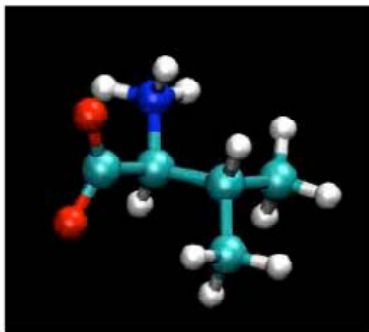
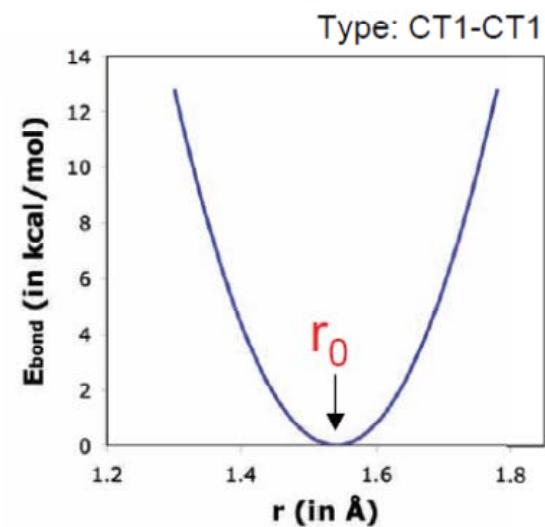


共价键：键长和键角

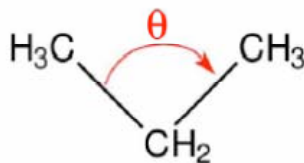
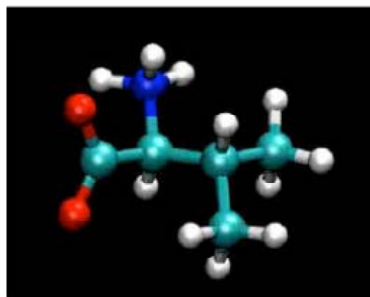
Bonds



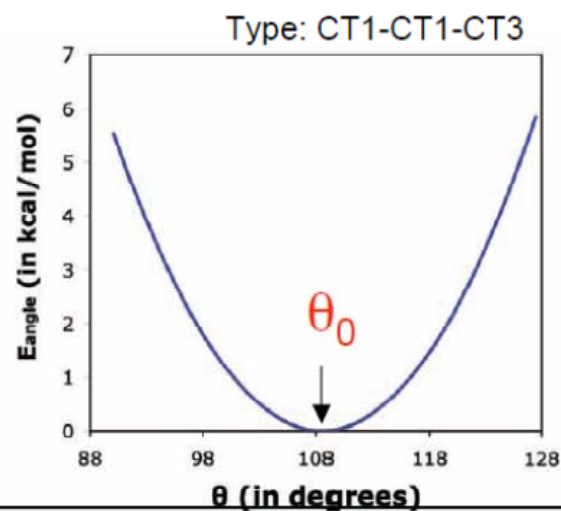
$$E_{\text{bond}} = K_b (r - r_0)^2$$



Angles

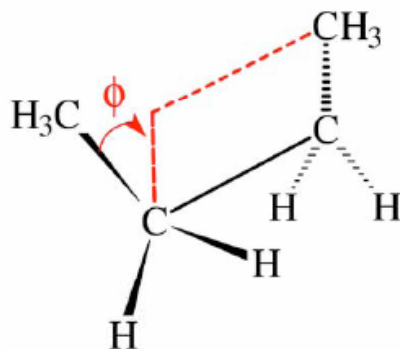
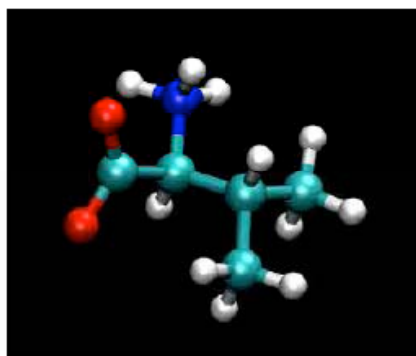


$$E_{\text{angle}} = K_{\theta} (\theta - \theta_0)^2$$

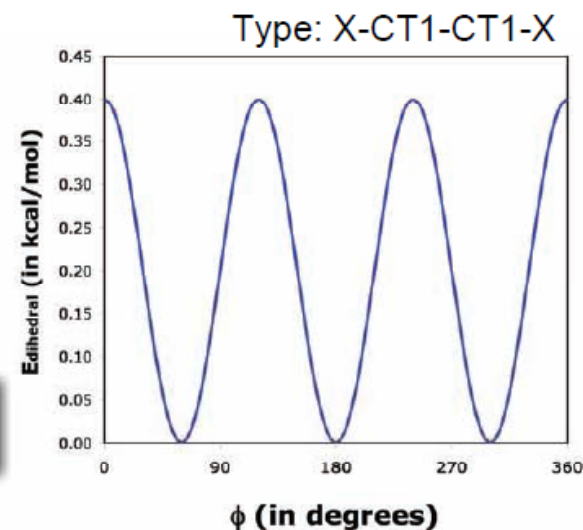


共价键：二面角和扭转角

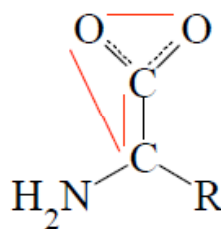
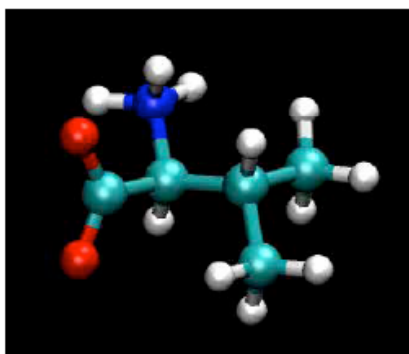
Dihedral angles



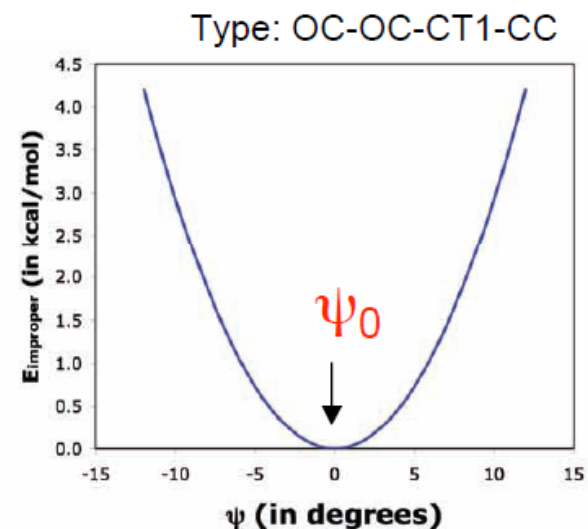
$$E_{\text{dihedral}} = K_{\phi} [1 + \cos(n\phi - \delta)]$$



Improper angles



$$E_{\text{improper}} = K_{\psi} (\psi - \psi_0)^2$$



非键相互作用：范德华力

Lennard-Jones potential :

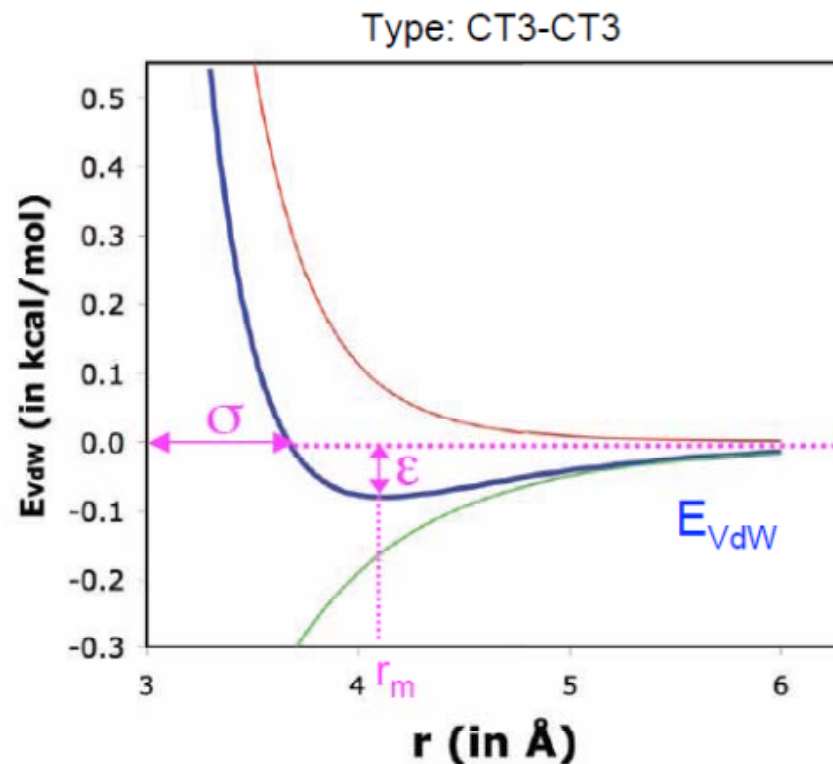
$$E_{\text{vdW}} = 4\varepsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^6 \right] = \varepsilon \left[\left(\frac{r_m}{r} \right)^{12} - 2 \left(\frac{r_m}{r} \right)^6 \right]$$

σ : collision parameter

ε : well depth

r_m : distance at min $r_m = 2^{1/6} \sigma$

Combination rule for two different atoms i, j : $r_m = r_{m,i} + r_{m,j}$ $\varepsilon = \sqrt{\varepsilon_i \varepsilon_j}$



Repulsive :
Pauli exclusion principle

$$\propto \frac{1}{r^{12}}$$

Attractive:
induced dipole / induced dipole

$$\propto -\frac{1}{r^6}$$

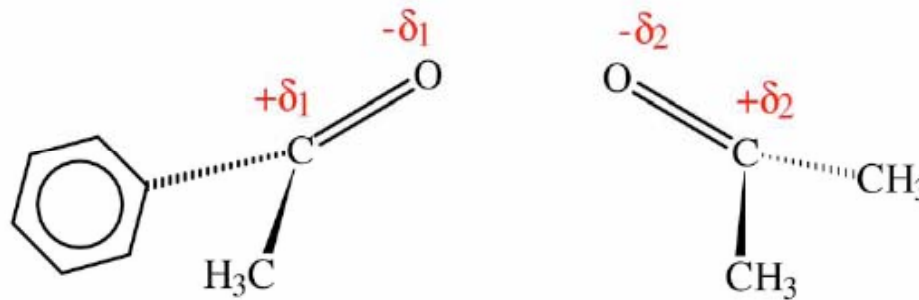
非键相互作用：静电力

Coulomb law

$$E_{\text{elec}} = \frac{q_i q_j}{4\pi\epsilon_0\epsilon r_{ij}}$$

where ϵ is the dielectric constant :

| | |
|------|-------------------|
| 1 | for vacuum, |
| 4-20 | for protein core, |
| 80 | for water |



The Coulomb energy decreases only as $1/r$

Despite dielectric shielding effects, it is a **long range interaction**

Special techniques to deal with this :

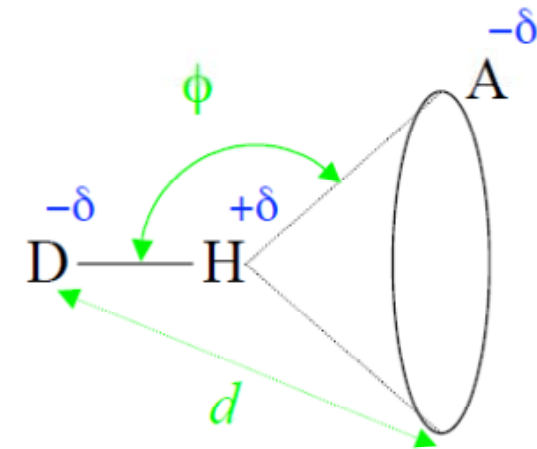
- PME : for systems with periodic boundary conditions
- Reaction Field : suppose homogeneous dielectric outside cutoff

衍生相互作用：氢键、斥水作用

Some interactions are often referred to as particular interactions, but they result from the two interactions previously described, i.e. the electrostatic and the van der Waals interactions.

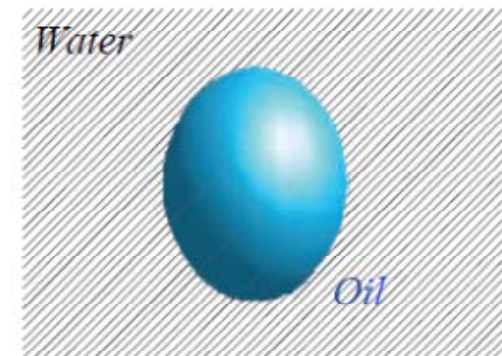
1) Hydrogen bonds (Hb)

- Interaction of the type $D-H \cdots A$
- The origin of this interaction is a dipole-dipole attraction
- Typical ranges for distance and angle:
 $2.4 < d < 4.5 \text{ \AA}$ and $180^\circ < \phi < 90^\circ$



2) Hydrophobic effect

- Collective effect resulting from the energetically unfavorable surface of contact between the water and an apolar medium (loss of water-water Hb)
- The apolar medium reorganizes to minimize the water exposed surface (compaction, association...)



总的相互作用能

$$E = \sum_{\text{bonds}} K_b (r - r_0)^2 + \sum_{\text{angles}} K_\theta (\theta - \theta_0)^2 + \sum_{\text{dihedrals}} K_\phi [1 + \cos(n\phi - \delta)] + \sum_{\text{impropers}} K_\psi (\psi - \psi_0)^2 \\ + \sum_{i>j} \epsilon \left[\left(\frac{r_m}{r} \right)^{12} - 2 \left(\frac{r_m}{r} \right)^6 \right] + \sum_{i>j} \frac{q_i q_j}{4\pi\epsilon_0 \epsilon r}$$

For a system with 1500 atoms

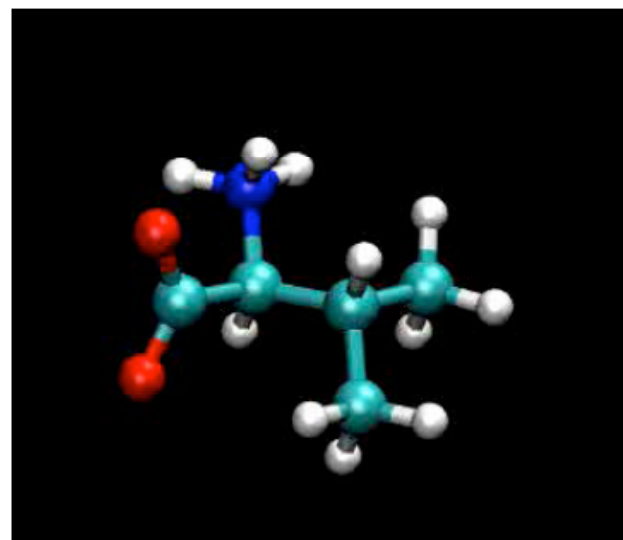


$\sim 10^6$ pairs of interacting atoms



Introduction of cutoff

N^2 的计算标度是不可接受的

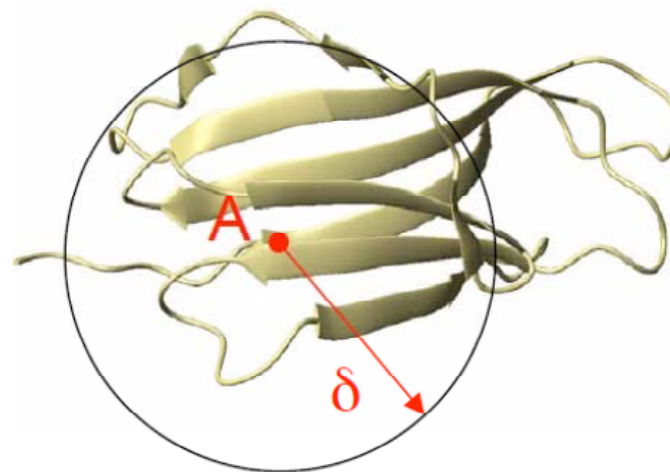


非键相互作用计算：Cutoff和Neighbour list

For an atom A, only non-bonded interactions with atoms within δ Å are calculated

➡ Non-bonded neighbour lists

Generally, $\delta = 8$ to 14 Å



Three cutoff schemes: strict, shift, switch

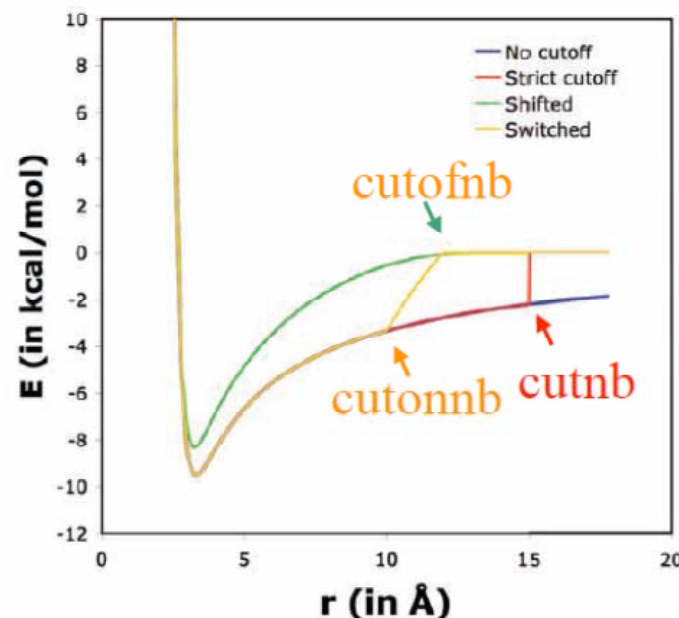
Shift and switch:

$$E'(r) = E(r) \times S(r)$$

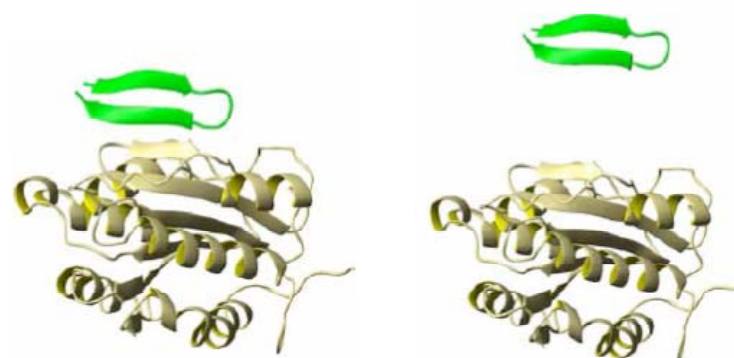
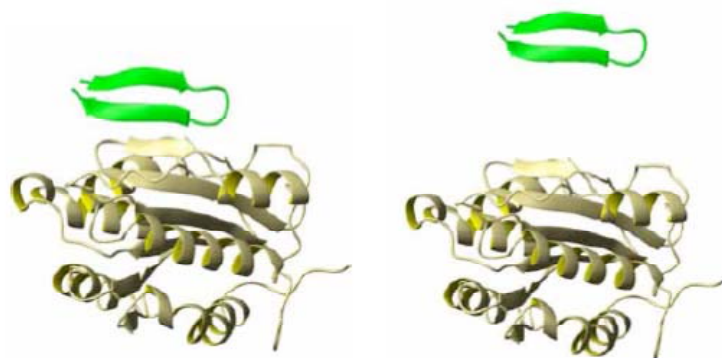
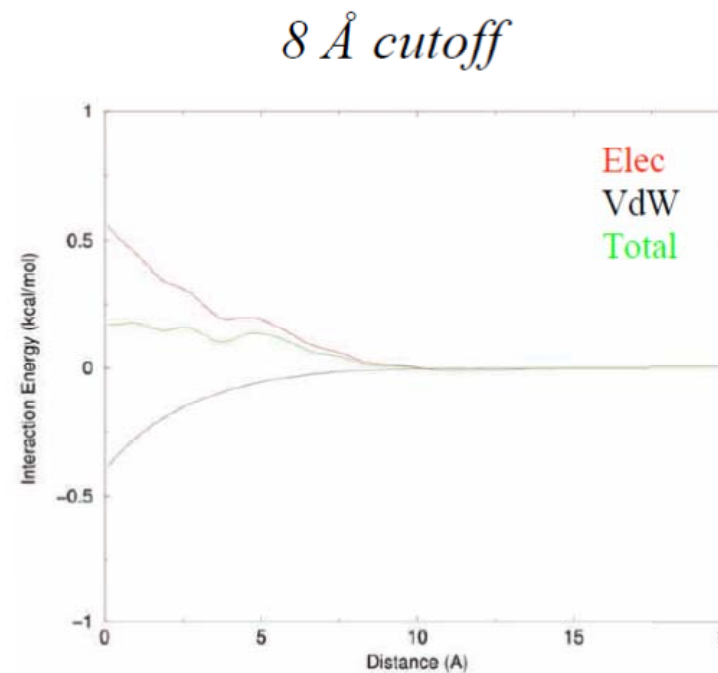
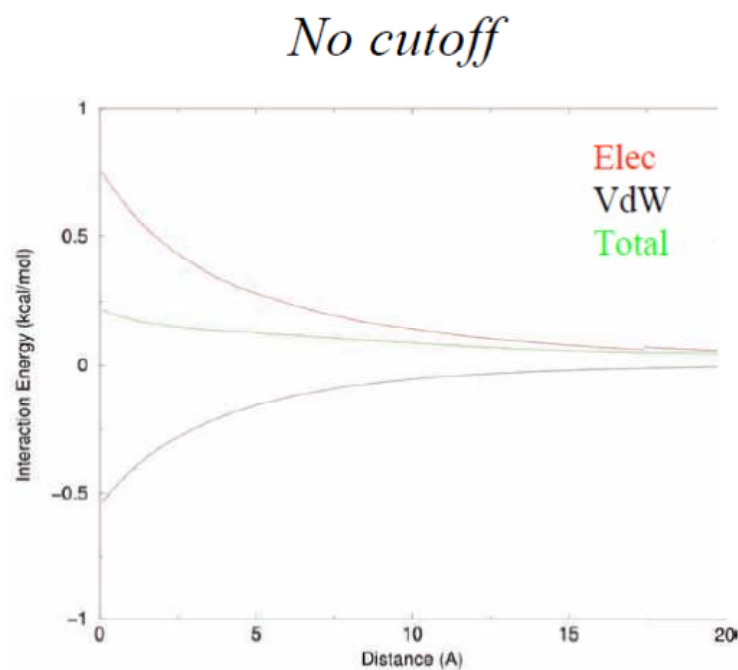
$S(r)$ differentiable

问题：静电相互作用是长程的！

Solution: Ewald summation



MD模拟需要指明Cutoff的大小



确定力场参数：实验、量化计算、经验

$$E = \sum_{\text{bonds}} K_b (r - r_0)^2 + \sum_{\text{angles}} K_\theta (\theta - \theta_0)^2 + \sum_{\text{dihedrals}} K_\phi [1 + \cos(n\phi - \delta)] + \sum_{\text{impropers}} K_\psi (\psi - \psi_0)^2 + \sum_{i>j} 4\epsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^6 \right] + \sum_{i>j} \frac{q_i q_j}{4\pi\epsilon_0\epsilon r}$$

| Type of data | Type of system | Phase | Type of properties | Force field parameters |
|---|---------------------------------|-------------------------|---|---|
| structural data (exp.) | small molecules | crystalline solid phase | molecular geometry: bond lengths, angles | r_0, θ_0, ψ_0 |
| spectroscopic data (exp.) | small molecules | gas phase | intra-molecular vibrations: force constants | K_b, K_θ, K_ψ |
| quantum-chemical calculations : energy profiles (theor.) | small molecules | gas phase | torsional-angle rotational profiles | K_ϕ, δ, n |
| quantum-chemical calculations : electron densities (theor.) | small molecules | gas phase | atom charges | charges q_i (initial) |
| thermodynamic data (exp.) | molecules in solution, mixtures | condensed phase | heat of vaporisation, density, free energy of solvation | v. d. Waals : σ_i, ϵ_i charges q_i (final) |
| dielectric data (exp.) | small molecules | condensed phase | dielectric permittivity, relaxation | charges q_i |
| transport data (exp.) | small molecules | condensed phase | transport coefficients: diffusion, viscosity | v. d. Waals : σ_i, ϵ_i charges q_i |

数值方法求解牛顿方程

Newton's law of motion:

$$F_i = m_i a_i = - \frac{dE_i}{dr_i}$$

In discrete time : integration algorithm.

Example: Verlet algorithm

$$r(t + \delta t) = r(t) + v(t) \times \delta t + \frac{1}{2} a(t) \times \delta t^2$$

$$r(t - \delta t) = r(t) - v(t) \times \delta t + \frac{1}{2} a(t) \times \delta t^2$$

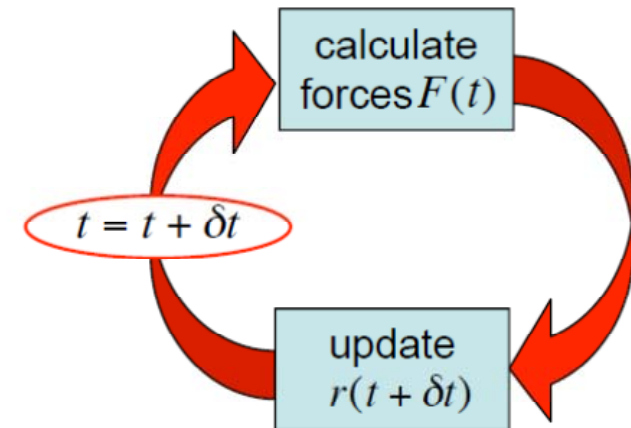
➔

$$r(t + \delta t) = 2r(t) - r(t - \delta t) + \frac{F(t)}{m} \times \delta t^2$$

Propagation of time: position at time $t+\delta t$ is determined by position at time t and $t-\delta t$, and by the acceleration at time t (i.e., the forces at time t)

The equations of motion are deterministic, e.g., the positions and the velocities at time zero determine the positions and velocities at all other times, t .

MD algorithm



$$\delta t \sim 1 \text{ fs} = 10^{-15} \text{ s}$$

外界条件1： 溶剂化效应

Fundamental influence on the structure, dynamics and thermodynamics of biological molecules

Effect through:

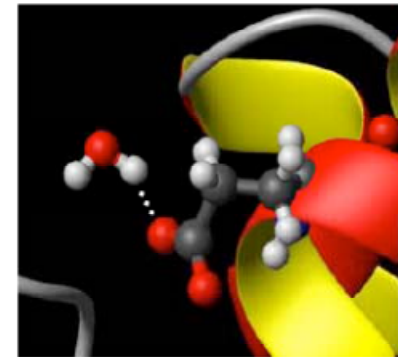
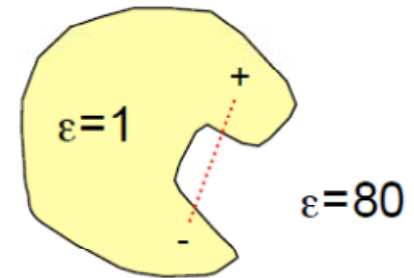
- Solvation of charge
- Screening of charge - charge interactions

$$E_{\text{elec}} = \frac{q_i q_j}{4\pi\epsilon_0\epsilon(r) r}$$

- Hydrogen bonds between water molecules and polar functions of the solute

Taken into account via:

- ☐ Explicit solvation. Water molecules are included.
 - Stochastic boundary conditions
 - Periodic boundary conditions
- ☐ Implicit solvation. Water effect is modeled.
 - Screening constant
 - Implicit solvation models (Poisson Boltzmann, Generalized Born)



隱式溶劑模型

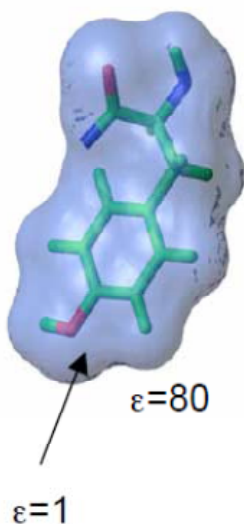
Screening constant

$$\epsilon = Nr$$

N=4,8. The dielectric constant is a function of atom distance.
Mimic screening effect of solvent. Simple, unphysical but efficient.

In CHARMM: `NBOND RDIE EPS 4.0`

Implicit solvent models



- Poisson Boltzmann (PB) equation.

$$\nabla \cdot \{ \epsilon(r) \nabla \phi(r) \} - \kappa' \sinh[\phi(r)] = -4\pi\rho(r)$$

$\phi(r)$: electrostatic potential,
 $\rho(r)$: charge density

Equation solved numerically. Very time consuming.
In CHARMM: PBEQ module.

- Generalized born (GB) equation.

$$G_{elec} = \sum_{i>j} \frac{q_i q_j}{4\pi\epsilon_0 r} - \underbrace{\frac{1}{2} \left(1 - \frac{1}{\epsilon} \right) \sum_i \sum_j \frac{q_i q_j}{\sqrt{r^2 + a_i a_j} \exp(-r^2/4a_i a_j)}}_{\text{solvation energy}}$$

a_i : Born radius

Others: EEF1, SASA, etc...

Explicit hydrogen bonds with water molecules are lost!