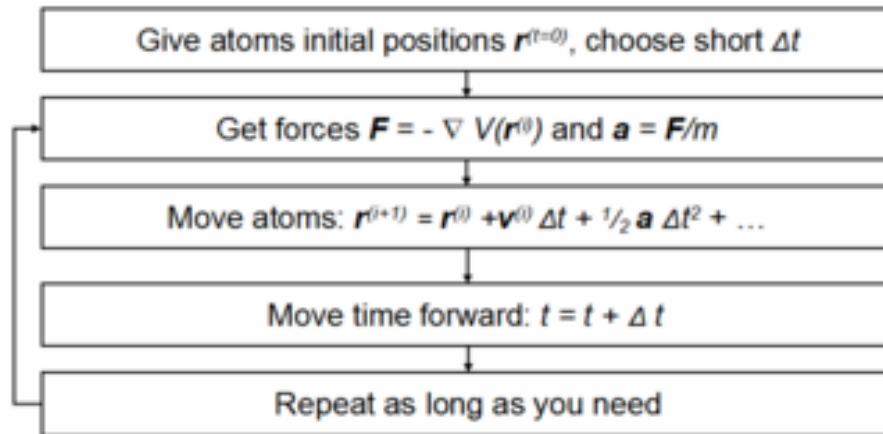
Derivatives, Hessian matrix

Algorithms

Applications

MM/MD (force field) methods: molecular simulations

Molecular mechanics (MM): optimization of molecular geometry

Molecular dynamics (MD): dynamical trajectory (t, T, …p, V, PBC)

Give atoms initial positions $r^{(t=0)}$, choose short Δt
Get forces $\boldsymbol{F} = - \nabla\ V(\boldsymbol{r}^{(i)})$ and $\boldsymbol{a} = \boldsymbol{F}/m$
Move atoms: $\boldsymbol{r}^{(i+1)} = \boldsymbol{r}^{(i)} + \boldsymbol{v}^{(i)} \Delta t + \frac{1}{2} \boldsymbol{a}\ \Delta t^2 + \dots$
Move time forward: $t = t + \Delta t$
Repeat as long as you need

(Dis)advantages: universal parametrization

Systems: 100.000 atoms can be studied conveniently (more on the coarse-grained level

Limitations: *standard* force fields are not able to describe chemical reactions; heterocompounds poorly described
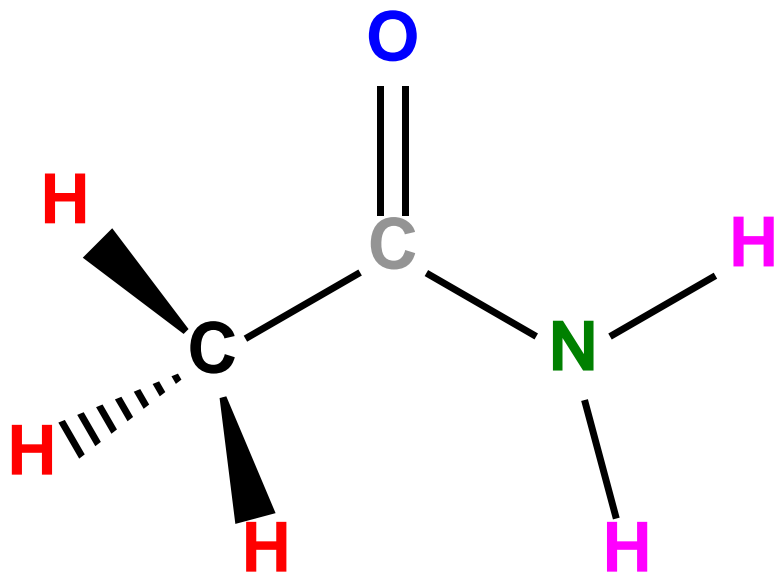
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Force Field = Potential Energy of Molecular System

$$U \;=\; \sum_{i<j} \sum 4\varepsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right]$$

$$+ \; \sum_{i<j} \sum \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}}$$

$$+ \; \sum_{bonds} \frac{1}{2}k_b(r - r_0)^2$$

$$+ \; \sum_{angles} \frac{1}{2}k_a(\theta - \theta_0)^2$$

$$+ \; \sum_{torsions} k_\phi\left[1 + \cos(n\phi - \delta)\right]$$

Force Field = Functional Form + Parametrization

Example: acetamide

acetamide

$3N$-6 = 21 internal coordinates

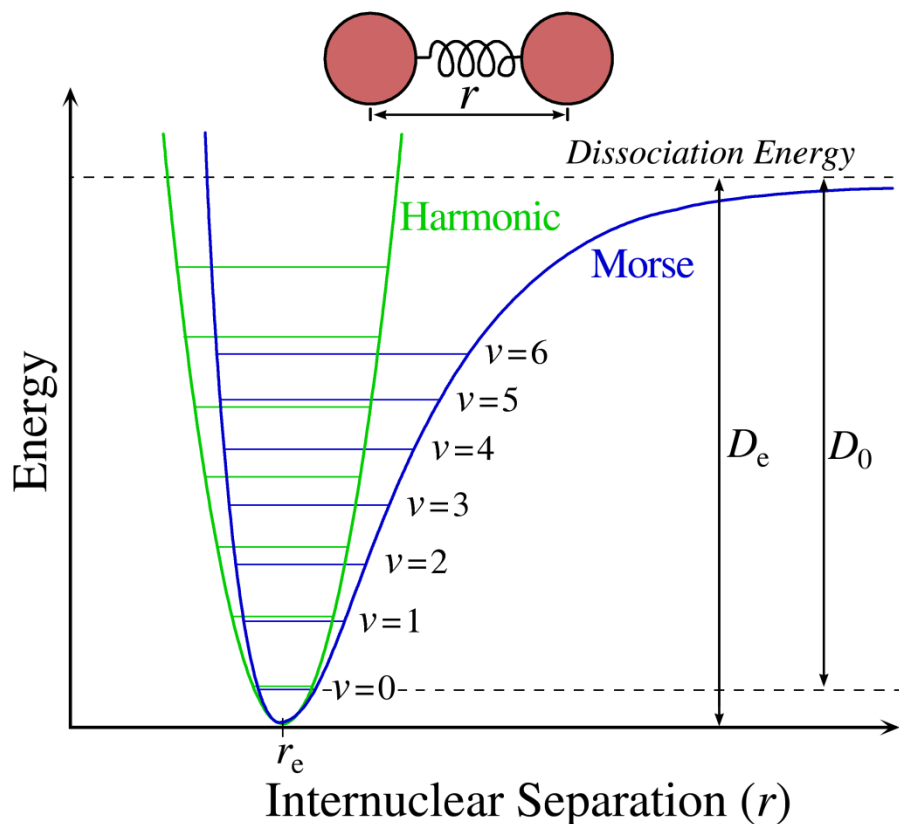*vs.* redundant internals

8 bonds
12 valence angles
10 torsions

Simplicity vs. complexity
universal parametrization
derivatives

Bond Stretching

Morse potential

$$V(r) = D_e(1 - e^{-a(r-r_e)^2})$$

$$a = \omega\sqrt{\mu/2D_e}$$

Harmonic

Morse

$v=6$
$v=5$
$v=4$
$v=3$
$v=2$
$v=1$
$v=0$

Dissociation Energy

D_e D_0

r_e

Energy

Internuclear Separation (r)

r

Good description of chemical bond

3 parameters
NOT efficient computation

Harmonic potential

$$V(r) = {k}/{2}\,(r - r_e)^2$$

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Equilibrium vs. reference bond lengths

Typical values of *k* (in kcal.mol^{-1}.$\mathring{A}^{-2}$)

C-C   ~300
C=C   ~650
C=O ~780

Higher-order terms can be used (cubic, quartic)

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Angle Bending

$$V(\Theta) = {}^{k}\!/_{2}\,(\Theta - \Theta_{e})^{2}$$

Typical values of *k (in kcal.mol^{-1}.deg^{-2})*

C-C-C   ~0.01

Higher-order terms can be used (cubic, quartic)

Torsions

$$V(\omega) = \sum_{n=0}^{N} \frac{V_n}{2} [1 + \cos(n\omega - \gamma)]$$

AMBER
One or two terms

MM2
Mostly 3 terms

Improper Torsions or Out-of-Plane Bending

For cyclic or conjugated systems

To keep atoms in plane (e.g. cyclobutanone)

Cross-terms in force fields

Bond-bond, bond-stretch, bend-bend-torsion, …
e.g.

$$V(r_1, r_2, \Theta) = \frac{k_{r_1, r_2, \Theta}}{2} [(r_1 - r_{1,e}) + (r_2 - r_{2,e})](\Theta - \Theta_e)$$

Electrostatic Interactions

Coulomb's law

$$V_{el} = \sum_{i<j} \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}}$$

Central multipole expansion

Methods for deriving partial atomic charges

Atomic charge … not observable!

QM: Mulliken, Lowdin, Bader AIM, ESP

Rapid Methods: partial equalisation of orbital electronegativity

ESP: Electrostatic Potential Fits

Solvent dielectric models

Van der Waals interactions

Dispersive interactions (London force, 1930)

Two Drude Oscillators

$$V(r) = -\frac{\alpha^4 \hbar \omega}{2(4\pi\varepsilon_0)^2 r^6}$$

$$V_{LJ} = 4\varepsilon \left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^6 \right] = \varepsilon \left[\left(\frac{r_m}{r}\right)^{12} - 2\left(\frac{r_m}{r}\right)^6 \right],$$

Solvent Effects

Water Models

Polarized FFs

United Atoms Force Field (Coarse-Grained Models)

Force Field Parametrization (Transferability, Heterocompounds, Inorganic Molecules)