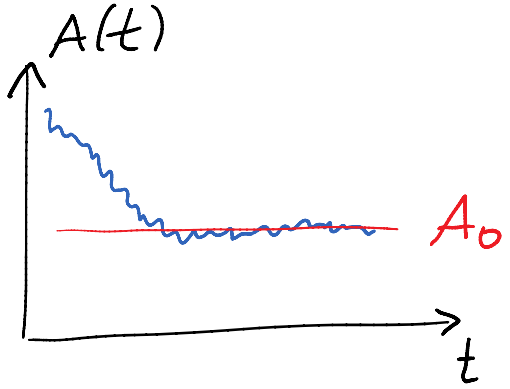
判断趋向平衡

$$A(t) = A_0 + C e^{-t/\tau_{eq}}$$

A(t) short time average to eliminate fluctuations)

What is τ_{eq} , i.e. how long do we have to wait? Hard to know a priori.



常见的热力学性质计算

- Thermodynamic Properties
  - Kinetic Energy:

$$\langle K.E. \rangle = \left\langle \frac{1}{2} \sum_{i}^{N} m_i v_i^2 \right\rangle$$

  - Temperature:

$$T = \frac{2}{3Nk_B} \langle K.E. \rangle$$

- Configuration Energy:

$$U_c = \left\langle \sum_i \sum_{j>i}^{N} V(r_{ij}) \right\rangle$$

- Pressure:

$$PV = Nk_BT - \frac{1}{3}\left\langle \sum_{i=1}^{N-1} \sum_{j>i}^{N} \vec{r}_{ij} \cdot \vec{f}_{ij} \right\rangle$$

- Specific Heat

$$\left\langle \delta(U_c)^2 \right\rangle_{NVE} = \frac{3}{2} Nk_B^2 T^2 \left(1 - \frac{3Nk_B}{2C_v}\right)$$

结构性质

- Structural Properties
  - Pair correlation (Radial Distribution Function):

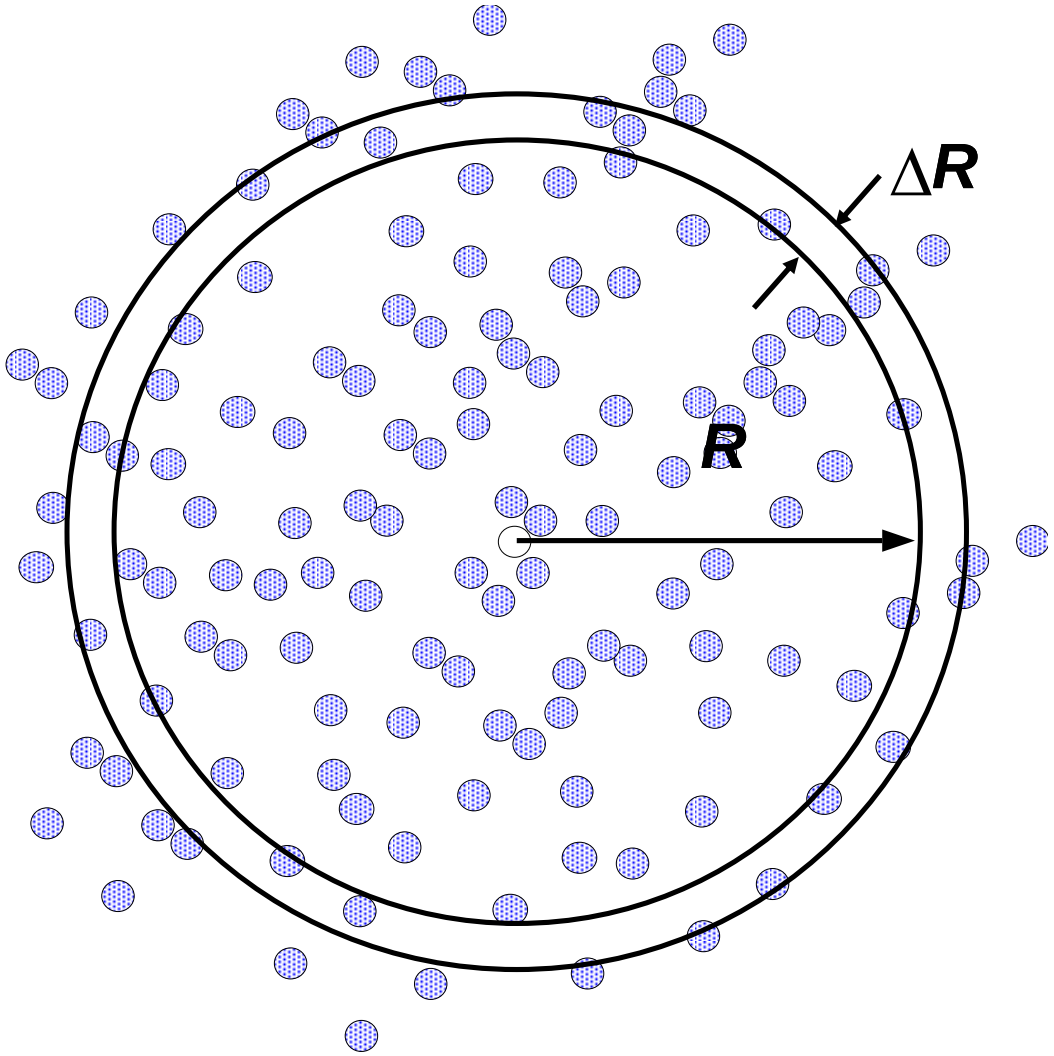
$$g(r) = \frac{\langle n(r) \rangle}{4\pi\rho r^2 \Delta r} = \frac{V}{N^2} \left\langle \sum_i \sum_{j \neq i}^{N} \delta(r - r_{ij}) \right\rangle$$

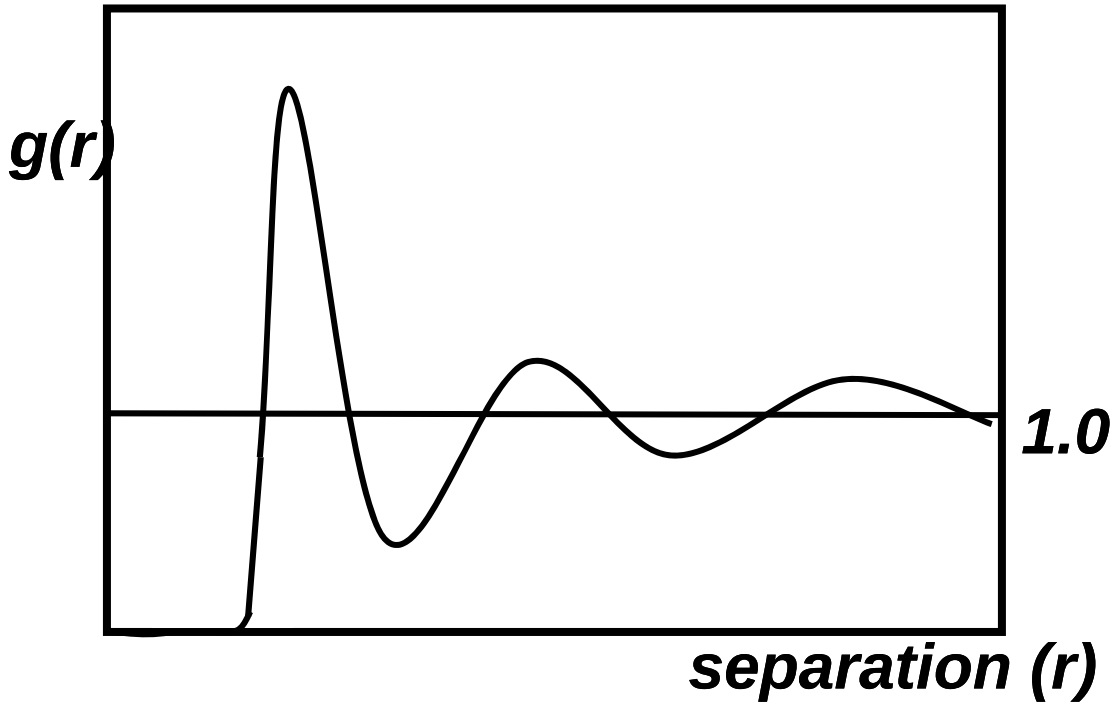
  - Structure factor:

$$S(k) = 1 + 4\pi\rho \int_0^\infty \frac{\sin(kr)}{kr} \big(g(r) - 1\big) r^2 dr$$

Note: S(k) available from x-ray diffraction

径向分布函数
Radial Distribution Function





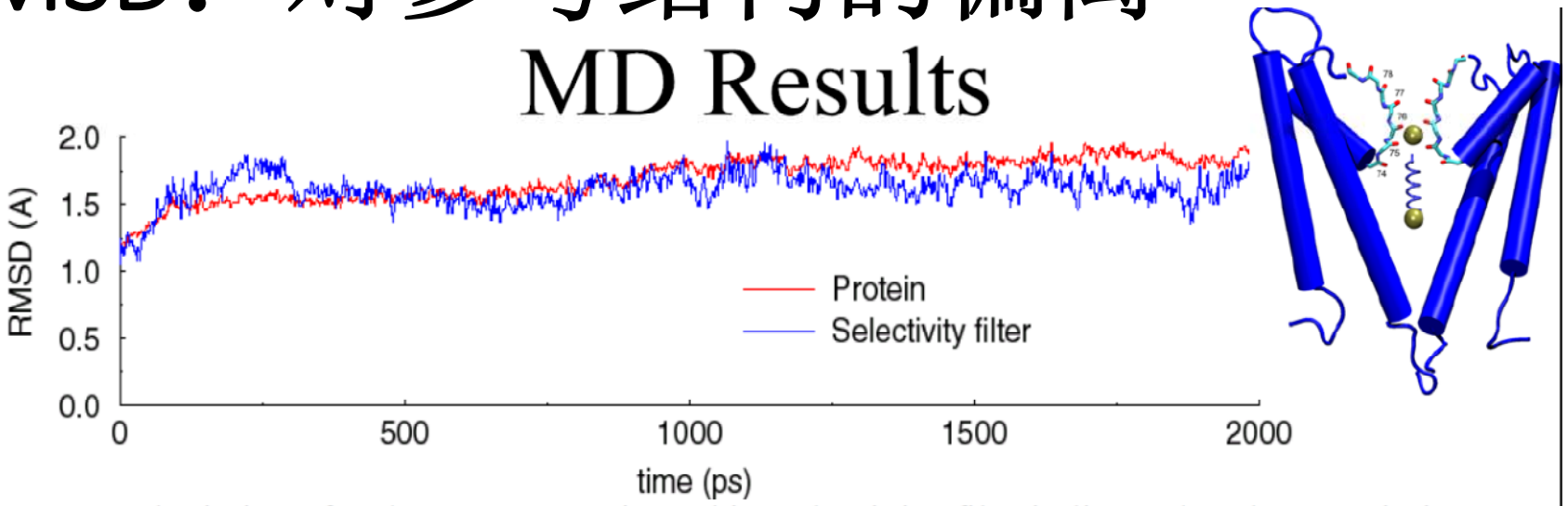
Particles independent, uniformly distributed:

$$\langle \delta(\vec{r} - \vec{r}_{ij}) \rangle = \frac{1}{V} \int d^3 r_{ij}\, \delta(\vec{r} - \vec{r}_{ij}) = \frac{1}{V}$$

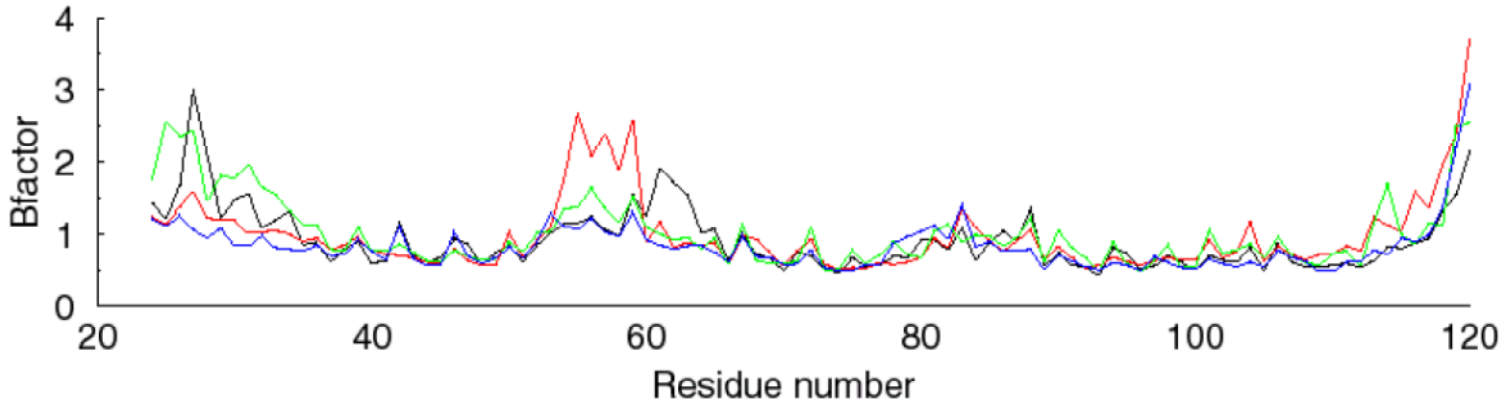
$$g(\vec{r}) = \frac{V}{N} \frac{1}{N} \sum_i \sum_{j \neq i} \frac{1}{V} = \frac{1}{N^2} N(N-1) \longrightarrow 1$$

Any deviation from 1 describes correlations between particles!

RMSD：对参考结构的偏离



RMS deviations for the KcsA protein and its selectivity filer indicate that the protein is stable during the simulation with the selectivity filter the most stable part of the system.



Temperature factors for individual residues in the four monomers of the KcsA channel protein indicate that the most flexible parts of the protein are the N and C terminal ends, residues 52-60 and residues 84-90. Residues 74-80 in the selectivity filter have low temperature factors and are very stable during the simulation.

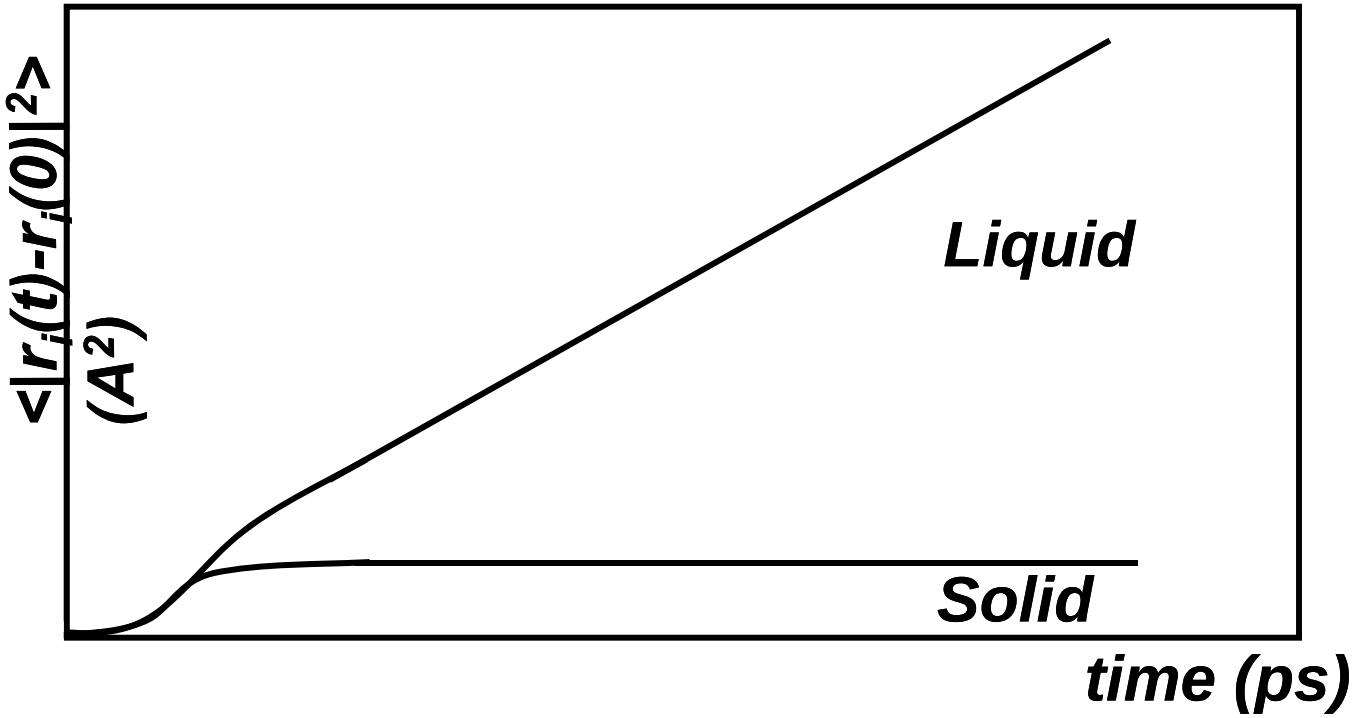
扩散系数

Mean squared displacement (Einstein relation)

$$2Dt = \frac{1}{3}\left\langle \left| \mathbf{r}_i(t) - \mathbf{r}_i(0) \right|^2 \right\rangle$$

Velocity Autocorrelation (Green-Kubo relation)

$$D = \frac{1}{3}\int_0^\infty \left\langle \mathbf{v}_i(t) \cdot \mathbf{v}_i(0) \right\rangle dt$$



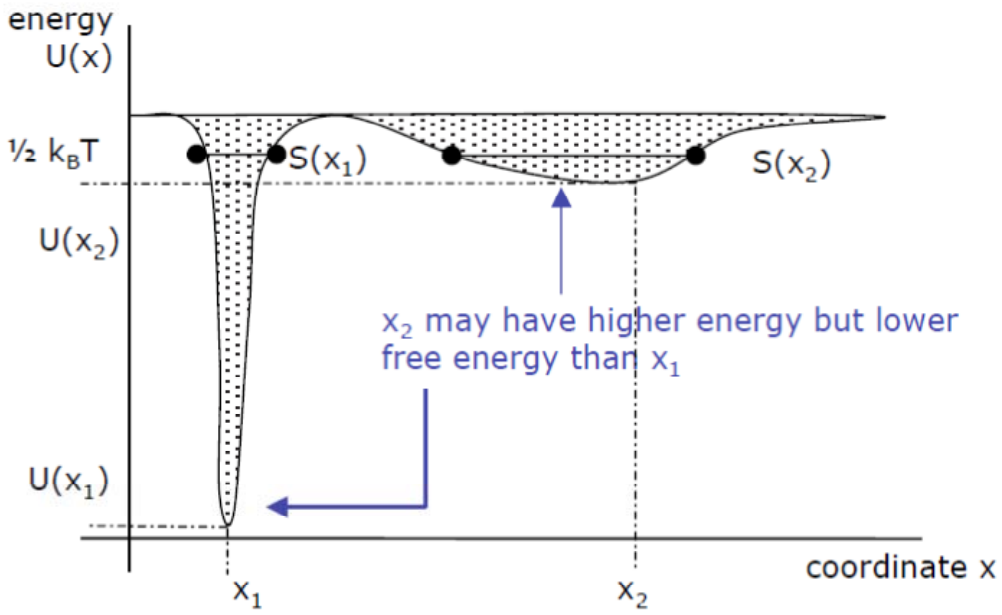
自由能计算：熵的作用

Mechanics: A state is characterised by ***one*** **minimum energy structure** (global minimum)

Statistical mechanics: A state is characterised by ***an ensemble*** **of structures**

Very small energy differences between states (~k_BT = 2.5 kJ/mol) resulting from summation over very many contributions

Entropic effects : Not only energy minima are of importance but whole range of x-values with energies ~k_BT

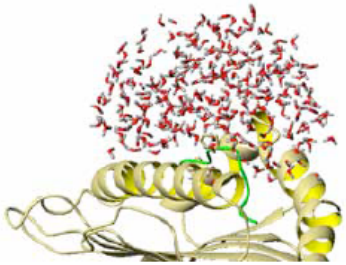


The free energy (F) governs the system

$F = U - TS$

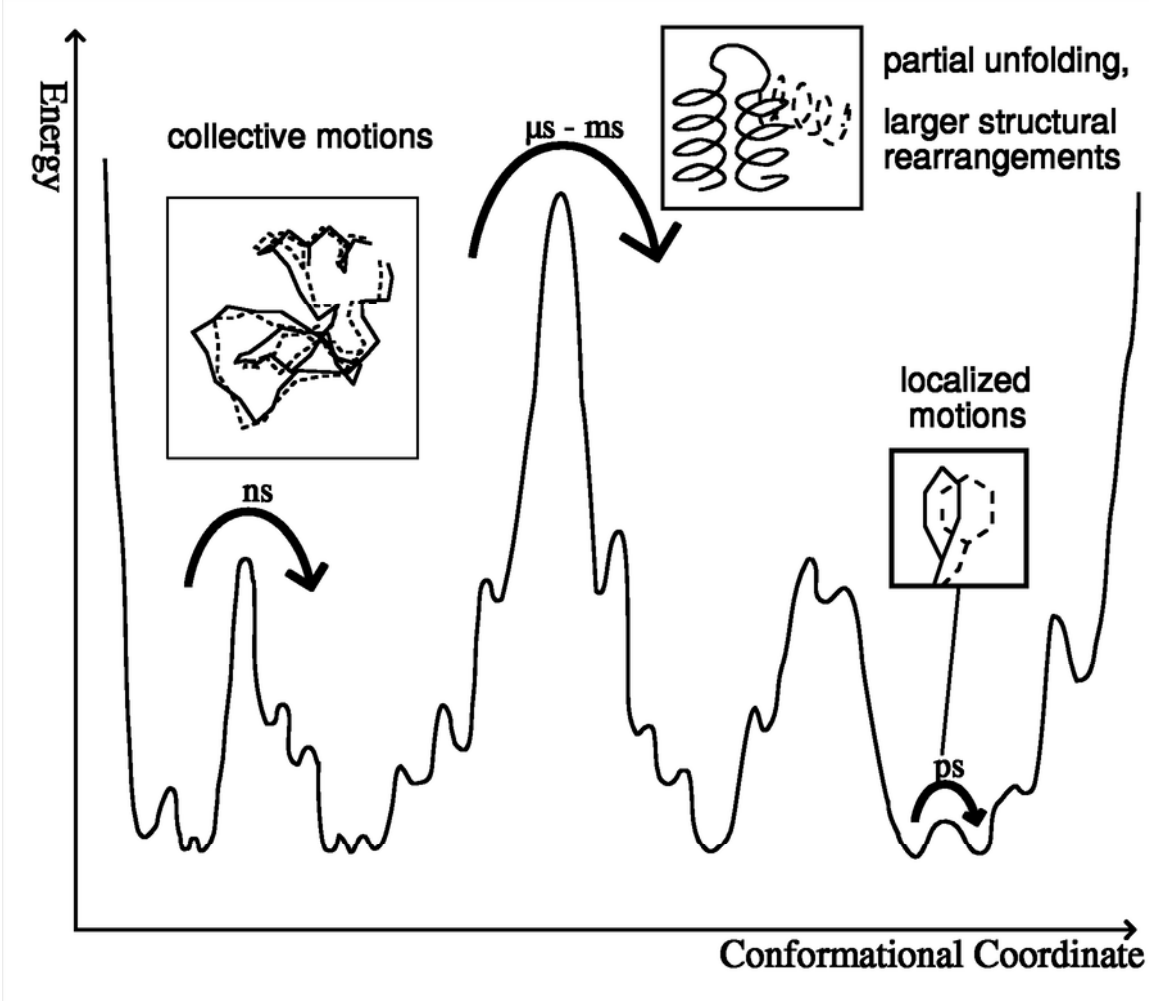
Energy (U) – entropy (S) compensation at finite temperature T

MD模拟局限性1：相互作用精度

Problems	Solutions
1) **Fixed set of atom types**	
2) **No electronic polarization:** - fixed partial charges allow for *conformational* polarization but not *electronic* polarization 	• Fluctuating charges treated as dynamical parameters • Charges on springs representing e^- clouds • QM-MM • Full QM simulations
3) **Quadratic form of potentials:** - problematic far from equilibrium values - no bond creation or deletion 	• QM-MM • Full QM simulations

•更加精确的相互作用模型
•多尺度方法

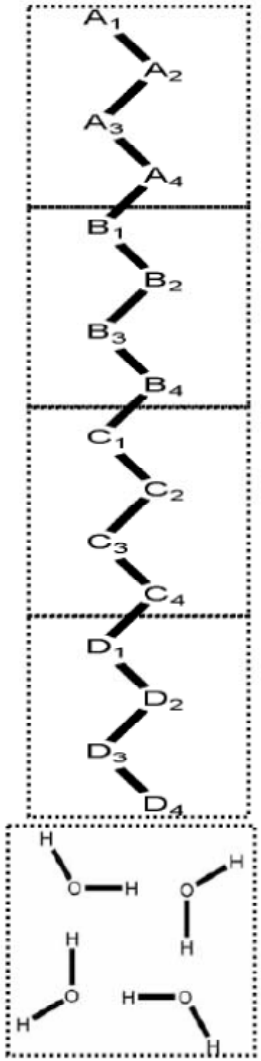
MD模拟局限性2：时间尺度



- 增强抽样方法
- 粗粒化模型、多尺度方法

粗粒化模型

All-atom model
16 (CH_2 or CH_3) atoms



Map
to all-atom configurations

Centre of mass
$A_1 - A_4$

Centre of mass
$B_1 - B_4$

Centre of mass
$C_1 - C_4$

Centre of mass
$D_1 - D_4$

Centre of mass
$W_1 - W_4$

Coarse-grained model
4 atoms