7. Classical Force Fields

Observables in classical statistical mechanics

- for a system with constant number of particles N, volume V, and temperature T, the Boltzmann distribution on the positions of the particles is

$$p(\mathbf{r}_1, \mathbf{r}_2, \ldots) = \frac{\exp(-\beta U(\mathbf{r}_1, \mathbf{r}_2, \ldots))}{Q_{\text{pos}}},$$

where $Q_{\text{pos}} = \int \exp(-\beta U(\mathbf{r}_1, \mathbf{r}_2, \ldots))\, d\mathbf{r}_1\, d\mathbf{r}_2\, \ldots$

- the average value of an observable A is

$$\begin{aligned}\langle A \rangle &= \int p(\mathbf{r}_1, \mathbf{r}_2, \ldots) A(\mathbf{r}_1, \mathbf{r}_2, \ldots)\, d\mathbf{r}_1\, d\mathbf{r}_2\, \ldots \\ &= \frac{\int \exp(-\beta U(\mathbf{r}_1, \mathbf{r}_2, \ldots)) A(\mathbf{r}_1, \mathbf{r}_2, \ldots)\, d\mathbf{r}_1\, d\mathbf{r}_2\, \ldots}{\int \exp(-\beta U(\mathbf{r}_1, \mathbf{r}_2, \ldots))\, d\mathbf{r}_1\, d\mathbf{r}_2\, \ldots}\end{aligned}$$

- need to specify the potential energy function $U(\mathbf{r}_1, \mathbf{r}_2, \ldots)$ for the system

Classical force fields

- in classical molecular simulations, the potential energy function $U(\mathbf{r}_1, \mathbf{r}_2, \ldots)$ is often approximated using empirical potentials
- such empirical potentials are called classical force fields
- approximate the true potential energy of a system for which the exact calculation requires quantum mechanics
- are much faster to evaluate than quantum mechanical methods
- are often parameterized to reproduce quantum mechanical calculations or experimental data

Outline

Energy terms

Periodic boundary conditions

Force fields and software

Potential energy terms in classical force fields

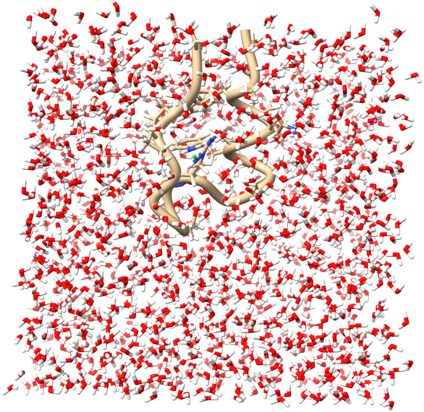
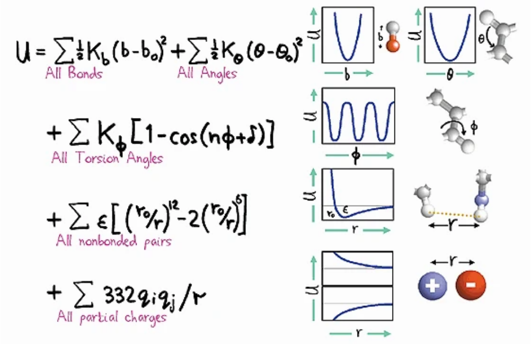


Figure: A small protein in a water box



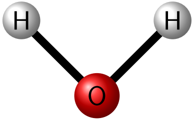
Potential energy of bonds

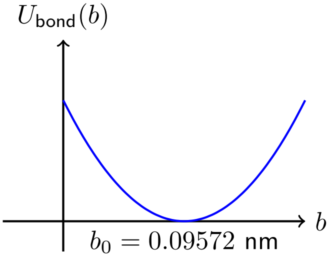
- harmonic bond stretching

$$U_{\mathsf{bond}(b)} = \frac{1}{2} k_b (b - b_0)^2$$

- example: O-H bond in water

$$b_0 = 0.09572 \text{ nm}, \quad k_b = 376560 \text{ kJ mol}^{-1} \text{ nm}^{-2}$$





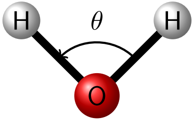
Potential energy of angles

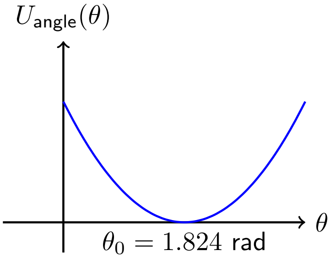
- harmonic angle bending

$$U_{\text{angle}(\theta)} = \frac{1}{2}k_\theta(\theta - \theta_0)^2$$

- example: H-O-H angle in water

$$\theta_0 = 1.824 \text{ rad}, \quad k_\theta = 460.24 \text{ kJ mol}^{-1} \text{ rad}^{-2}$$





Potential energy of torsions

- periodic torsion potential

$$U_{\text{torsion}}(\phi) = k_\phi[1 + \cos(n\phi - \delta)],$$

  where ϕ is the torsion angle, n is the periodicity, and δ is the phase shift

- example: torsion $\mathrm{C}_\alpha - \mathrm{C} - \mathrm{N} - \mathrm{C}_\alpha$ in a protein

$$U_{\text{torsion}}(\phi) = 6.7\,[1 + \cos(\phi - 0°)] + 10.5\,[1 + \cos(2\phi - 180°)]\ \text{kJ mol}^{-1}$$

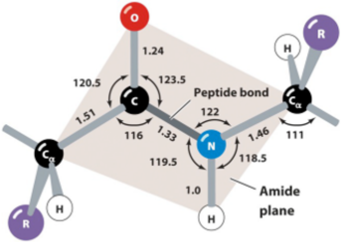


Figure 8-1
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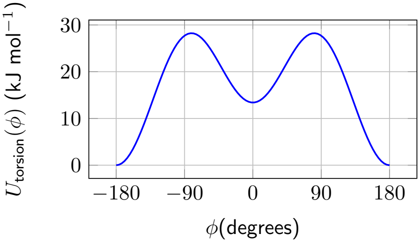


Electrostatic potential energy

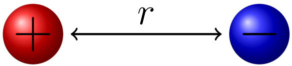
- Coulombic interactions between charged particles

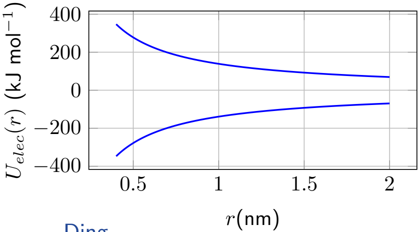
$$U_{\text{elec}} = \frac{1}{4\pi\epsilon_0}\frac{q_i q_j}{r_{ij}},$$

  where q_i and q_j are the charges of particles i and j, and r_{ij} is the distance between them

- when the units of charges, distances, and energies are elementary charge, nm, and kJ mol^{-1}

$$U_{\text{elec}} = 138.9 \cdot \frac{q_i q_j}{r_{ij}}$$





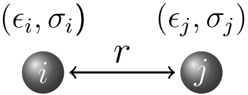
Van der Waals potential energy

- Lennard-Jones potential

$$U_{\mathsf{vdW}}(r_{ij}) = 4\epsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right],$$

  where ϵ_{ij} is the well depth and σ_{ij} is the distance at which the potential is zero

- Lorentz-Berthelot combining rules



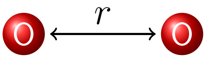
$$\epsilon_{ij} = \sqrt{\epsilon_i \epsilon_j}, \quad \sigma_{ij} = \frac{\sigma_i + \sigma_j}{2}$$

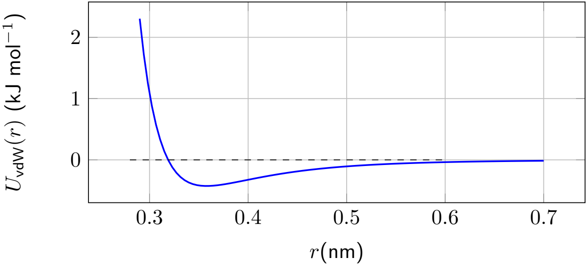
Van der Waals potential energy

- example O-O interaction between water molecules

$$\epsilon = 0.426768 \text{ kJ mol}^{-1}, \quad \sigma = 0.318799 \text{ nm}$$

- at what distance is the potential energy zero or minimum?
- attractive at long distances and repulsive at short distances





Range of interactions

- bond stretching, angle bending, and torsion are only among atoms that are bonded
- van der Waals and electrostatic interactions are among all pairs of atoms, excluding atoms that are connected by 1 and 2 bonds
- van der Waals interactions are short-ranged, reducing to zero much faster than Coulombic interactions
- Coulombic interactions are long-ranged, reducing to zero as $1/r$
- in practice, van der Waals interactions are often truncated at a cutoff distance
- because of the long-range nature of Coulombic interactions, special techniques are needed to evaluate them efficiently and accurately

Relative strength of interactions

- k_b for bond stretching is on the order of 10^5 kJ mol^{-1} nm^{-2}
- k_θ for angle bending is on the order of 10^2 kJ mol^{-1} rad^{-2}
- k_ϕ for torsion is on the order of 10^1 kJ mol^{-1}
- bonds are the stiffest, followed by angles, and then torsions
- in terms of fluctuations, the bond length fluctuates the least, followed by the angle, and then the torsion
- for many bonds and angles, their distributions can be well approximated by Gaussian distributions
- torsion distributions can be multimodal

Relative strength of interactions

- non-bonded interactions, such as van der Waals and electrostatic interactions, are much weaker than bonded interactions
- there are much more non-bonded interactions than bonded interactions
- electrostatic interactions are stronger than van der Waals interactions
- repulsive and attractive electrostatic interactions can partially cancel each other out when charges with opposite signs are close to each other, leading to a net weaker interaction

Outline

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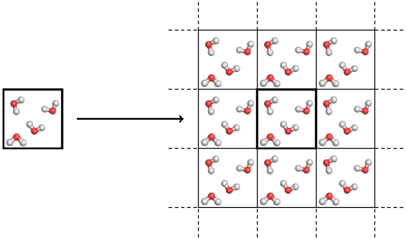
Periodic boundary conditions

- the number of atoms in a typical bulk system is on the order of 10^{23}
- that is far larger than what can be simulated with current computers
- the trick is to approximate a bulk system by a small system with *periodic boundary conditions*
- the small system is periodically replicated in all three dimensions

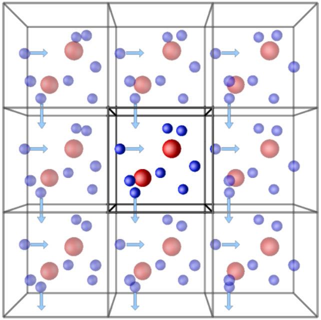
Periodic boundary conditions

- atoms in a relatively small *unit cell* are explicitly represented in the simulation
- the unit cell is replicated in all three dimensions, creating an infinite lattice; each atom in the unit cell is just one of many identical atoms in the lattice
- assume the unit cell is a box with side length L, an atom at position (x, y, z) means there are also same atoms at positions $(x + nL, y + mL, z + pL)$ for all integers n, m, and p



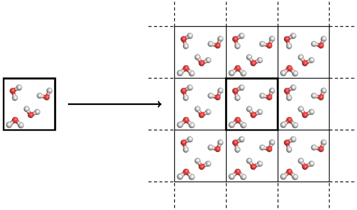
Periodic boundary conditions

- when an atom moves outside a unit cell, another copy of it enters the unit cell from the opposite side
- the unit cell can have any shape that can be replicated in all three dimensions to form a lattice, such as a cube, a rectangular box, or a parallelepiped, etc.
- in some applications, the unit cell is only replicated in one or two dimensions, creating a 1D or 2D lattice.
- 2D lattices are often used to model cell membranes



Nonbonded interactions in periodic boundary conditions

- an atom in a unit cell interact with other atoms in the same unit cell and with all atoms in all other unit cells
- van der Waals interactions are short-ranged and often truncated at a cutoff distance
- electrostatic interactions are long-ranged and using a cutoff distance can lead to substantial errors
- the Ewald summation method is used to evaluate long-range electrostatic interactions in a periodic system



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Commonly used all-atom classical force fields for biomolecules

- CHARMM (Chemistry at HARvard Macromolecular Mechanics)
- AMBER (Assisted Model Building with Energy Refinement)
- OPLS-AA/M force field for proteins

Software for computing potential energy and forces

- OpenMM
- CHARMM
- AMBER
- GROMACS
- NAMD