

# 显式溶剂模型

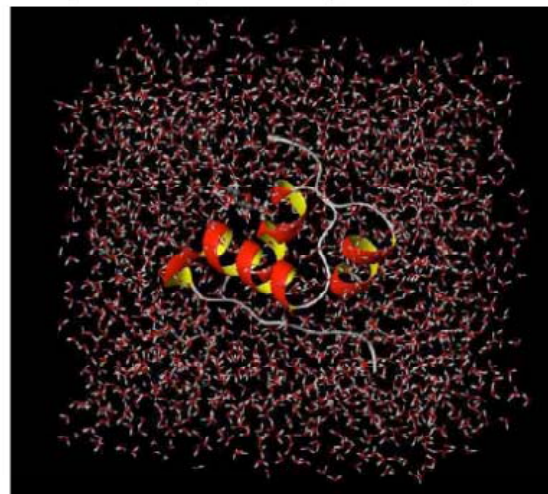
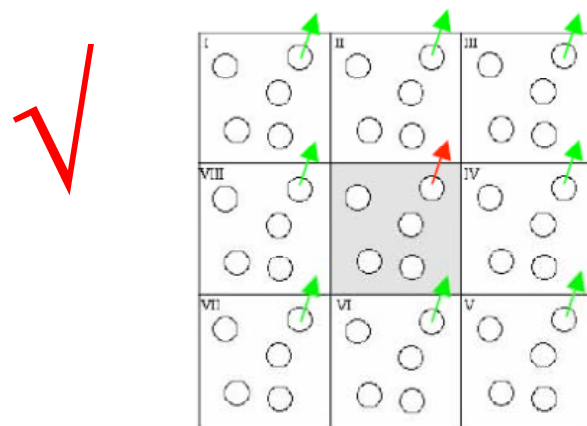
## Stochastic boundary conditions

The region of interest is solvated in a water sphere at 1atm. The water molecules are submitted to an additional force field that restrain them in the sphere while maintaining a strong semblance to bulk water.

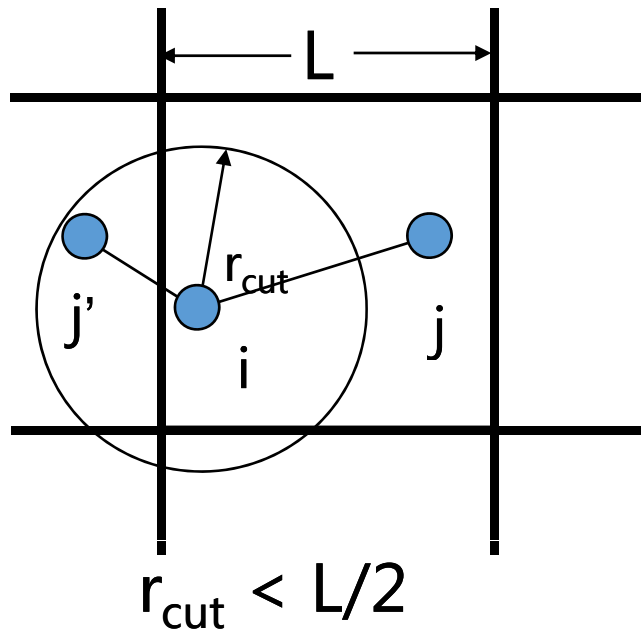


## Periodic boundary conditions

The fully solvated central cell is simulated, in the environment produced by the repetition of this cell in all directions.



# 周期性边界条件：Minimum Image原则

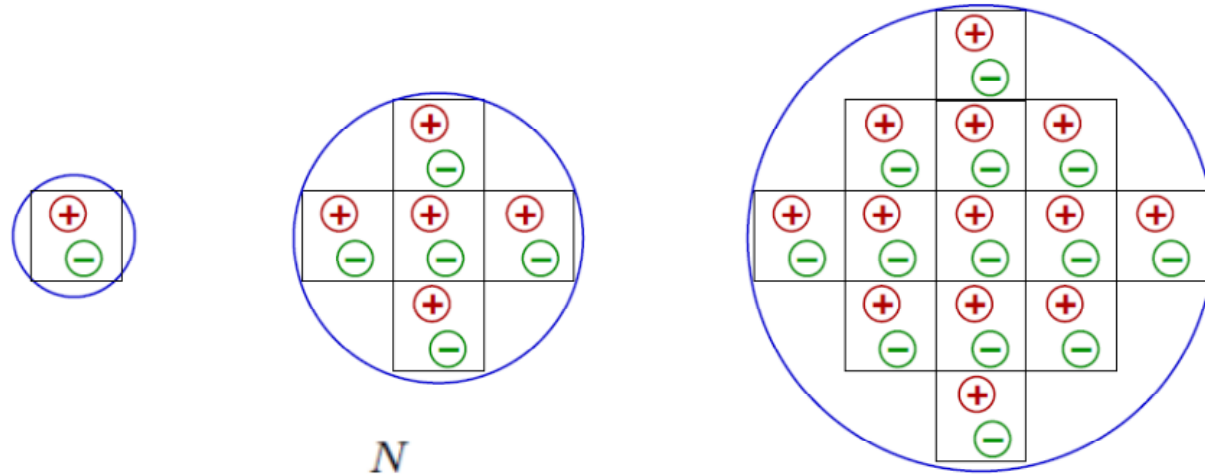


Use  $r_{ij'}$  not  $r_{ij}$

$$x_{ij} = x_{ij} - L * \text{Nint}(x_{ij}/L)$$

$\text{Nint}(a)$ =nearest integer to  $a$

# 周期性边界条件下的静电作用：Ewald Sum

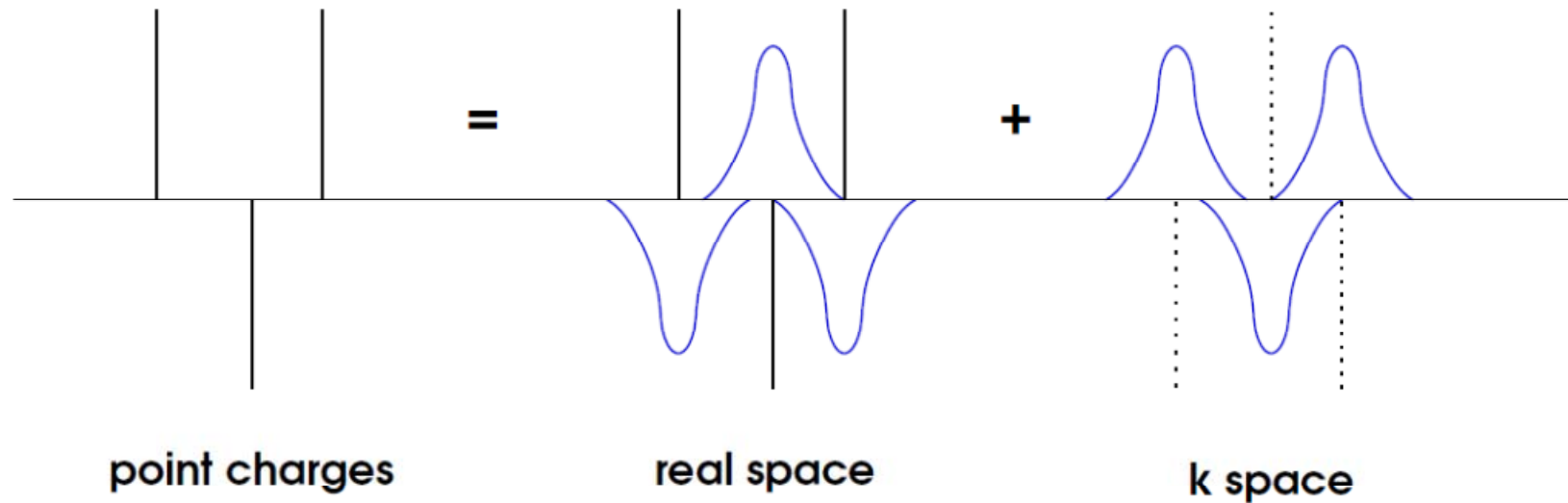


$$V_s(r_i) = \sum_n' \sum_{j=1}^N \frac{q_j}{|r_{ij} + n|}$$

n=2L

1. 长程的静电相互作用包含所有周期格子的贡献，不只是 Minimum Image
2. 静电相互作用的收敛是有条件的，tin-foil

3. Ewald sum是借助于实空间和K空间两部分来实现的，  
计算量标度为NlogN

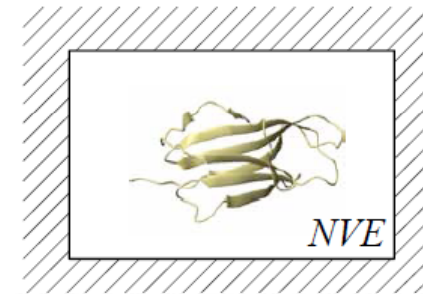


$$V_E(r_i) = \sum_{\mathbf{n}} ' \sum_{j=1}^N q_j \frac{\text{erfc}(\alpha |\mathbf{r}_{ij} + \mathbf{n}|)}{|\mathbf{r}_{ij} + \mathbf{n}|} + \frac{4\pi}{L^3} \sum_{\mathbf{k} \neq 0} \sum_j q_j \exp\left(\frac{-|\mathbf{k}|^2}{4\alpha^2}\right) \exp\{i\mathbf{k} \cdot (\mathbf{r}_j - \mathbf{r}_i)\} - \frac{2\alpha}{\pi^{1/2}} q_i$$

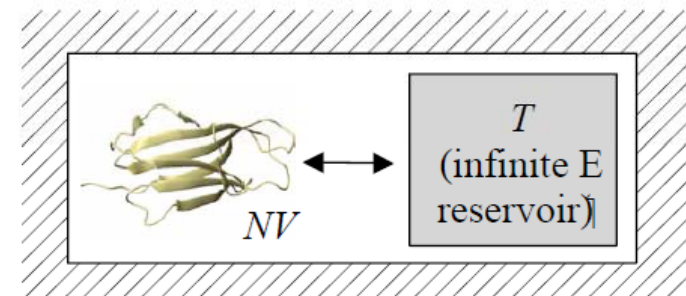
4. 静电相互作用的处理在MD模拟中很重要！

# 外界条件2：热力学条件

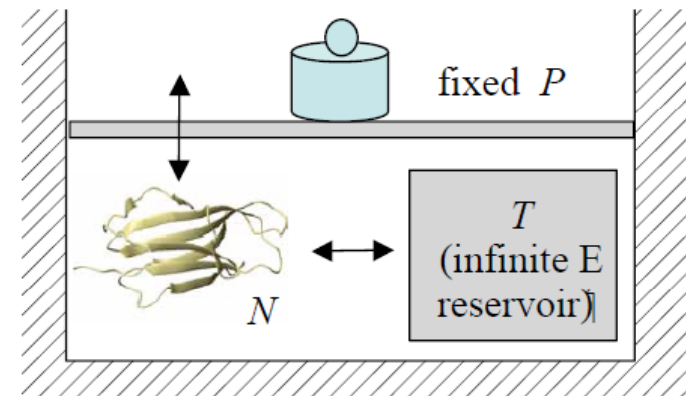
- 1) **Microcanonical ensemble** (constant  $N, V, E$ )  
sampling is obtained by simple integration of the Newtonian dynamics:  
- Verlet, Leap-Frog, Velocity Verlet, Gear



- 2) **Canonical ensemble** (constant  $N, V, T$ )  
sampling is obtained using thermostats :
- 1) **Berendsen**: scaling of velocities to obtain an exponential relaxation of the temperature to  $T$
  - 2) **Nose-Hoover**: additional degree of freedom coupled to the physical system acts as heat bath.



- 3) **Isothermic-isobaric ensemble** (constant  $N, P, T$ )  
In addition to the thermostat, the volume of the system is allowed to fluctuate, and is regulated by barostat algorithms.



# Nose-Hoover 恒温热耦

Phase space extended by two extra variables :

$$\underbrace{(r, p)}_{\text{physical variables}}, \eta, p_\eta$$

$$\begin{aligned} \dot{r}_i &= \frac{p_i}{m_i} && \leftarrow \text{Newton} \\ \dot{p}_i &= -\frac{\partial \Phi}{\partial r_i}(r, t) - \frac{p_\eta}{Q} p_i && \leftarrow \text{friction term} \\ \dot{\eta} &= \frac{p_\eta}{Q} \\ \dot{p}_\eta &= \sum_i \frac{p_i^2}{m_i} - N_{df} k_B T && \leftarrow \text{temperature regulation} \end{aligned}$$

- One can demonstrate that the **canonical distribution is reproduced** for the physical variables

$$Z(N, V, T) = \int dr dp e^{-\beta H(r, p)}$$

- Conserved quantity :

$$H'(\Gamma, t) = \sum_{i=1}^N \frac{p_i^2}{2m_i} + \Phi(r) + \frac{p_\eta^2}{2Q} + k_B T \bar{\eta}$$

- Non-Hamiltonian** dynamics...



# 朗之万动力学

## Langevin Dynamics (LD)

In Langevin Dynamics, two additional forces are added to the standard force field:

- a *friction* force:  $-\gamma p_i$   
whose direction is opposed to the velocity of atom  $i$
- a *stochastic* (random) force:  $\zeta(t)$  such that  $\langle \zeta(t) \rangle = 0$ .

This leads to the following equation for the motion of atom  $i$ :

$$\dot{r}_i = \frac{p_i}{m_i} \quad \dot{p}_i = F_i(r) + \gamma p_i + \zeta(t)$$

This equation can for example simulate the friction and stochastic effect of the solvent in implicit solvent simulations. The temperature is adjusted via  $\gamma$  and  $\zeta$ , using the *dissipation-fluctuation* theorem.

The stochastic term can improve barrier crossing and hence sampling.

LD does *not* reproduce dynamical properties

# 分子动力学模拟发展历史

## Theoretical milestones:

Newton (1643-1727):	Classical equations of motion: $F(t)=m a(t)$
Boltzmann(1844-1906):	Foundations of statistical mechanics
Schrödinger (1887-1961):	Quantum mechanical eq. of motion: $-i\hbar \partial_t \Psi(t)=H(t) \Psi(t)$

## Molecular mechanics milestones:

Metropolis (1953):	First Monte Carlo (MC) simulation of a liquid (hard spheres)	<i>Liquids</i>
Wood (1957):	First MC simulation with Lennard-Jones potential	
Alder (1957):	First Molecular Dynamics (MD) simulation of a liquid (hard spheres)	
Rahman (1964):	First MD simulation with Lennard-Jones potential	
Karplus (1977) & McCammon (1977)	First MD simulation of proteins	<i>Proteins</i>
Karplus (1983):	The CHARMM general purpose FF & MD program	
Kollman(1984):	The AMBER general purpose FF & MD program	
Car-Parrinello(1985):	First full QM simulations	
Kollmann(1986):	First QM-MM simulations	



# 常用分子动力学模拟软件、力场

Package name

supported force fields

- CHARMM

[www.charmm.org](http://www.charmm.org)

CHARMM (E / I; AA / UA), Amber

- Amber

[amber.scripps.edu](http://amber.scripps.edu)

Amber (E / I ; AA)

- GROMOS

[www.igc.ethz.ch/GROMOS](http://www.igc.ethz.ch/GROMOS)

Gromos (E / vacuum ; UA)

- Gromacs

[www.gromacs.org](http://www.gromacs.org)

Amber, Gromos, OPLS - (all E)

- NAMD

[www.ks.uiuc.edu/Research/namd](http://www.ks.uiuc.edu/Research/namd)

CHARMM, Amber, Gromos, ...

E = explicit solvent

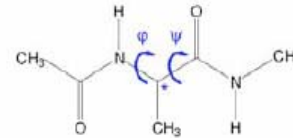
I = implicit solvent

AA = all atom

UA = united atom (apolar H omitted)

# MD模拟的输入文件

## 1) Topological properties:



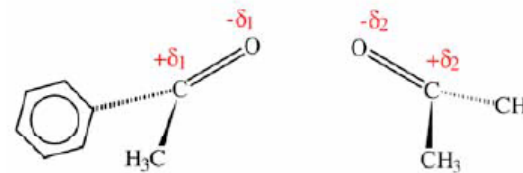
description of the covalent **connectivity** of the molecules to be modeled

## 2) Structural properties:



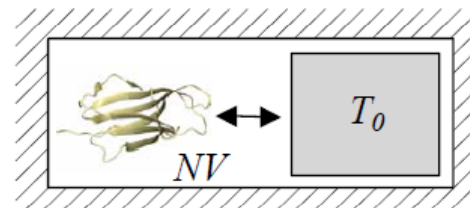
the starting **conformation** of the molecule, provided by an X-ray structure, NMR data or a theoretical model

## 3) Energetical properties:



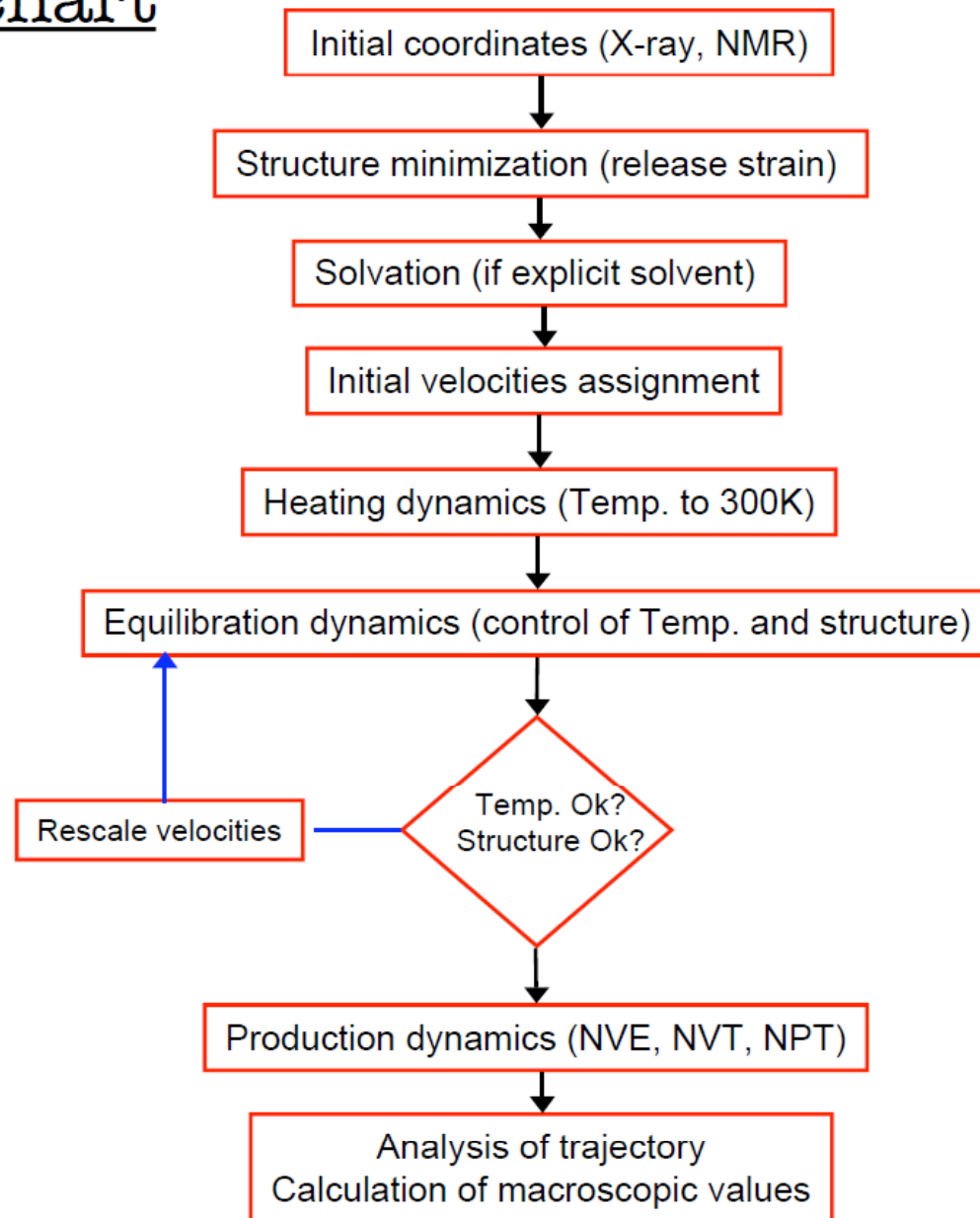
a **force field** describing the force acting on each atom of the molecules

## 4) Thermodynamical properties:



a sampling **algorithm** that generates the thermodynamical ensemble that matches experimental conditions for the system, e.g.  $N, V, T$ ,  $N, P, T$ , ...

# MD flowchart



# 各态历经假设：时间平均=系综平均

The *ergodic hypothesis* is that the **ensemble averages** used to compute expectation values can be **replaced by time averages** over the simulation.

$$\begin{aligned} \langle O \rangle_{ensemble} &\stackrel{\text{Ergodicity}}{=} \langle O \rangle_{time} \\ \frac{1}{Z} \int O(r, p) e^{-\beta E(r, p)} dr dp &= \frac{1}{\tau} \int_0^\tau O(t) dt \end{aligned}$$

The microstates sampled by molecular dynamics are usually a small subset of the entire thermodynamical ensemble.

The validity of this hypothesis depends on the quality of the sampling produced by the molecular modelling technique. The sampling should reach all important minima and explore them with the correct probability,

- <i>NVE</i> simulations	⇔	Microcanonic ensemble	⇔ $P = cst.$
- <i>NVT</i> simulations	⇔	Canonical ensemble	⇔ $P(E) = e^{-\beta E}$
- <i>NPT</i> simulations	⇔	Isothermic-isobaric ensemble	⇔ $P(E) = e^{-\beta(E+PV)}$

Note that the Boltzmann weight  $e^{-\beta E}$  is not present in the time average because it is assumed that conformations are sampled from the right probability.