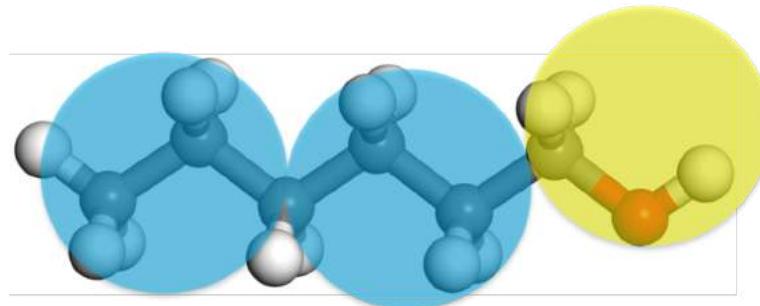


工业中的多尺度力学方法讲习班，清华大学，2021.1.10-15

粗粒化计算方法

施兴华
2021.1.14





一、粗粒化原理

二、耗散粒子动力学

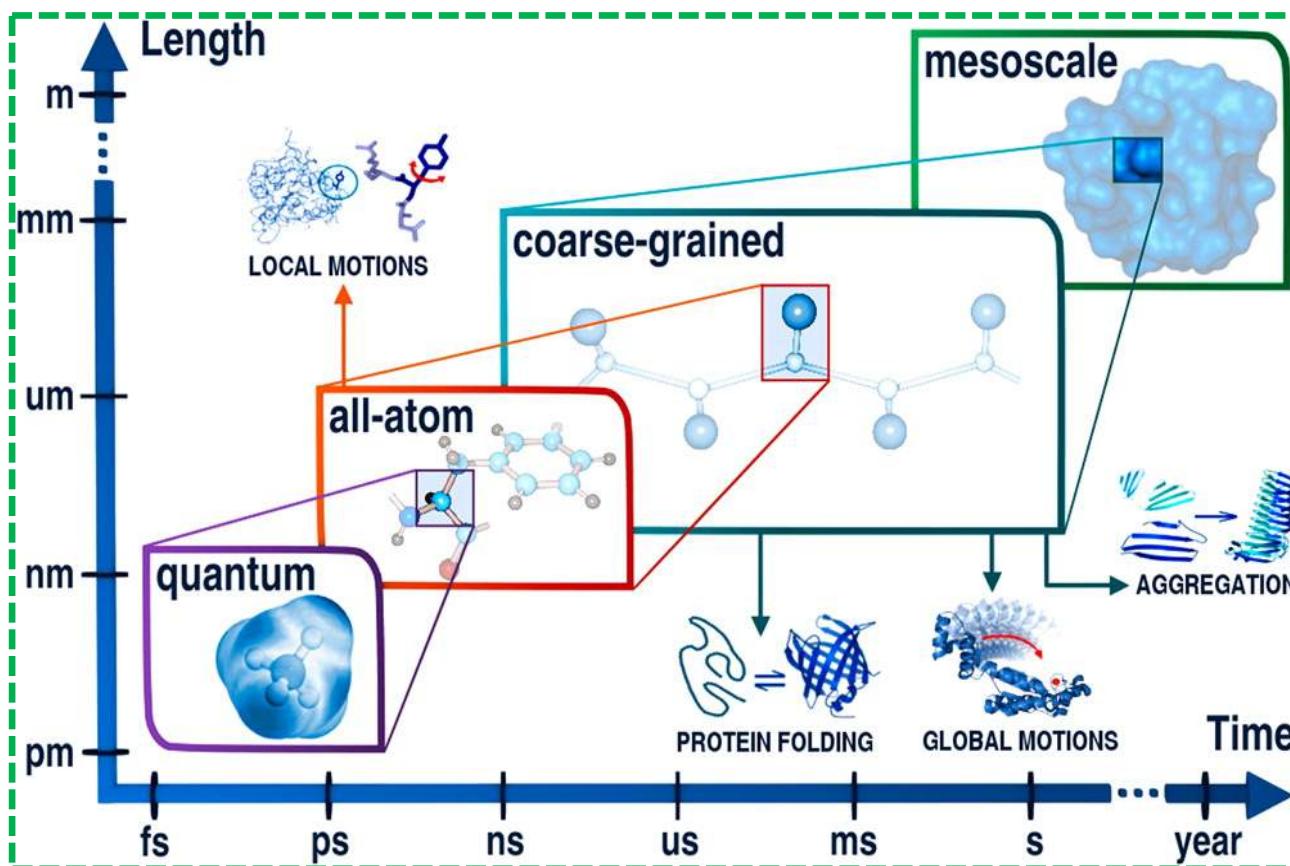
三、模拟实例

- 棒状纳米粒子的入胞过程
- 细胞内化过程中的刚度效应
- 细胞膜介导的协同效应

四、加速分子动力学



一、粗粒化分子动力学基本原理



- ◆ 精度和成本成正比
- ◆ 精度越高所需成本越大
- ◆ 选择合适的模型和方法

很大一部分模拟只关心介观尺度上的性质，连续模型精度不够，全原子分子动力学成本太高。因此，发展介于两者之间的粗粒化模拟十分必要！

一、粗粒化分子动力学基本原理

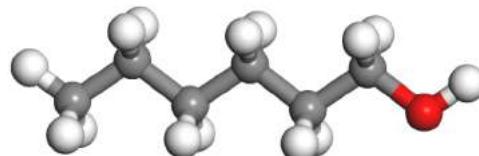
粗粒化分子动力学简介

什么是粗粒化 (coarse-grained) ?

全原子



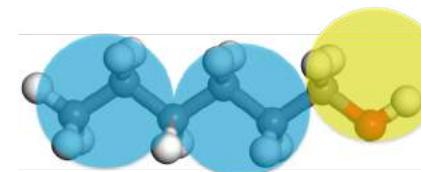
- ✓ 局部结构清晰
- ✓ 包含信息量大
- ✓ 分析提取所需信息工作量巨大且成本高昂



粗粒化



- ✓ 忽略局部信息但保留主要特征
- ✓ 结构可以由所需的主要信息构成
- ✓ 可以提升时空尺度



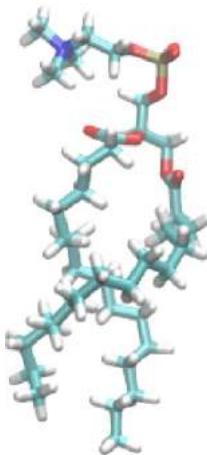
粗粒化-把一群原子归为一个整体，以在更大时空尺度研究其行为。

二、粗粒化分子动力学基本原理

粗粒化分子动力学简介

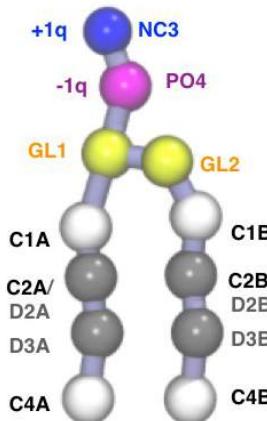
粗粒化的益处?

全原子 DPPC



130 atoms

粗粒化 DPPC



12 CG beads

- ✓ 降低体系的自由度数目，尤其是对于包含原子数较多的大分子
- ✓ 提升模拟体系的时空尺度

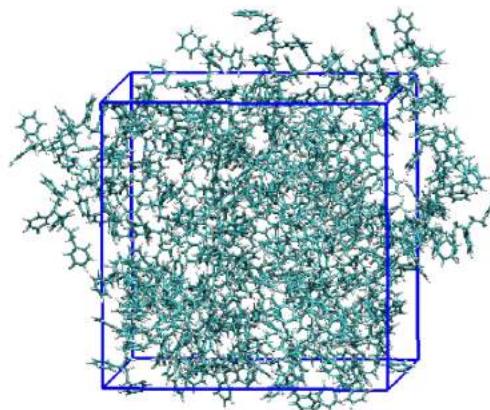
time step: *fs* for atomistic model to *ps* for CG model $\omega = \sqrt{\frac{k}{m}}$

length scale: *Angstrom* for atomistic model to *nm* for CG model

二、粗粒化分子动力学基本原理

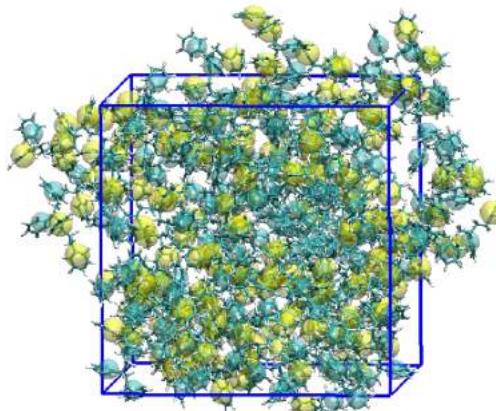
粗粒化分子动力学简介

粗粒化的益处?



体系: 聚苯乙烯
链数: 520条
分子量: 52 kDa
模拟时长: 1 μs

模型: 全原子
程序: GROMACS
(国际通用)
计算核心: 24个CPU并行
所需时间: **54年**



体系: 聚苯乙烯
链数: 520条
分子量: 52 kDa
模拟时长: 1 μs

模型: 粗粒化
(1 styrene/bead)
程序: IBIsCO
计算核心: GTX780(TI)
所需时间: **11天**

一、粗粒化分子动力学基本原理

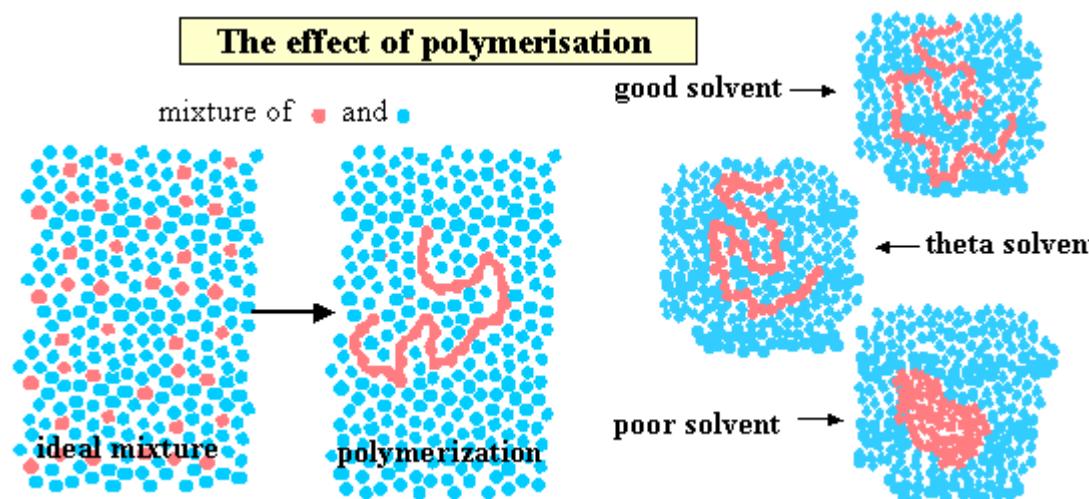
粗粒化分子动力学简介

粗粒化的基础

尺度分离 小尺度对大尺度的影响只是定量而非定性。

演变较快的过程用随机过程描述，而演变较慢的则进行拟真处理。

例如，若只关注溶质行为，则模拟溶剂加剧模拟负担且没有必要。为此可将溶剂的影响用随机力和摩擦力表示（郎之万动力学）



一、粗粒化分子动力学基本原理

粗粒化分子动力学简介

布朗运动

郎之万动力学 (LD) 基本方程 : $\dot{r} = v = p/m ; \dot{p} = f - \xi v + \sigma \dot{w}$ 。

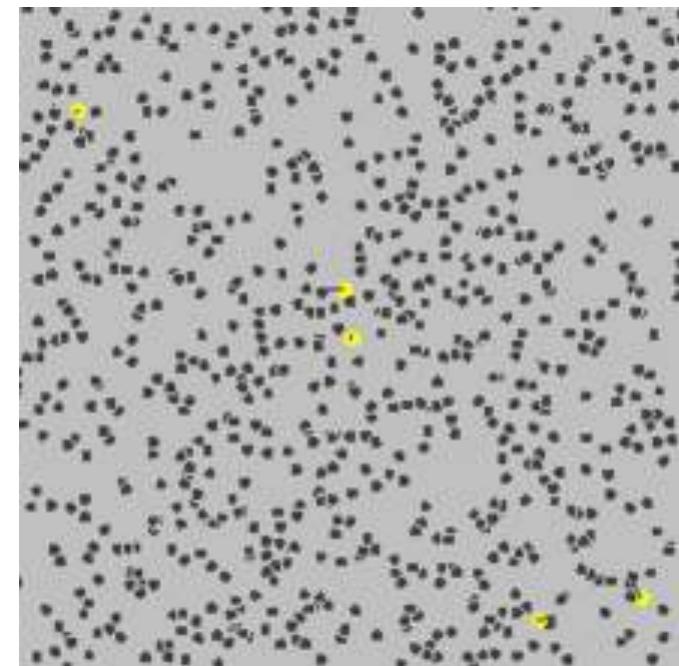
摩擦系数 ξ ; σ 为随机力强度 , \dot{w} 决定随机的分布。

两者关系由涨落耗散定理决定 : $\sigma = \sqrt{2\xi k_B T}$

在高摩擦环境 , 动量瞬间松弛 , $\dot{p} = 0$,

即布朗 (BD) 动力学 (无惯性 LD)

$\dot{r} = \xi^{-1}(f + \sigma \dot{w}) = \frac{D}{k_B T}(f + \sigma \dot{w})$; D 为扩散系数。





一、粗粒化分子动力学基本原理

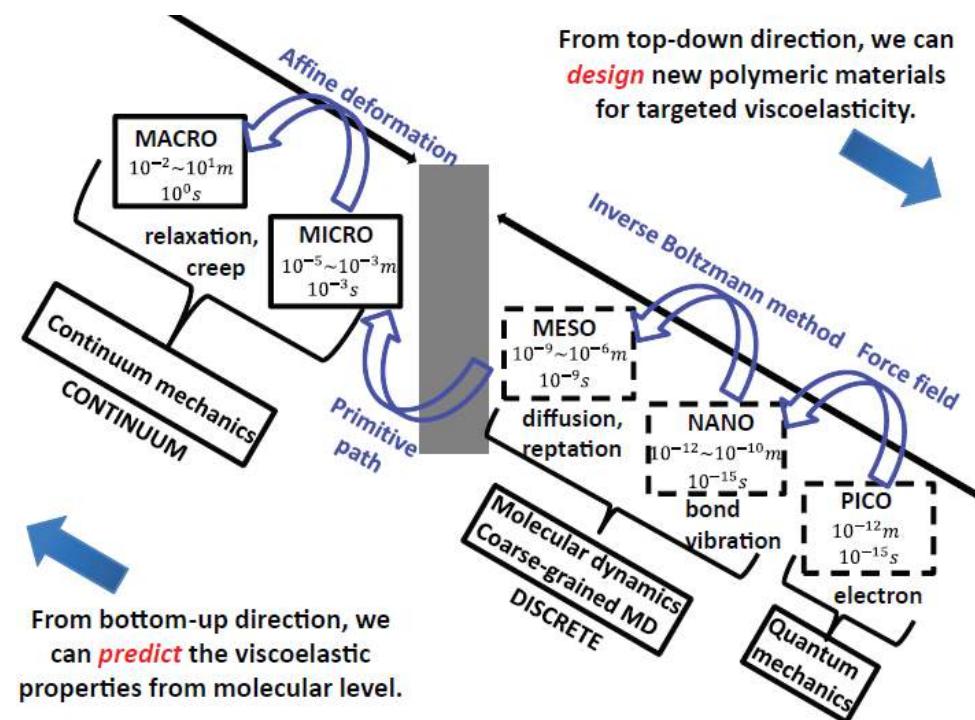
粗粒化分子动力学简介

粗粒化的三种分类

1. 系统的粗粒化方法
2. 一般化的模型体系
3. 多尺度桥连方法

确定模型与参数，特定物质。
代表性的模型，一类物质的共性。
多个尺度模型并用，建立模型间的联系。

- ✓ 第1类，扩展时空尺度，但保留关键细节，与实验定量对比。
- ✓ 第2类，抓共有特征，与实验定性对比，检测、发展理论。
- ✓ 第3类，参数在尺度间传递，以预测宏观性质。

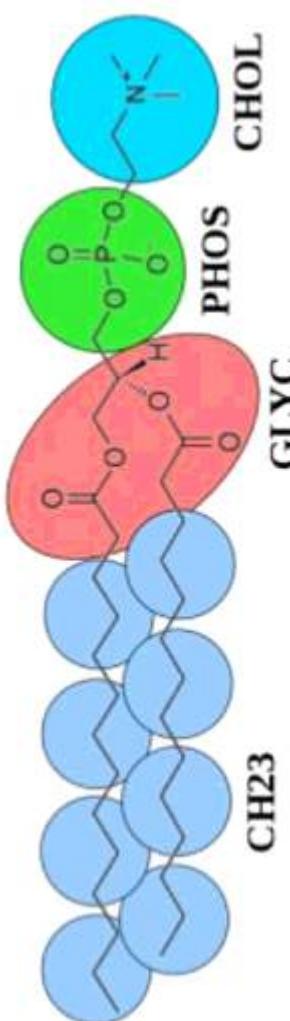




一、粗粒化分子动力学基本原理

粗粒化分子动力学的基本原理

从全原子到粗粒化



Define your goals → CG groups/beads

- ✓ Mimic, at least partially, the behavior of a group of atoms
- ✓ Assignment have not to be mandatory bijective

All-atomic model

MD simulation

Full information
(but limited scale)

Coarse-graining –
simplified model

Effective potentials
for selected sites

Reconstruct potentials
(inverse Monte Carlo)

RDFs for selected
degrees of freedom

Increase scale

Effective potentials

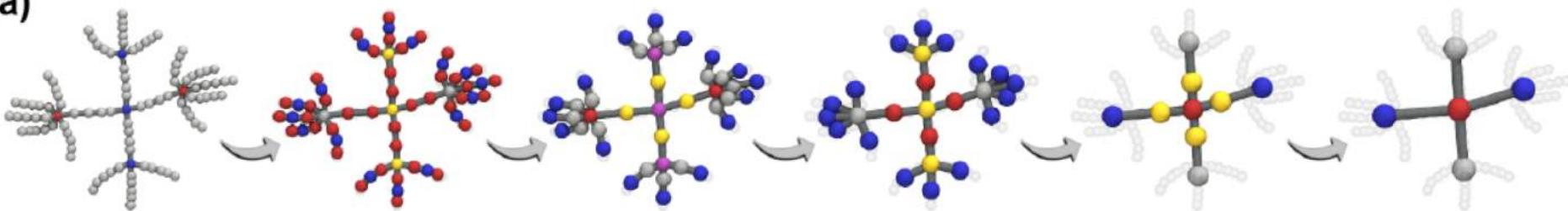
Properties on a larger
length time scale

- Effective potential = potential used to produce certain characteristics of the real system
- Reconstruct effective potential from experimental RDF

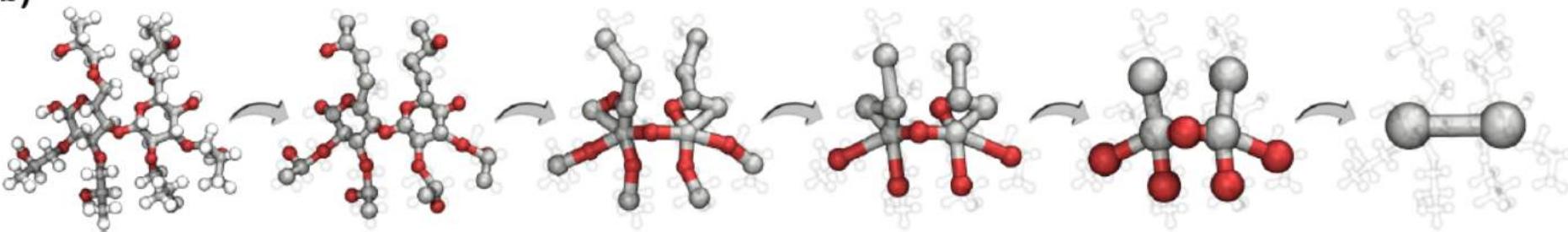
一、粗粒化分子动力学基本原理

系统的粗粒化过程

(a)



(b)



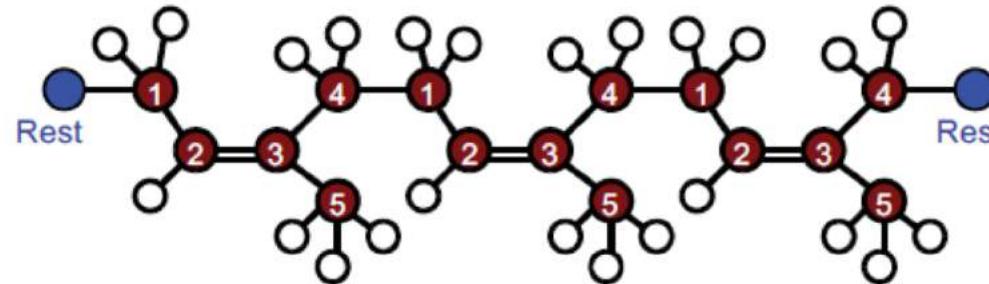
M. A. Webb, et al., JCTC 15 (2), 1199-1208 (2019).

一、粗粒化分子动力学基本原理

系统的粗粒化过程

从全原子到粗粒化

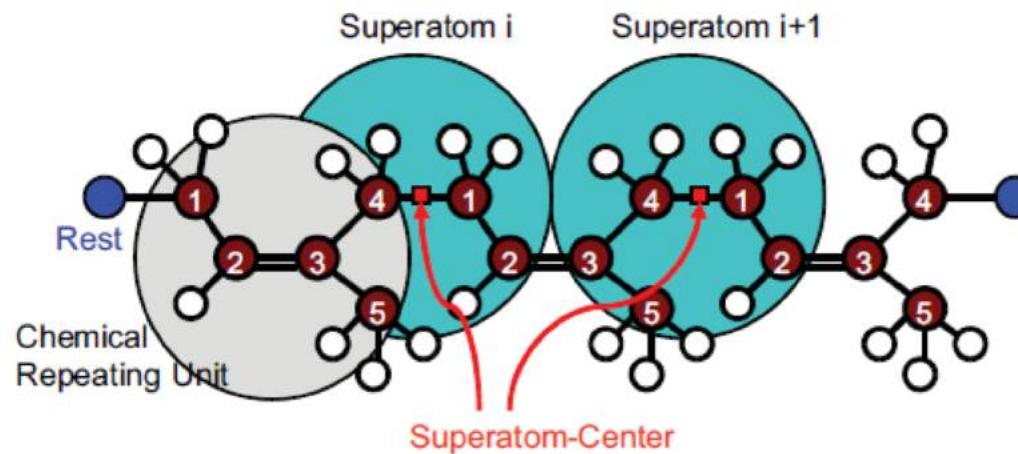
All-atomistic
Model r^n



Mapping Operator
 M_{RI}

$$R^N = M_{RI}(r^n) = \sum_{i=1}^n c_{li} r^i$$

Coarse-grained
Model R^N

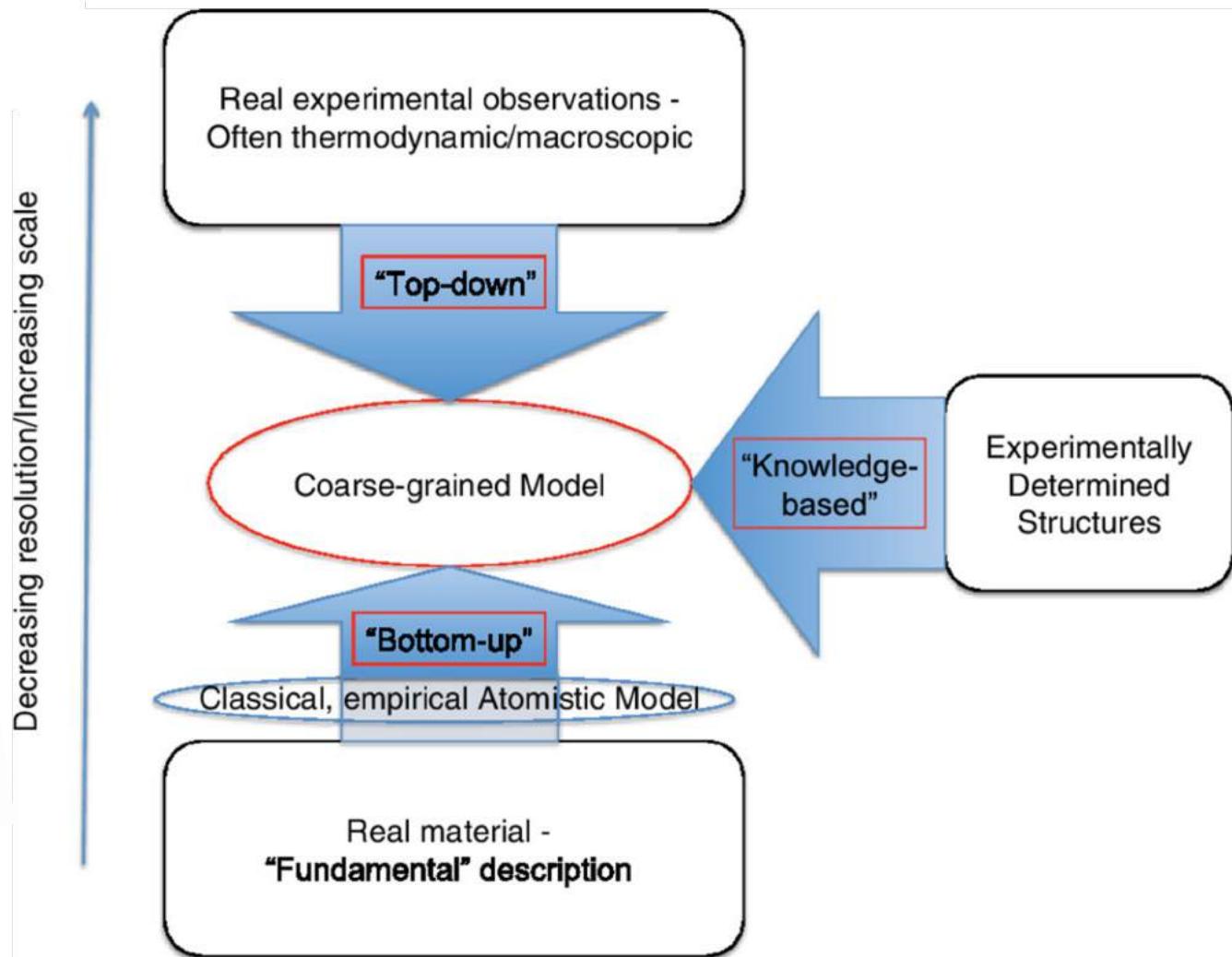
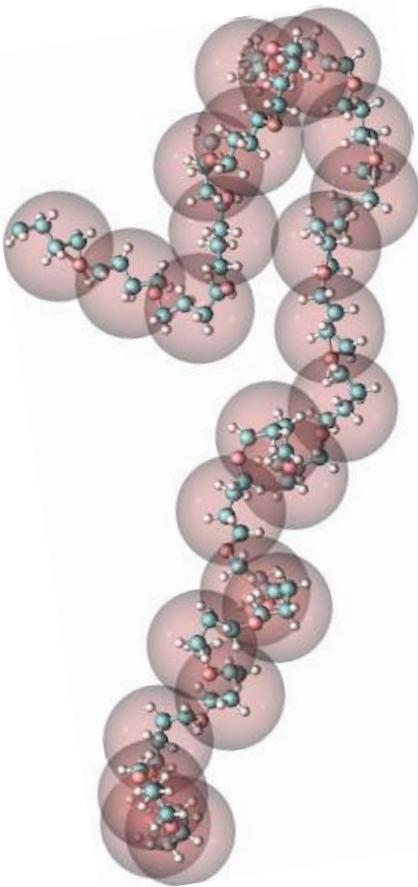


Y. Li, et al., Polymers 5 (2), 751-832 (2013).

一、粗粒化分子动力学基本原理

系统的粗粒化过程

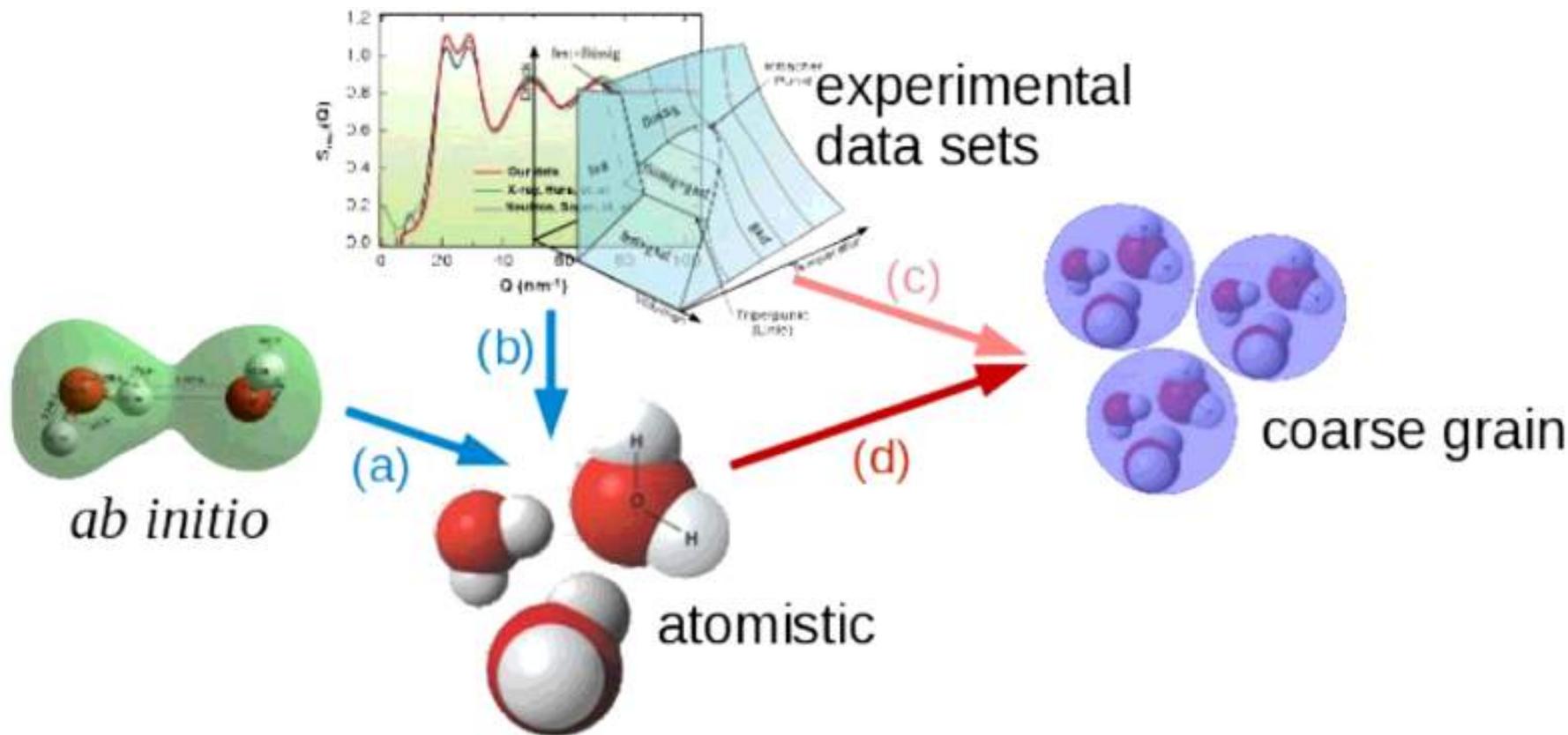
从全原子到粗粒化



一、粗粒化分子动力学基本原理

系统的粗粒化过程

力场的确定



- ✓ 通过全原子模拟拟合粗粒化模拟参数
- ✓ 对比实验和全原子模拟确定粗粒化模型的几何结构



一、粗粒化分子动力学基本原理

系统的粗粒化过程

Types of CG potentials

□ Physics-based potentials

- smoothing the energy surface by treating rigid objects as single interaction sites (e.g., the Kihara potentials),
- averaging out non-essential degrees of freedom,
- reproducing thermodynamic properties of small compounds.

□ Statistical potentials based on the “Boltzmann principle”

- database information implicit in the potentials,
- database information explicit in the potentials.

□ Arbitrary potentials

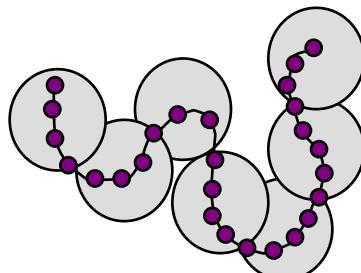
□ Structure-based potentials

- native secondary structure or other components of structure built in the potentials
- the native structure is the global minimum (Go-like potentials).

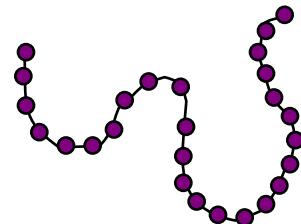
□ Elastic network potentials

一、粗粒化分子动力学基本原理

系统的粗粒化过程

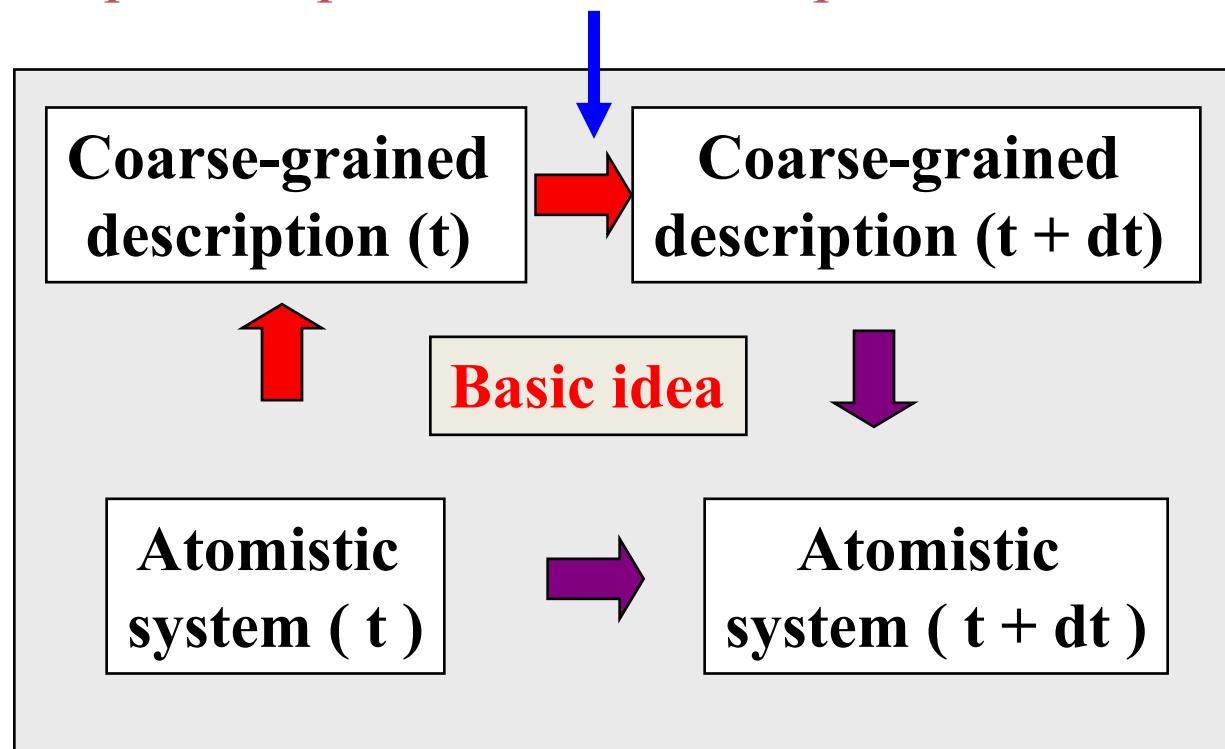


One CG particle describes
 n carbons of the
detailed polymer



高分子链粗粒化参数的确定方法

How do we derive physically consistent
particle-particle interaction potentials?

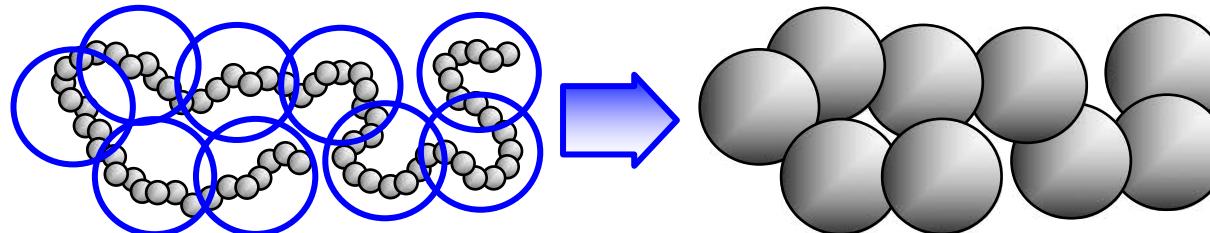


一、粗粒化分子动力学基本原理

系统的粗粒化过程

高分子链粗粒化参数的确定方法

通常情况下利用和全原子模拟的结果作对比来确定相互作用参数



- Perform molecularly detailed simulations (atomistic)
- Define coarse-grained beads by grouping backbone monomers
- Calculate structural correlations between coarse-grained beads
- Determine effective bead-bead interactions through comparison the results of atomistic and coarse-grained simulation

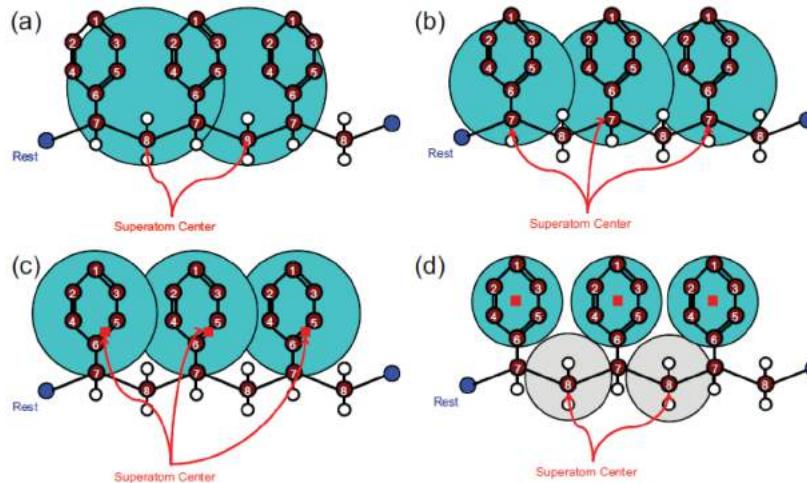


一、粗粒化分子动力学基本原理

系统的粗粒化过程

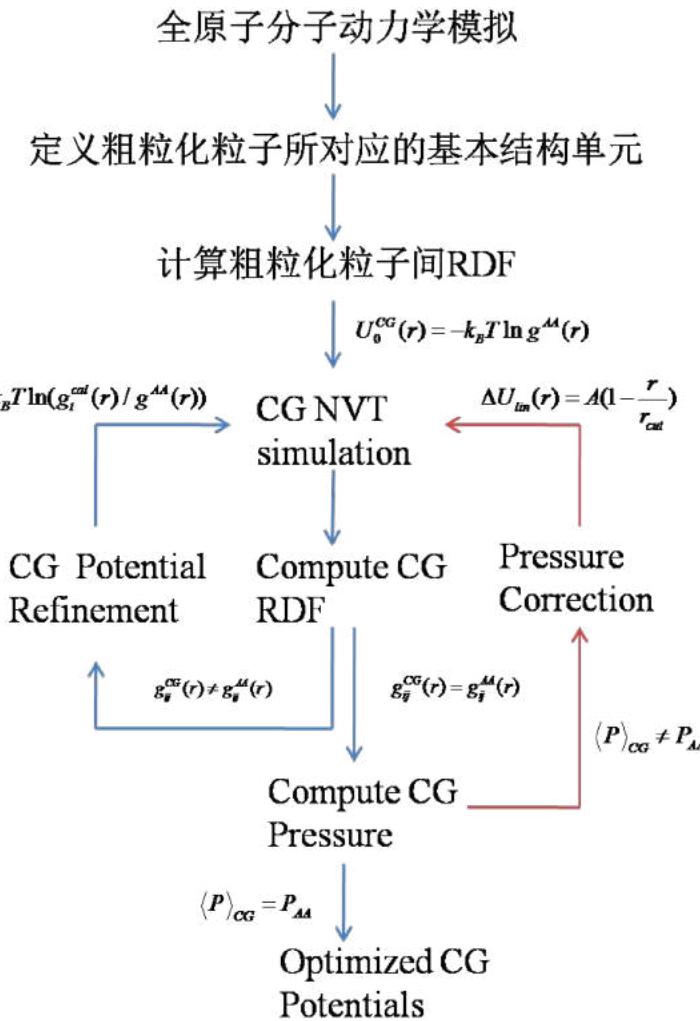
IBI的为一种迭代的粗粒化方法。

收敛标准为不同模型间在相同尺度上的**结构匹配**



四种对聚苯乙烯基本单元的定义

IBI (Iterative Boltzmann Inversion)



一、粗粒化分子动力学基本原理

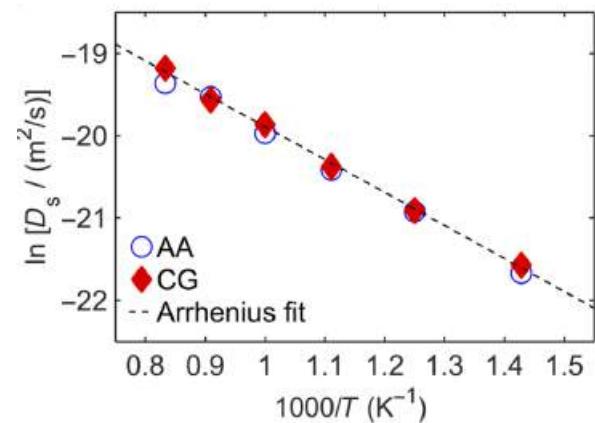
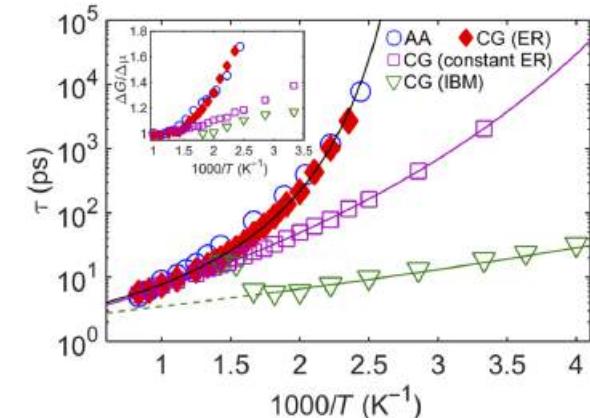
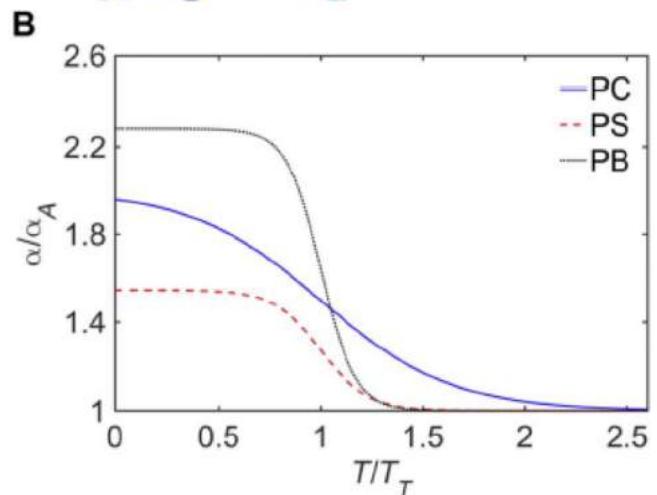
系统的粗粒化过程

IBI等传统粗粒化方法基于静态结构的匹配，而无法正确描述动力学。

如粗粒化的聚苯乙烯的动力学相对全原子加速很多，且温度依赖性不一致等。

最终目标：
实现力学与结构的
同时匹配。（机器学习？）

粗粒化动力学的匹配问题



动力学实现了匹配，但结构的一致性不佳

W. Xia, et al., Science Advances 5 (4), (2019).



一、粗粒化分子动力学基本原理

约化单位

两个用途：1. 不同模拟尺度之间的换算。2. 提高计算精度

density	$\rho^* = \rho\sigma^3$	DPD simulation		Conversion formula	Experiment
		Parameter	Value		
temperature	$T^* = k_B T / \epsilon$	r_c^*	1	$r_c = (\rho^* N_m v)^{1/3}$	8.52 Å
energy	$E^* = E / \epsilon$	ρ^*	6.88	$\rho_M = \rho^* N_m (M/N_A) / r_c^3$	997 kg m^{-3}
pressure	$P^* = P\sigma^3 / \epsilon$	P^*	0.1	$P = P^* k_B T / r_c^3$	0.67 MPa
time	$t^* = (\epsilon / m\sigma^2)^{1/2} t$	γ^*	12.4	$\gamma = \gamma^* k_B T / r_c^2$	70.3 mN m^{-1}
force	$f^* = f\sigma / \epsilon$	β_T^{-1*}	48.0	$\beta_T^{-1} = (\rho k_B T / N_m) \beta_T^{-1*}$	2.2 GPa
torque	$\tau^* = \tau / \epsilon$	δt^*	0.01	$\delta t = \delta t^* (N_m D_{\text{bead}}^* r_c^2 / D_{\text{water}})$	6.8 ps
surface tension	$\gamma^* = \gamma\sigma^2 / \epsilon$				

真实单位 → 约化单位
除去基本单位

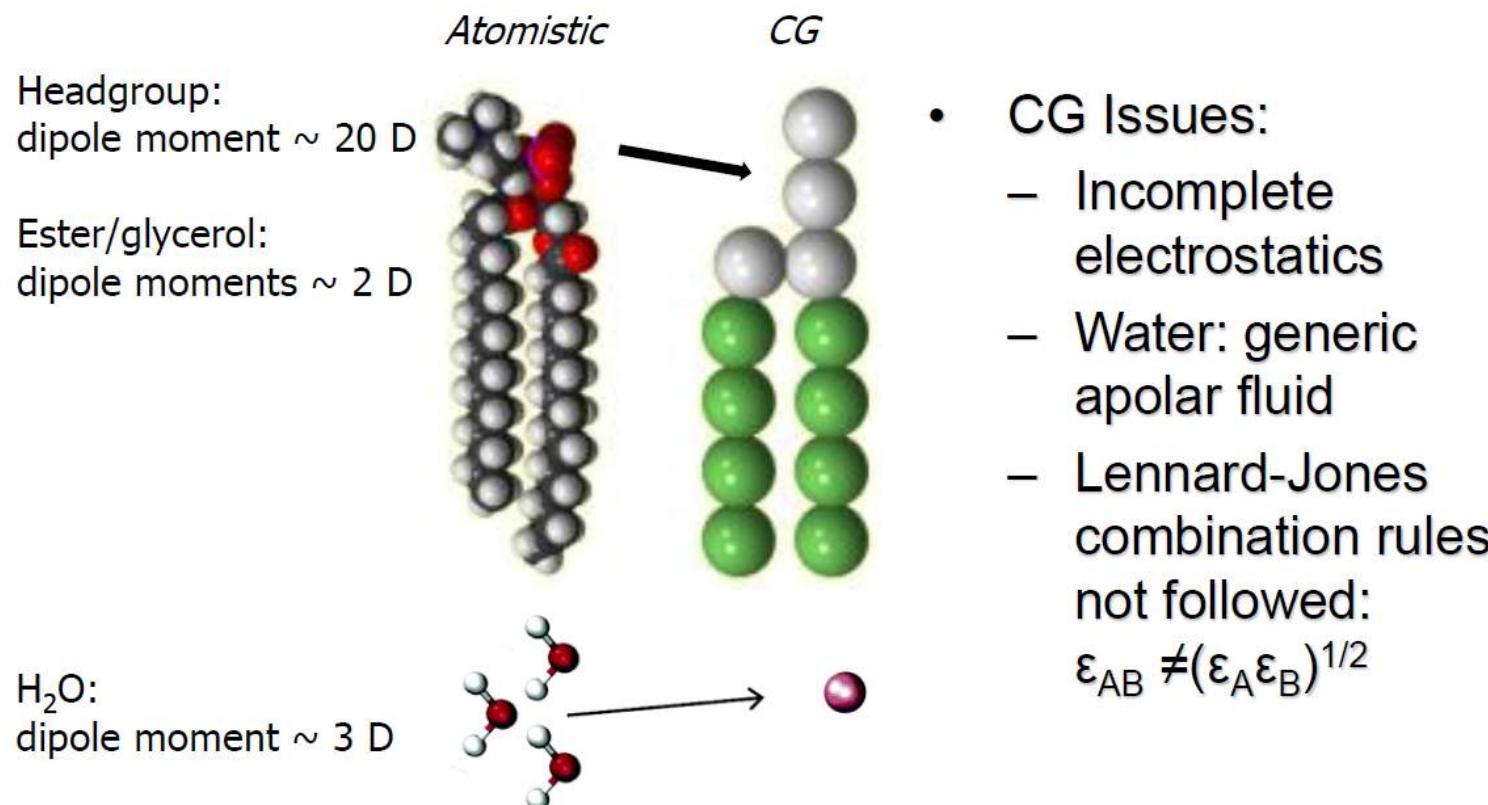
约化单位 → 真实单位
乘上基本单位

一、粗粒化分子动力学基本原理

Martini模型

Some CG models of lipids

Klein et al., *J Phys Chem B* (2001); Smit et al., *J Phys Chem B* (2003);
 Marrink et al., *J Phys Chem B* (2004, 2007); Izvekov and Voth, *J Phys Chem B* (2005);



Martini模型是一种自上而下的一种粗粒化方法。将常见的原子基团片段按物化性质定义成几类粗粒度珠子并赋予相应的参数，真实分子通过局部性质划分原子基团，然后对比定义珠子来确定粗粒化模型结构。



一、粗粒化分子动力学基本原理

Martini模型

Martini Force Fields (Non-bond interaction): Each pair combination is associated with an LJ energy level

TABLE 1: Interaction Matrix^a

		Q				P				N				C					
	sub	da	d	a	0	5	4	3	2	1	da	d	a	0	5	4	3	2	1
Q	da	O	O	O	II	O	O	O	I	I	I	I	I	IV	V	VI	VII	IX	IX
	d	O	I	O	II	O	O	O	I	I	I	III	I	IV	V	VI	VII	IX	IX
	a	O	O	I	II	O	O	O	I	I	I	I	III	IV	V	VI	VII	IX	IX
	0	II	II	II	IV	I	O	I	II	III	III	III	III	IV	V	VI	VII	IX	IX
P	5	O	O	O	I	O	O	O	O	I	I	I	I	IV	V	VI	VI	VII	VIII
	4	O	O	O	O	O	I	I	II	II	III	III	III	IV	V	VI	VI	VII	VIII
	3	O	O	O	I	O	I	I	II	II	II	II	II	IV	IV	V	V	VI	VII
	2	I	I	I	II	O	II	II	II	II	II	II	II	III	IV	IV	V	VI	VII
N	1	I	I	I	III	O	II	II	II	II	II	II	II	III	IV	IV	IV	V	VI
	da	I	I	I	III	I	III	II	II	II	II	II	II	IV	IV	V	VI	VI	VI
	d	I	III	I	III	I	III	II	II	II	II	II	II	IV	IV	V	VI	VI	VI
	a	I	I	III	III	I	III	II	II	II	II	II	II	III	IV	IV	V	VI	VI
C	0	IV	IV	IV	IV	IV	IV	IV	III	III	IV	IV	IV	IV	IV	IV	IV	V	VI
	5	V	V	V	V	V	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	V	V
	4	VI	VI	VI	VI	VI	V	IV	IV	V	V	V	IV	IV	IV	IV	V	V	V
	3	VII	VII	VII	VII	VI	VI	V	V	IV	VI	VI	VI	IV	IV	IV	IV	IV	IV
2	IX	IX	IX	IX	VII	VII	VI	VI	V	V	VI	VI	VI	V	V	V	IV	IV	IV
	1	IX	IX	IX	IX	VIII	VIII	VII	VII	VI	VI	VI	VI	V	V	IV	IV	IV	IV

^a Level of interaction indicates the well depth in the LJ potential: O, $\epsilon = 5.6 \text{ kJ/mol}$; I, $\epsilon = 5.0 \text{ kJ/mol}$; II, $\epsilon = 4.5 \text{ kJ/mol}$; III, $\epsilon = 4.0 \text{ kJ/mol}$; IV, $\epsilon = 3.5 \text{ kJ/mol}$; V, $\epsilon = 3.1 \text{ kJ/mol}$; VI, $\epsilon = 2.7 \text{ kJ/mol}$; VII, $\epsilon = 2.3 \text{ kJ/mol}$; VIII, $\epsilon = 2.0 \text{ kJ/mol}$; IX, $\epsilon = 2.0 \text{ kJ/mol}$. The LJ parameter $\sigma = 0.47 \text{ nm}$ for all interaction levels except level IX for which $\sigma = 0.62 \text{ nm}$. Four different CG sites are considered: charged (Q), polar (P), nonpolar (N), and apolar (C). Subscripts are used to further distinguish groups with different chemical nature: 0, no hydrogen-bonding capabilities are present; d, groups acting as hydrogen bond donor; a, groups acting as hydrogen bond acceptor; da, groups with both donor and acceptor options; 1–5, indicating increasing polar affinity.

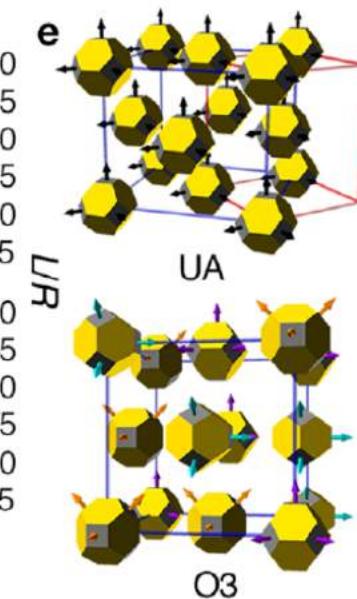
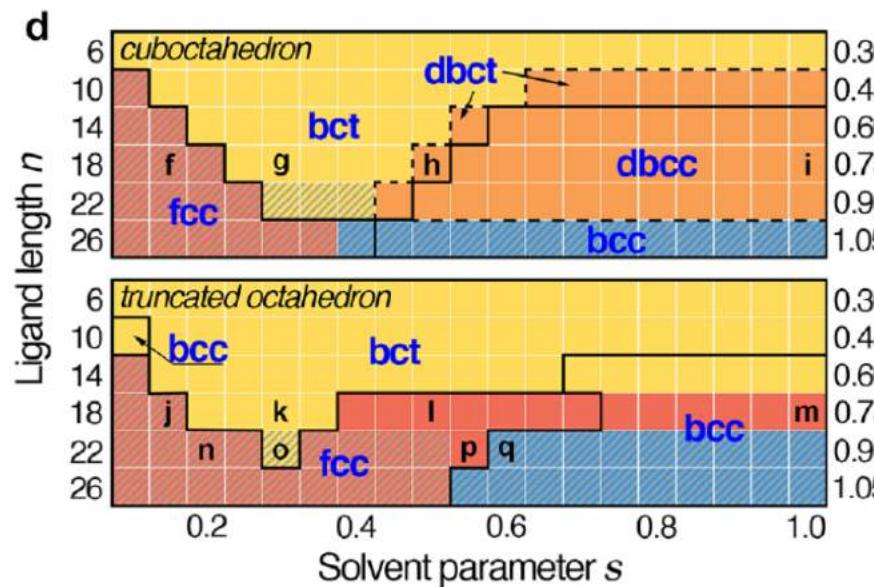
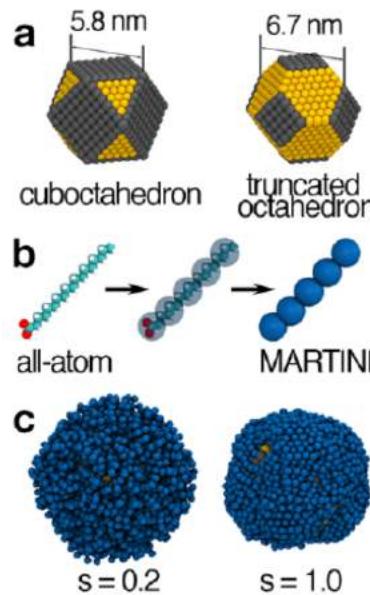
一、粗粒化分子动力学基本原理

Martini模型

Martini模型的应用

Z. Fan and M. Grünwald, J. Am. Chem. Soc. 141 (5), 1980-1988 (2019)

纳米尺度晶格的自组装

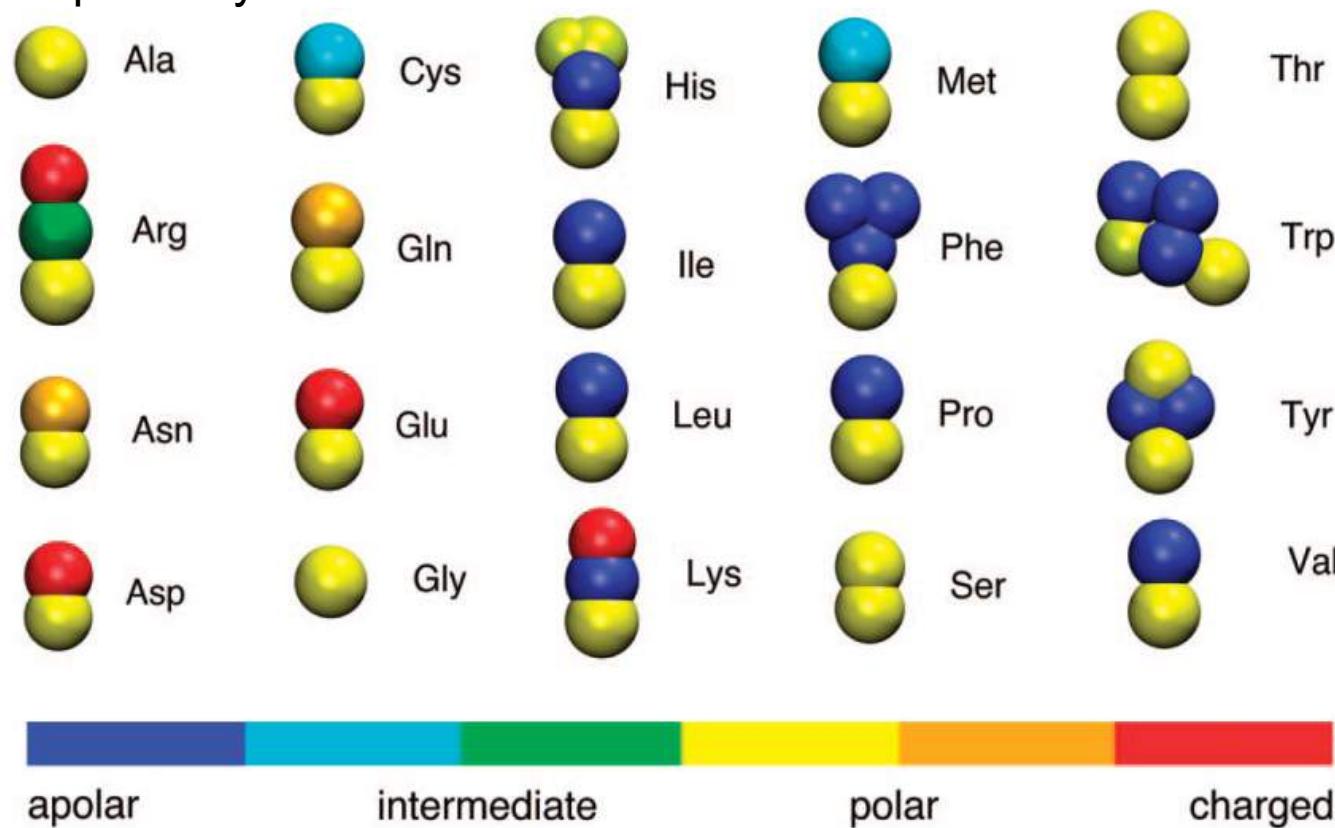


一、粗粒化分子动力学基本原理

Martini模型

Extension to Amino Acids

- 4:1 grouping parameterized by experimental comparison of free energy partitioning between water & butane
- Ring-like structures such as cyclohexane are mapped to as low as 2:1 to preserve geometric specificity





一、粗粒化分子动力学基本原理

Martini模型

Limitations of Martini Coarse-Graining

Martini力场一经问世就受到了广泛的关注和应用，并且还是分子动力学软件Gromacs最常用的粗粒化力场。随着分子模拟的不断发展也在不断的更新和修正，但还是存在一定的缺陷：

- Parameterized for liquids but not for solids & gases
- Parameterized within a narrow temperature range of 270-330 K
- Difficult in modeling partitioning of polar & charged particles in low dielectric medium
- Implicit screening leads to underestimation of polar particles in nonpolar solvents
- Long-range electrostatics beyond 1.2 nm were neglected

一、粗粒化分子动力学基本原理

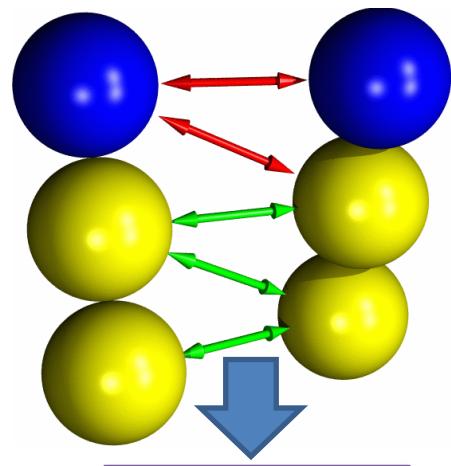
Lipid的粗粒化模型

常见的粗粒化力场-Solvent free Model

Cooke&Deserno model for lipid

“No solvent” is difficult in amphiphilic molecule

amphiphilic molecule have to self-assemble



attraction

weak



“gas” phase

strong



solid bilayer

$k_B T$, not eV!

One needs to introduce additional cohesive energy for the lipid tails!

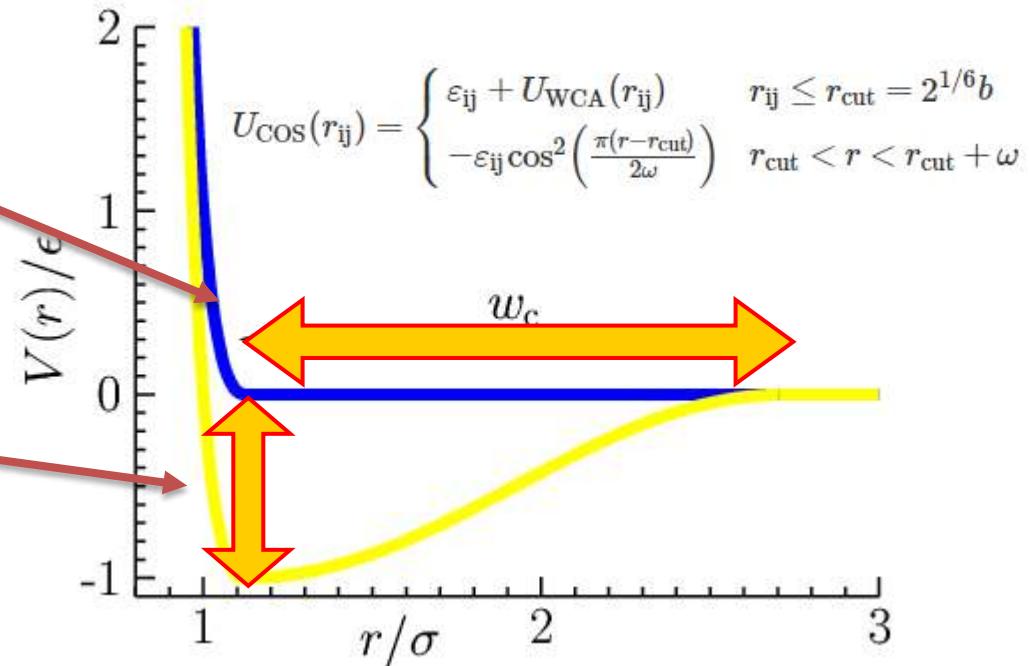
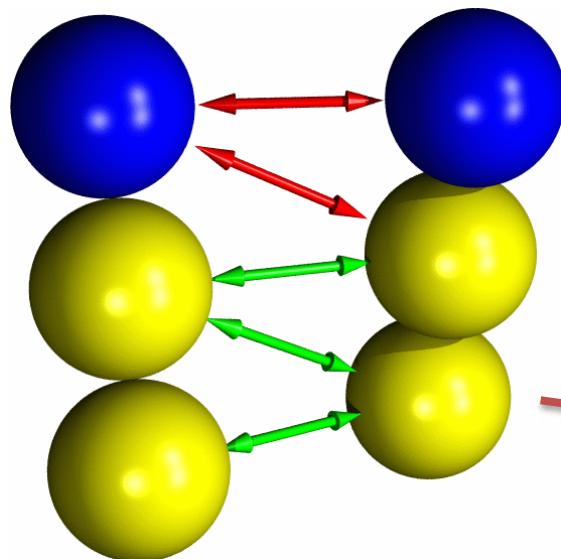
Fluidity has proven to be the main challenge

Need to choose the proper interaction potential

一、粗粒化分子动力学基本原理

Lipid的粗粒化模型

Cooke&Deserno model for lipid



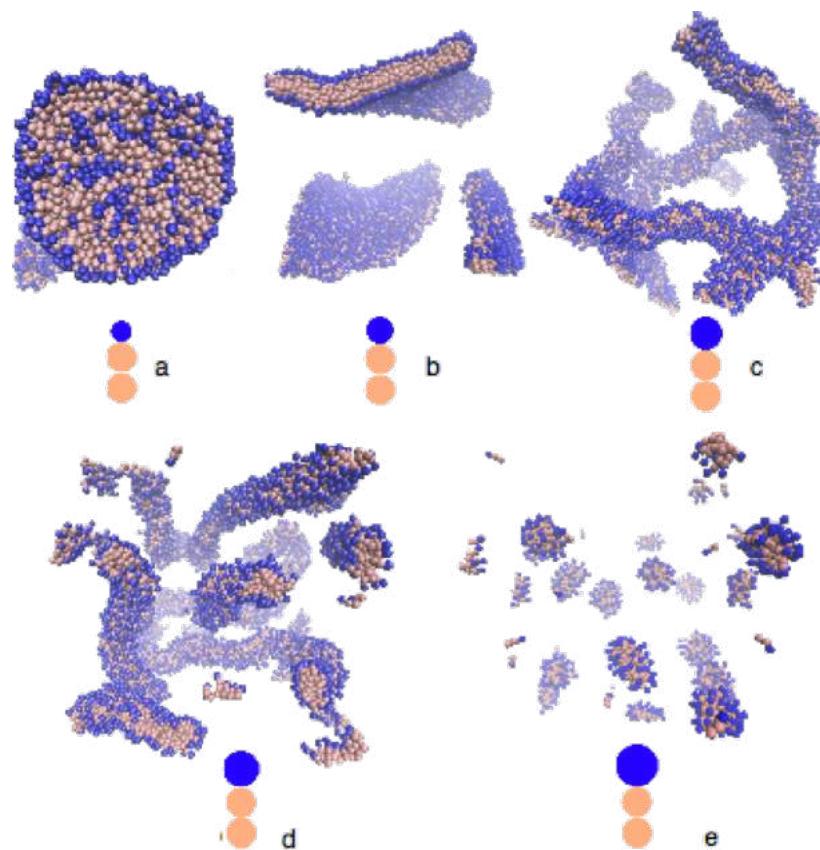
- ✓ Three bead
- ✓ Two bonds
- ✓ Tail attraction via some generic potential with *tunable range*
- ✓ Two parameters

一、粗粒化分子动力学基本原理

Lipid的粗粒化模型

Cooke&Deserno model for lipid

The aggregation morphologies of lipid influenced by the structure of lipid molecules



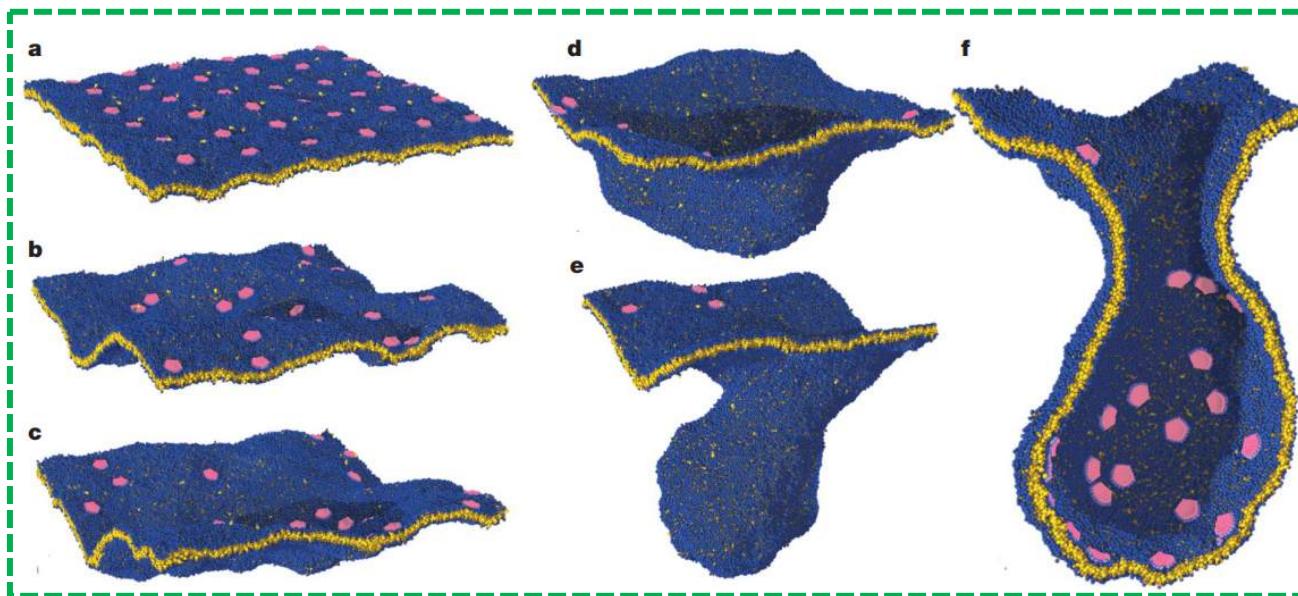
- 脂质分子聚集体的形态受单体结构的影响可以形成不同的形态
- 当头部尾部珠子的尺寸比为 $r_H : r_T = 0.95$ 时，聚集体为类细胞膜的双层膜结构

一、粗粒化分子动力学基本原理

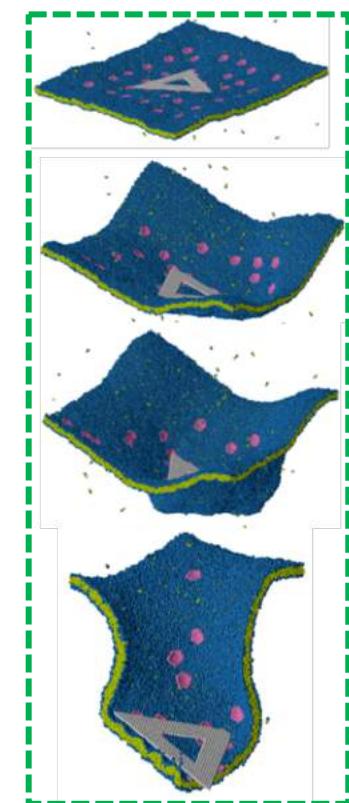
Lipid的粗粒化模型

Validation of Coarse-Graining

带曲率的纳米结构诱导的膜结构的形变



带曲率的蛋白协助的颗粒内吞





一、粗粒化分子动力学基本原理

Lipid的粗粒化模型

Limitations of Cooke&Deserno model

该力场是目前用于细胞膜结构模拟应用最广泛的无水力场，相比于传统的含溶剂的粗粒化模型和力场进一步提升了模拟的时空尺度，使模拟体系能够达到百纳米级和微秒级，能很好的捕捉到发生在细胞层面的一些现象，但该模型也存在一定的缺陷：

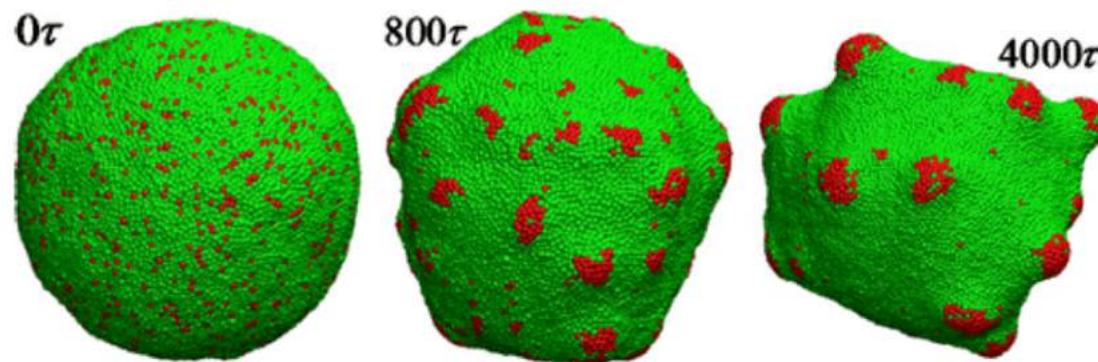
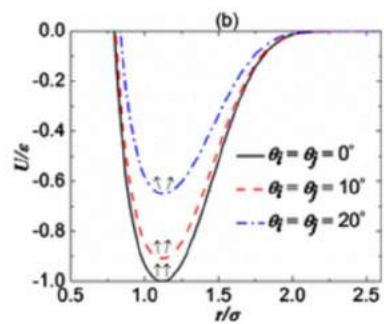
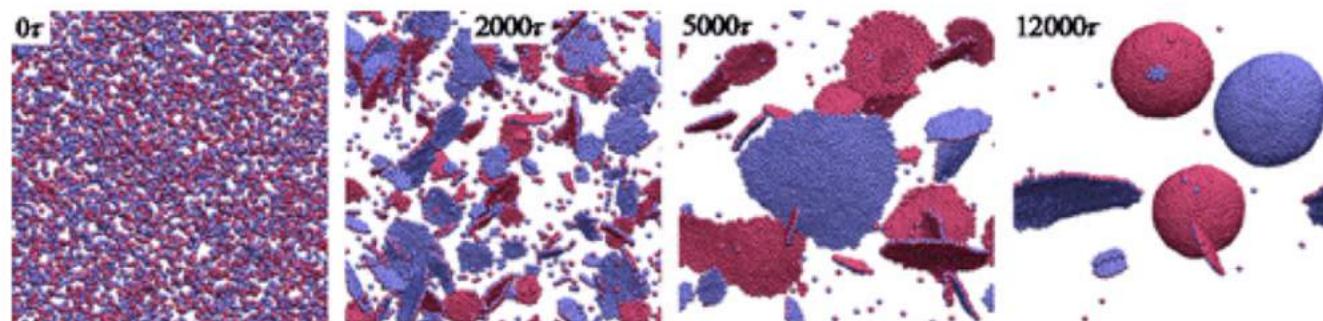
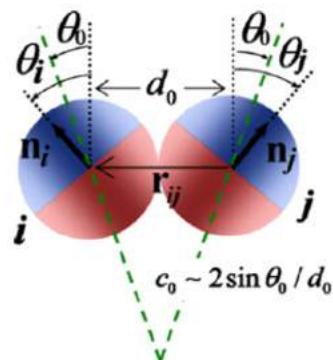
- 由于是隐溶剂模型，因此在模拟中压力和表面张力不好控制
- 高度粗粒化使得在该模型中很难引入静电作用，因此对于电荷性质的研究该模型无能为力

一、粗粒化分子动力学基本原理

Lipid的粗粒化模型

Some CG models of lipids

[Hongyan Yuan et al, PRE, 82, 011905, 2010]



一、粗粒化分子动力学基本原理

FENE模型

一般化模型，主要用于模拟聚合物和DNA。

非键粒子之间的作用势为Lennard-Jones (LJ)。粒子大小为 σ ，能量强度由 ε 决定。

$$U_{\text{LJ}}(r, r_{\text{cut}}) = 4\varepsilon \left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^6 - \left(\frac{\sigma}{r_{\text{cut}}}\right)^{12} + \left(\frac{\sigma}{r_{\text{cut}}}\right)^6 \right]$$

键连的粒子间的作用势为FENE (finitely extendible nonlinear elastic)

$$U_{\text{FENE}}(r) = -\frac{1}{2}kR_0^2 \ln \left[1 - \left(\frac{r}{R_0} \right)^2 \right] + U_{\text{LJ}}(r, r_{\text{cut}} = 2^{1/6}\sigma)$$

作用范围 $r < R_0$ ，弹簧系数 k 。

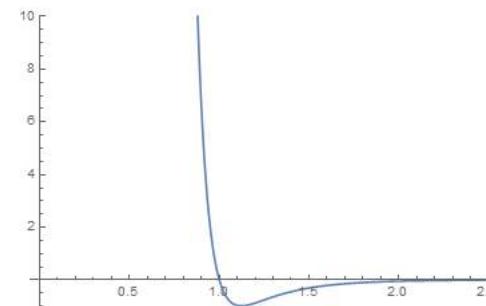
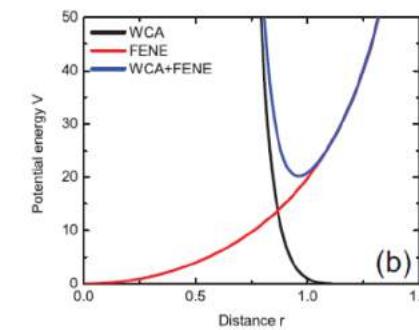
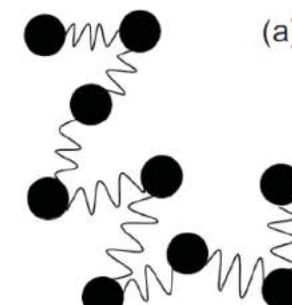


Figure 3. Depiction of (a) the FENE model and (b) its potential functions.



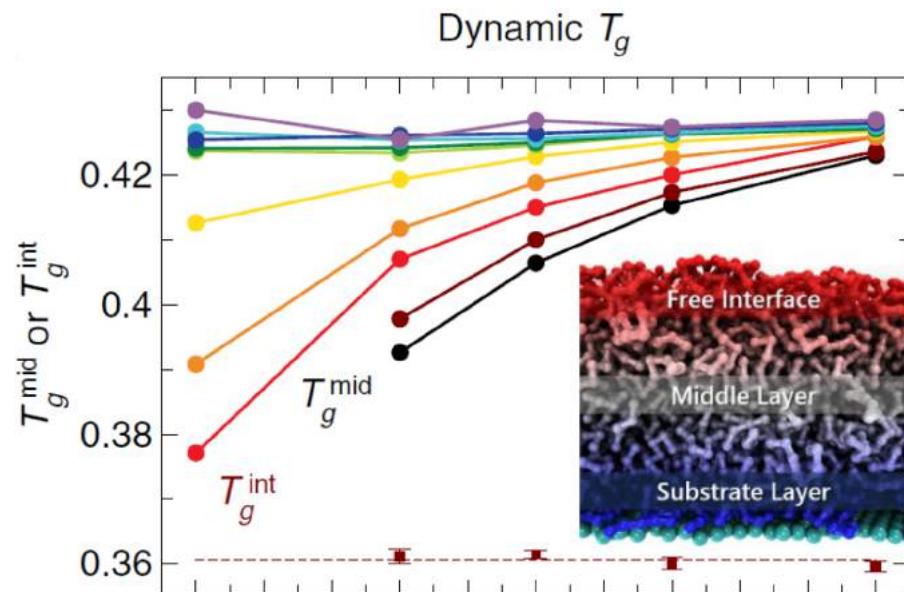
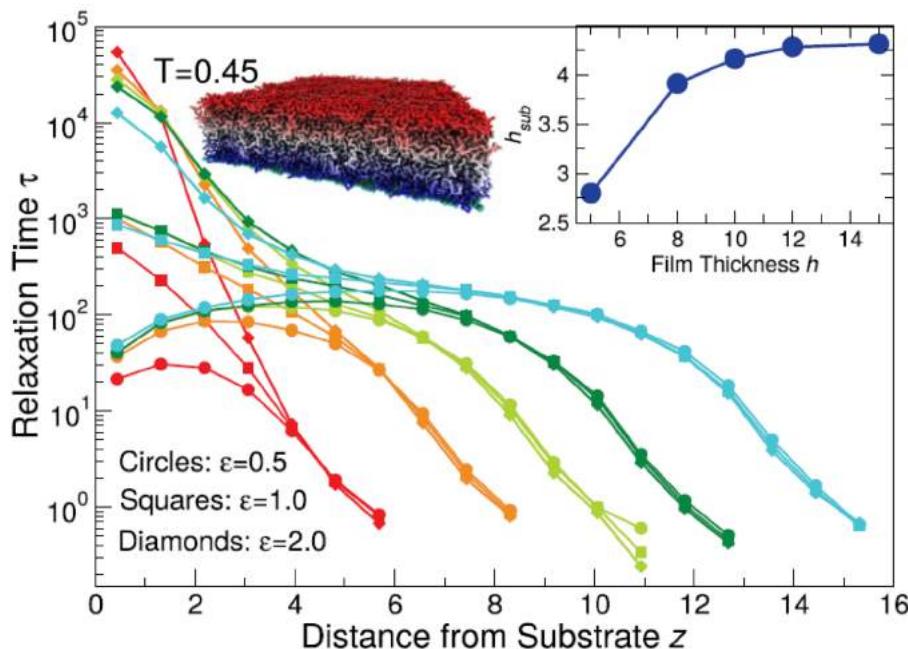
一、粗粒化分子动力学基本原理

FENE模型

FENE模型的应用

W. Zhang, et al., PNAS. 115 (22), 5641-5646 (2018).

聚合物薄膜玻璃化转变



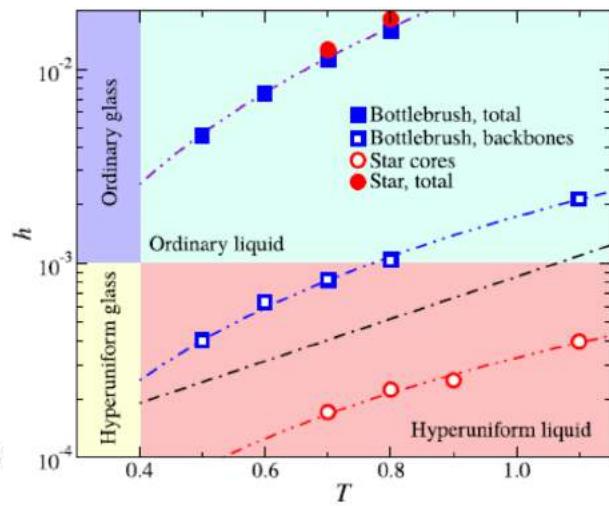
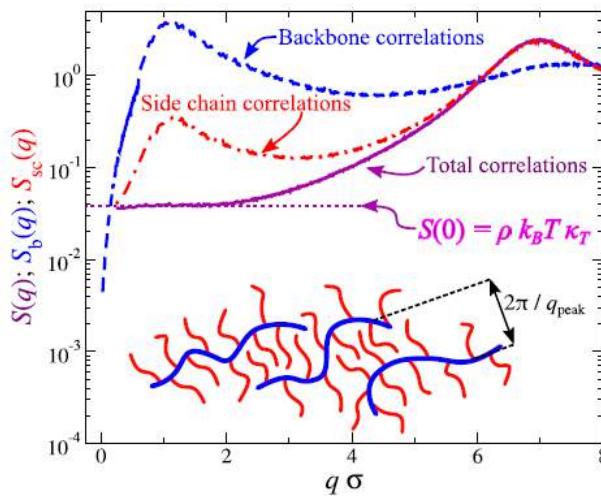
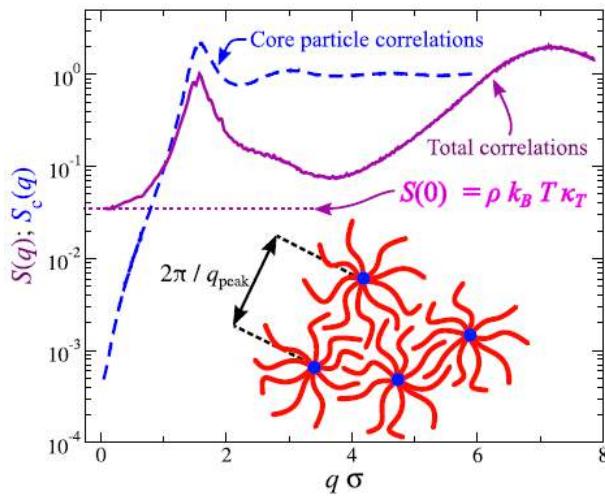
一、粗粒化分子动力学基本原理

FENE模型

FENE模型的应用

A. Chremos and J. F. Douglas, Phys. Rev. Lett. 121 (25), 258002 (2018)

聚合物拓扑结构对堆积的影响



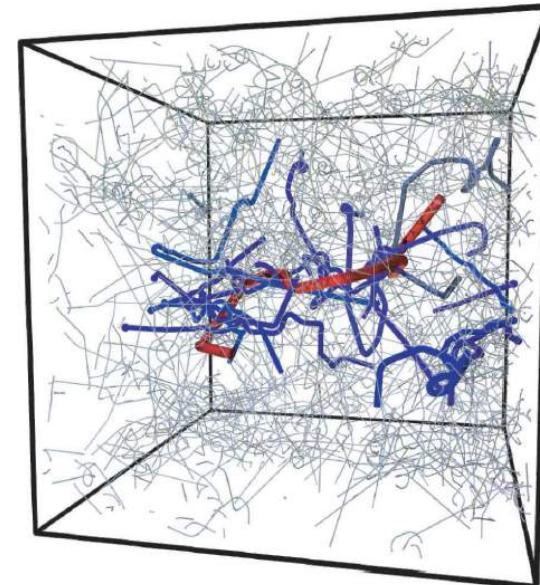
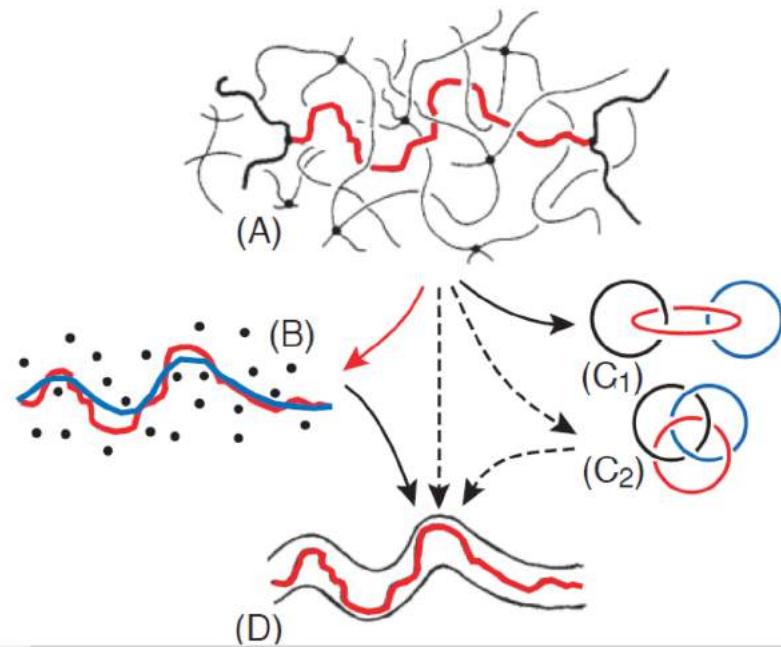
一、粗粒化分子动力学基本原理

FENE模型

FENE模型的应用

R. Everaers, et al., Science 303 (5659), 823-826 (2004)。

聚合物的拓扑与流变



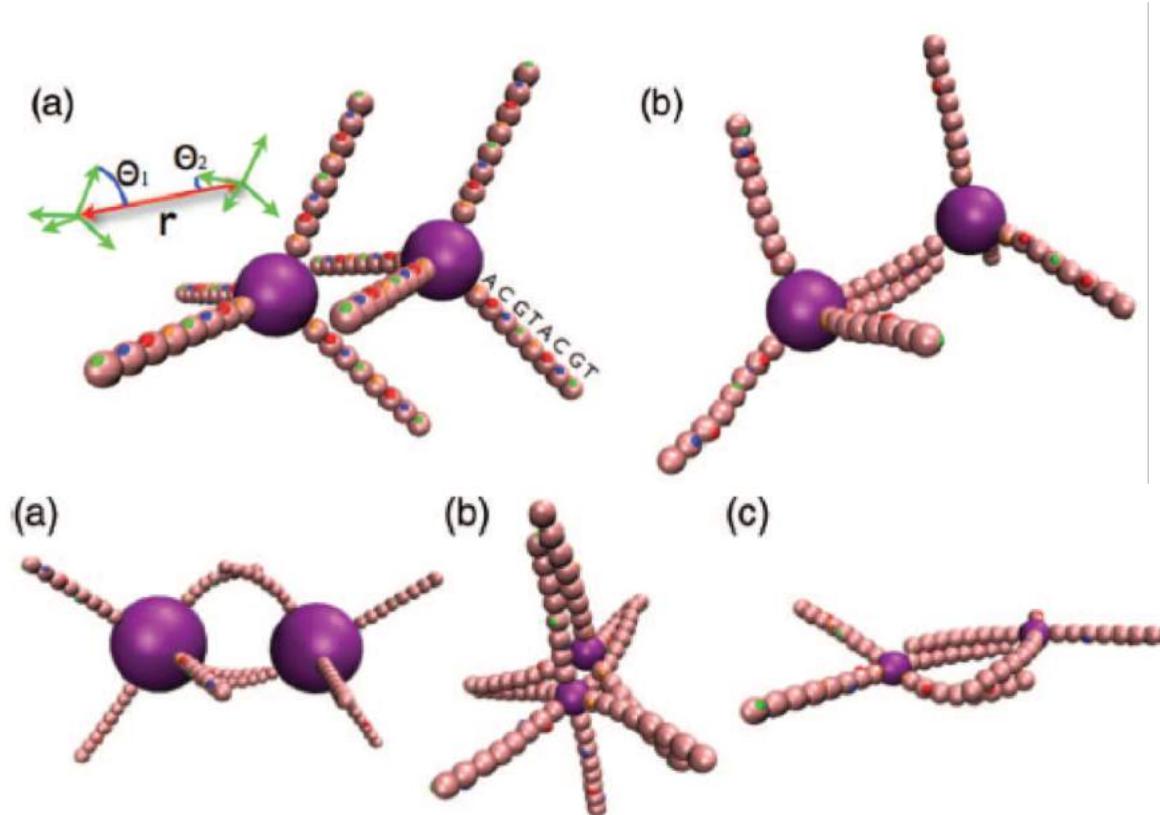
一、粗粒化分子动力学基本原理

FENE模型

FENE模型的应用

P. E. Theodorakis, et al., J. Chem. Phys. 138 (2), 025101 (2013).

DNA修饰的纳米胶体

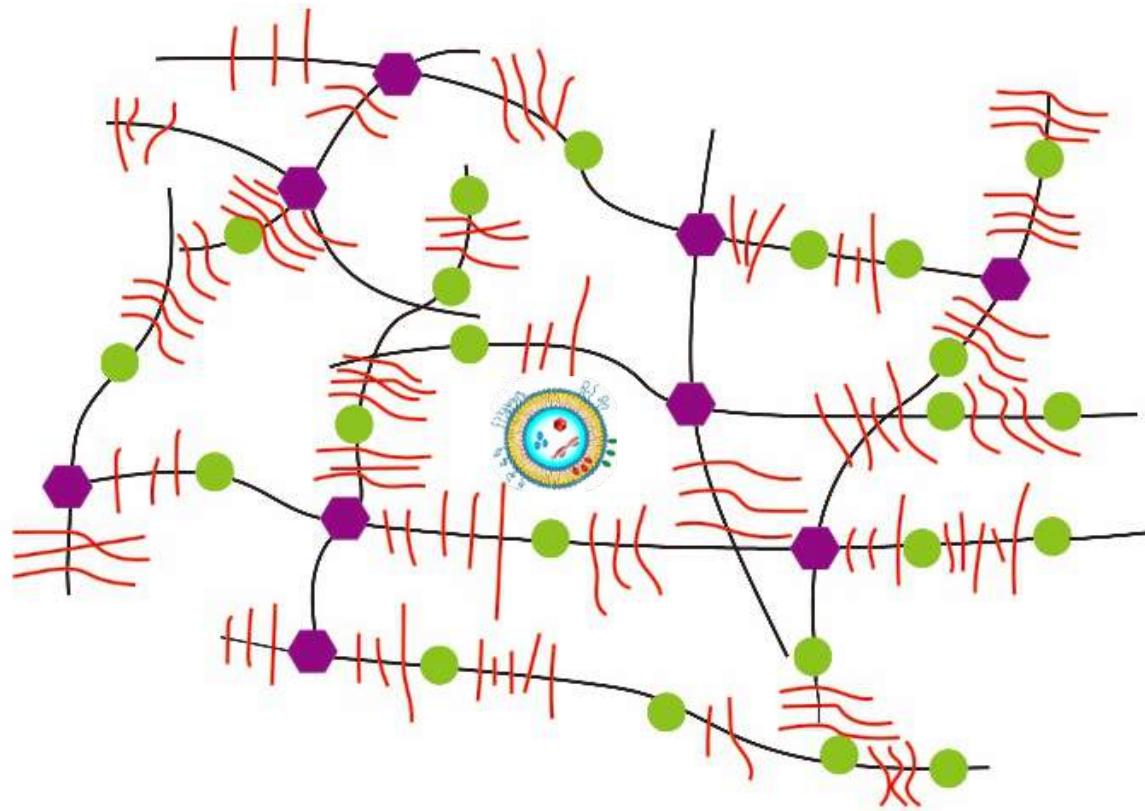


一、粗粒化分子动力学基本原理

粗粒化分子模拟

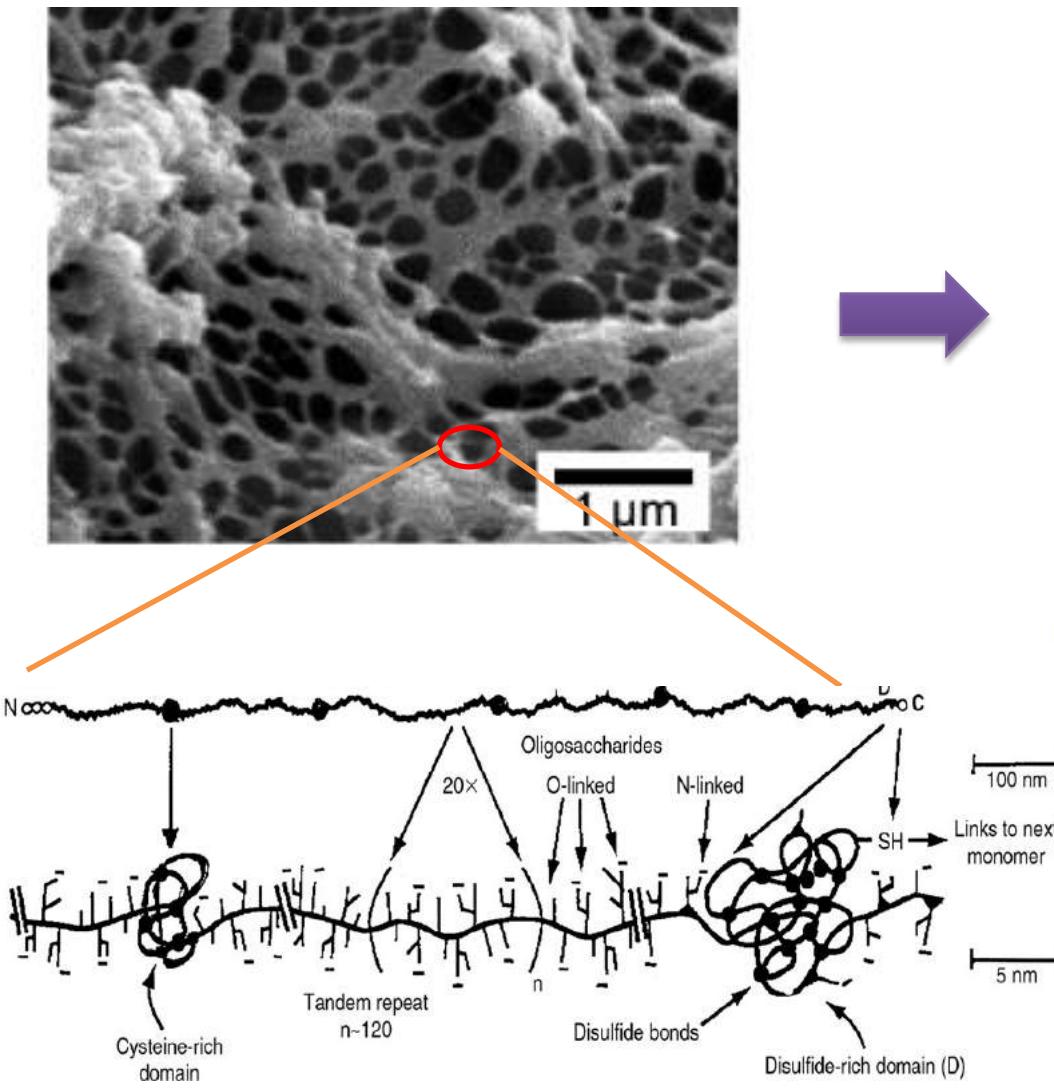
如何构建粗粒化模型

脂质体纳米药物载体在生理粘液中的扩散

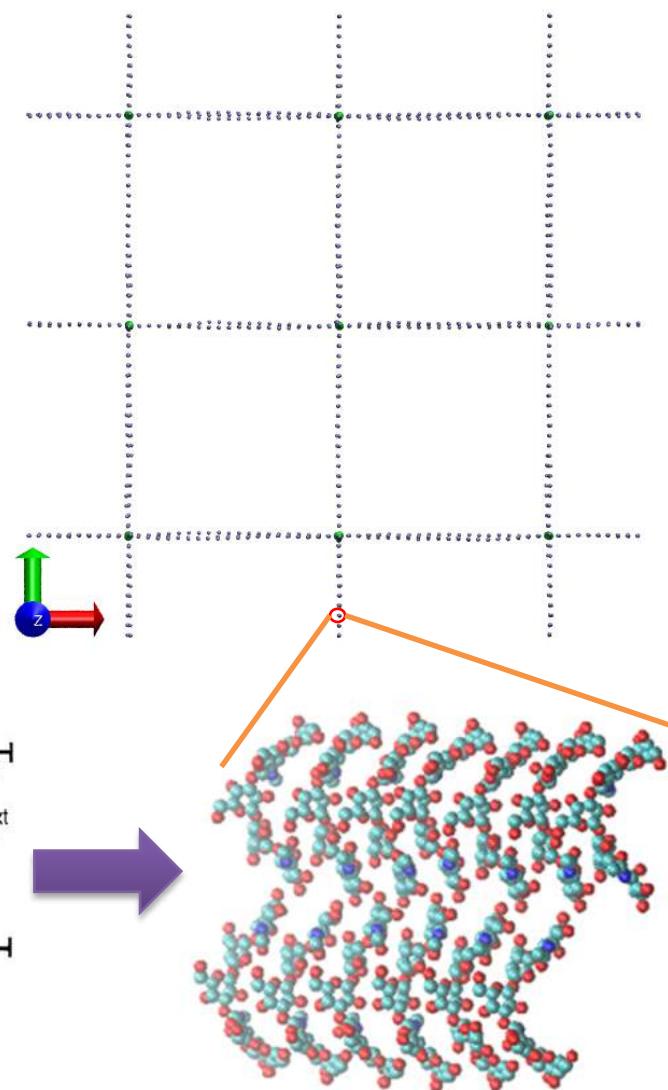


一、粗粒化分子动力学基本原理

粘液的主要成分-黏液素

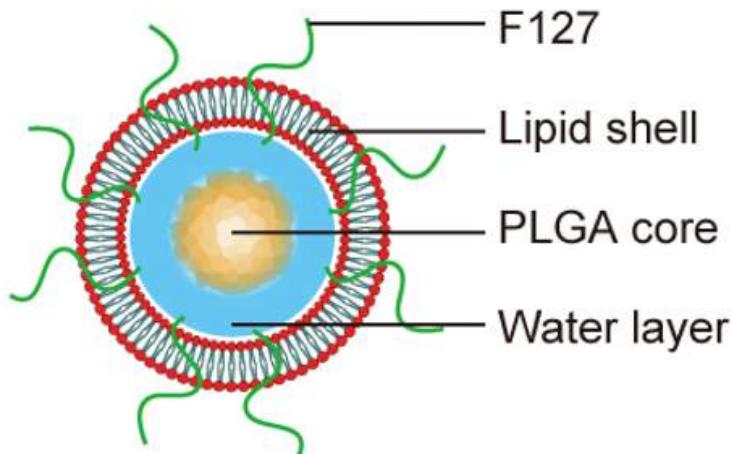


黏液素的粗粒化模型

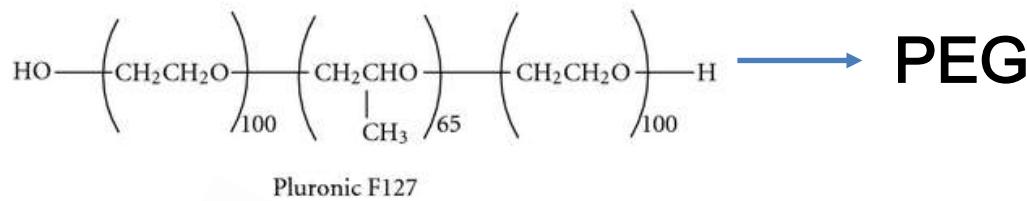




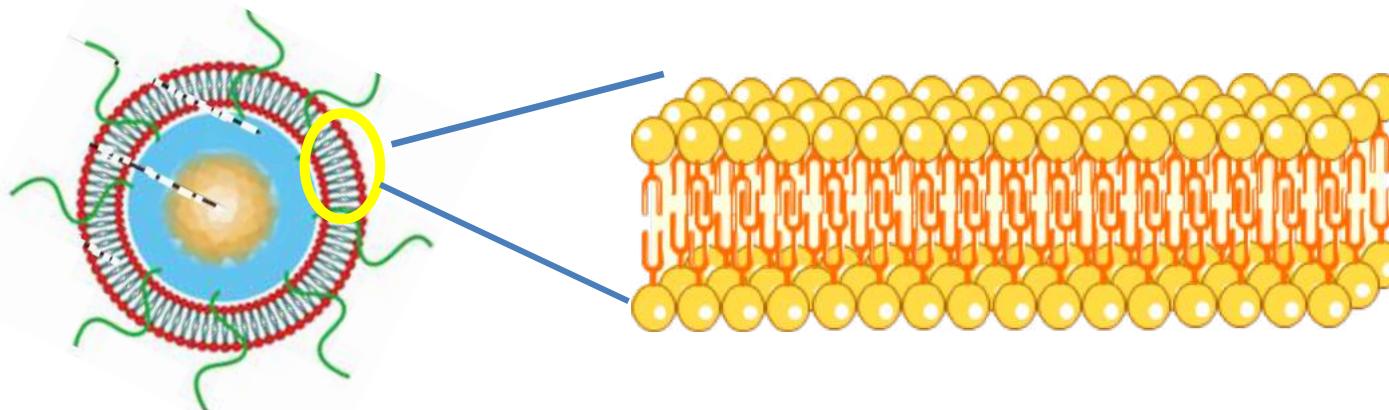
一、粗粒化分子动力学基本原理-如何构建粗粒化模型



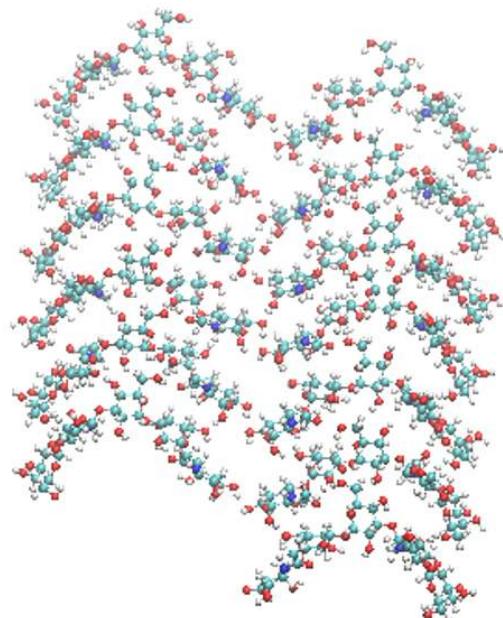
- 核-壳结构
- 主要通过表面F127
以及脂质体壳与黏
液接触并相互作用



相互作用：
1. 黏蛋白网络-磷脂膜
2. 黏蛋白网络-PEG



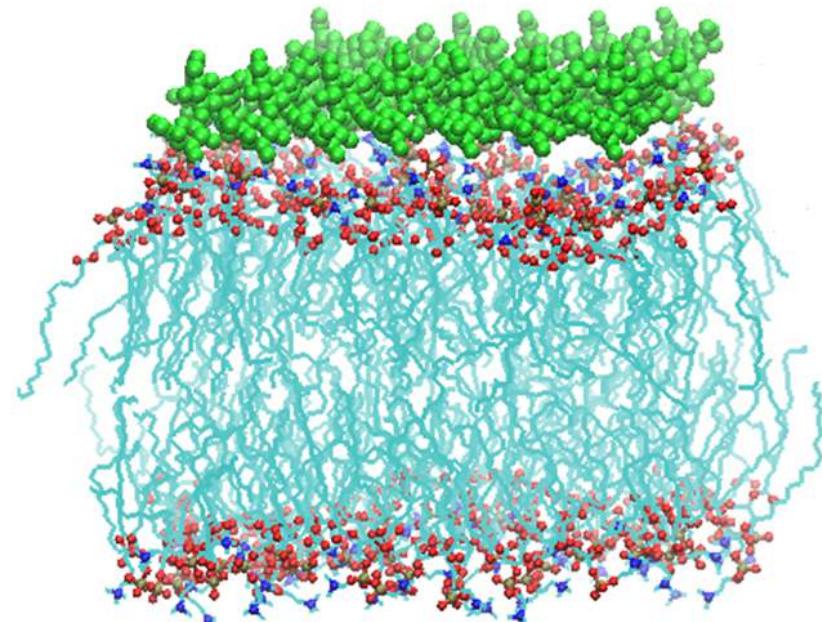
一、粗粒化分子动力学基本原理-如何构建粗粒化模型



13 O-Glycans

DGalpb1-3DGlcNAcb1-
3DGalpb1-
3DGalpb1-3DGalpNAcb1-OH

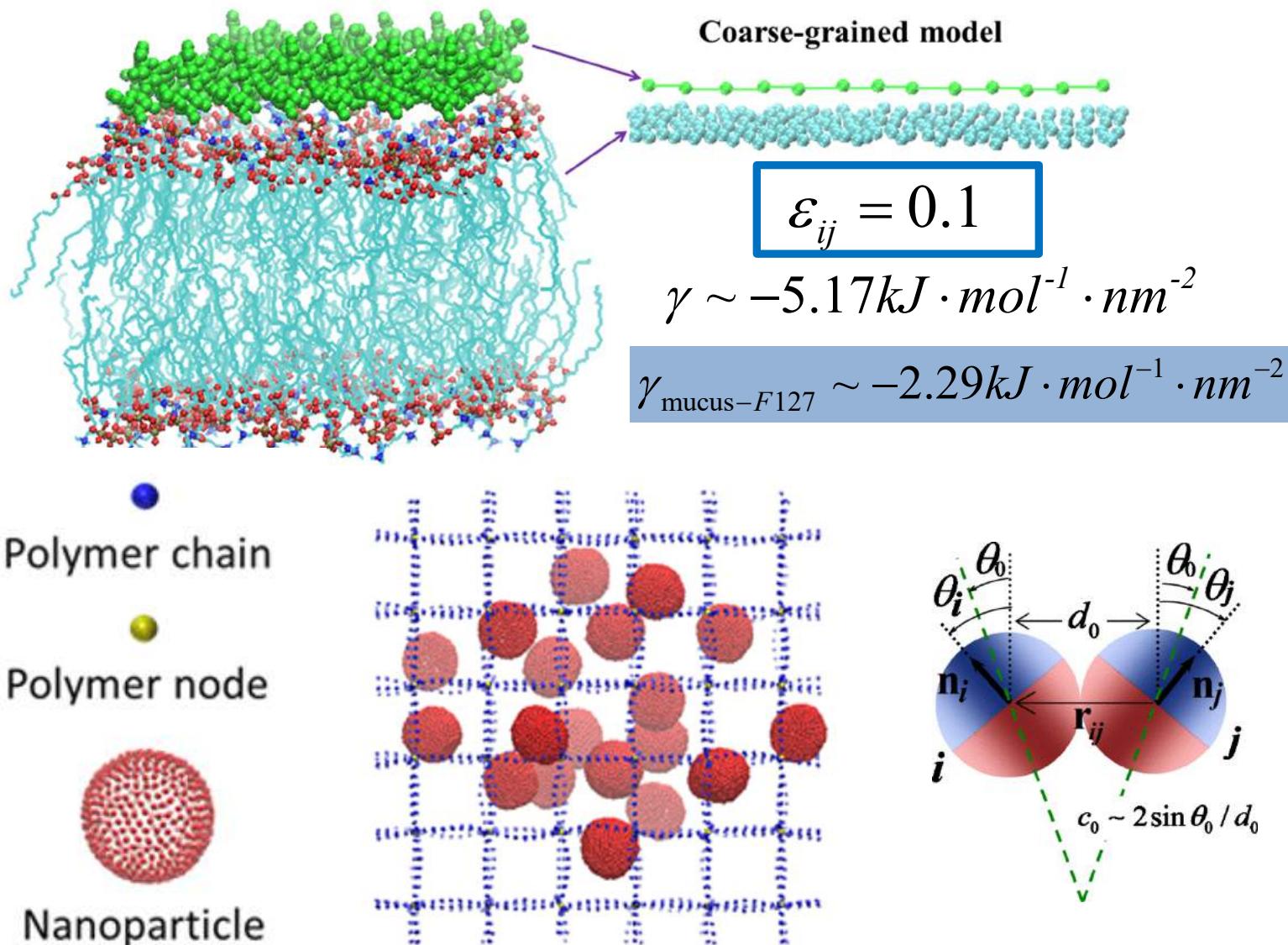
$$\gamma_{\text{mucus-lipid}} \sim -72.51 \text{ kJ} \cdot \text{mol}^{-1} \cdot \text{nm}^{-2}$$



$$\gamma_{\text{mucus-F127}} \sim -2.29 \text{ kJ} \cdot \text{mol}^{-1} \cdot \text{nm}^{-2}$$



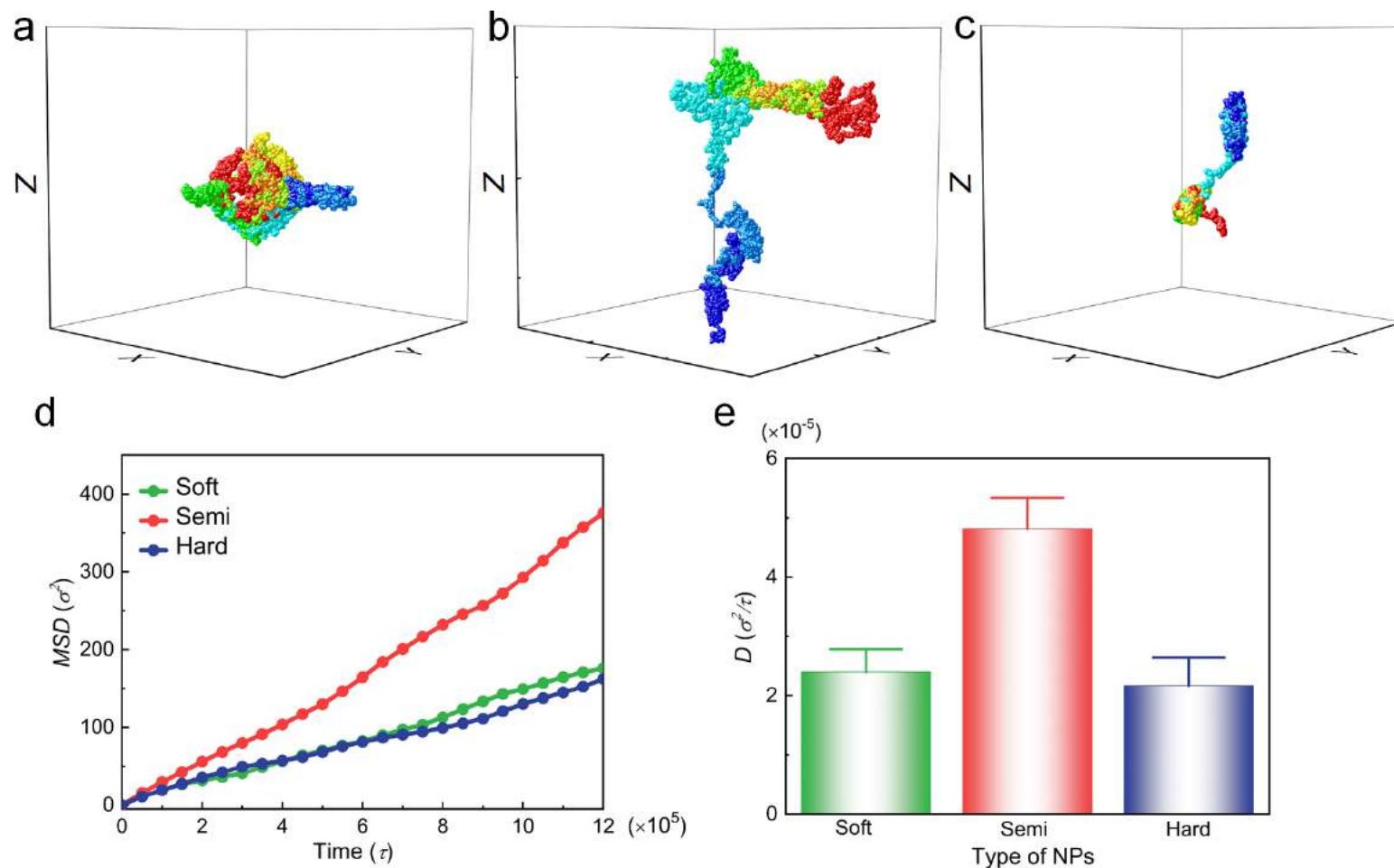
一、粗粒化分子动力学基本原理-如何构建粗粒化模型



一、粗粒化分子动力学基本原理-如何构建粗粒化模型



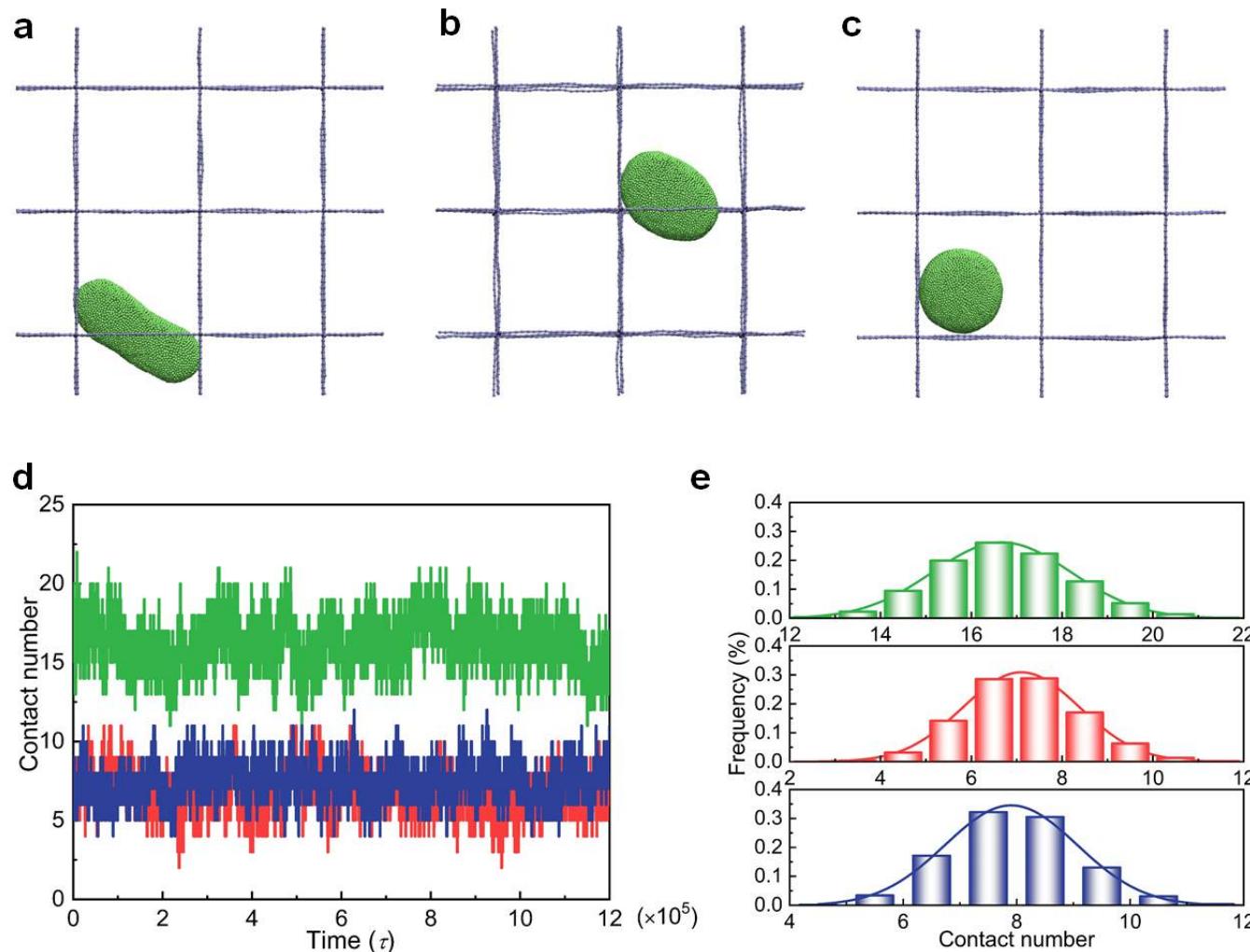
纳米粒子性质的影响-刚度效应



模拟证实半刚性的脂质体在网格中具有最优的扩散效率！

一、粗粒化分子动力学基本原理-如何构建粗粒化模型

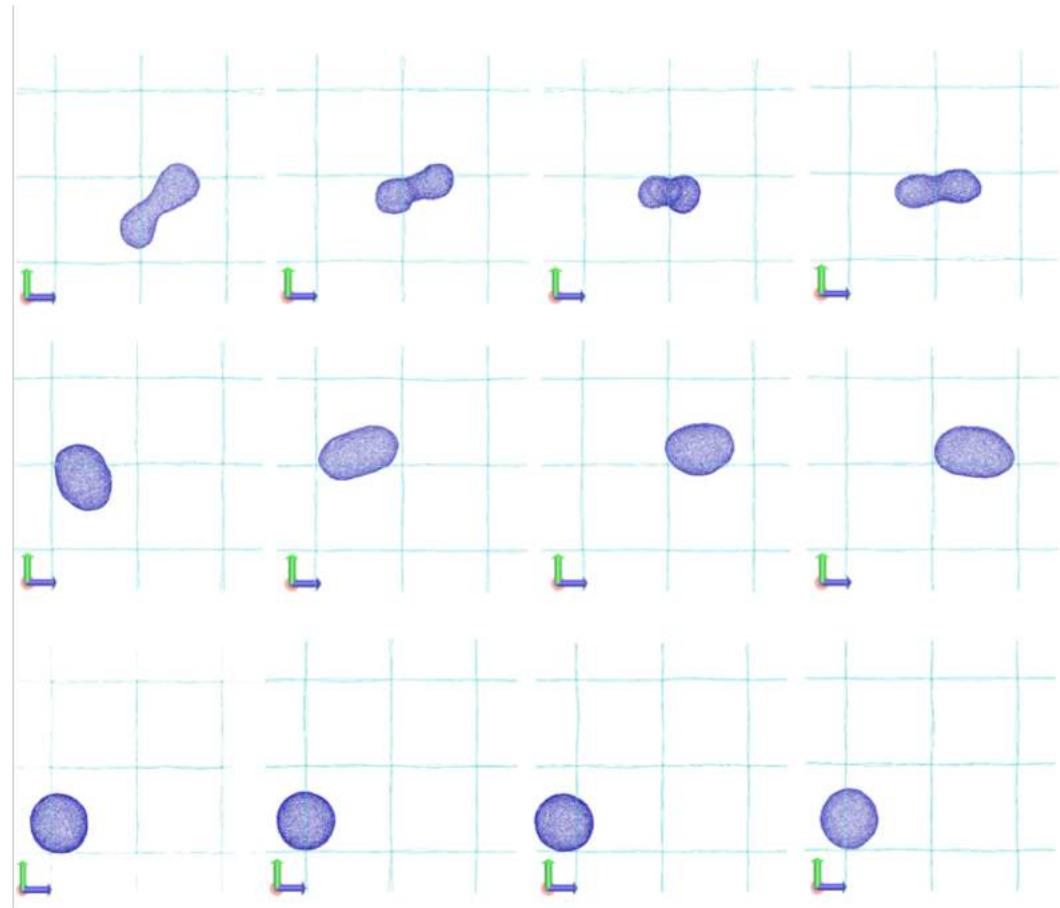
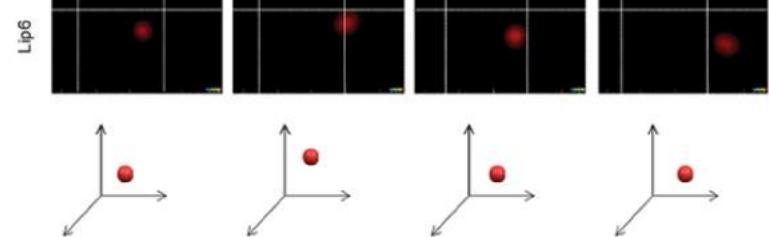
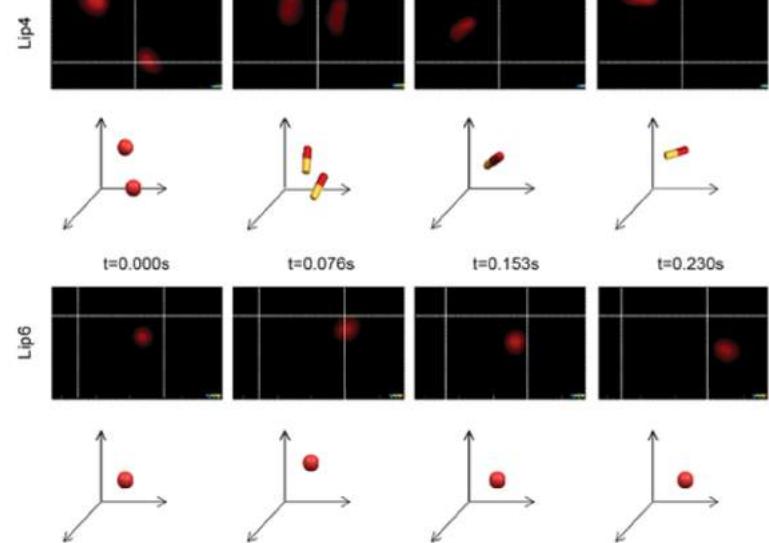
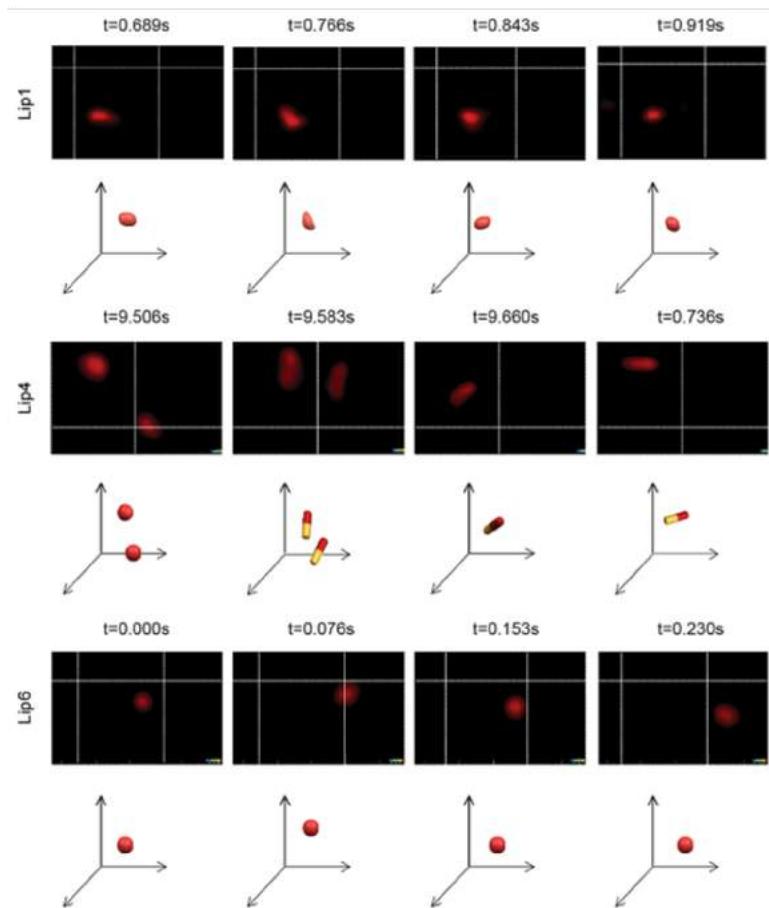
纳米粒子性质的影响-刚度效应



模拟发现脂质体与网格的接触点以及脂质体的形貌随其刚性的变化而变化

一、粗粒化分子动力学基本原理-如何构建粗粒化模型

纳米粒子性质的影响-刚度效应



由刚度主导的纳米粒子的形变程度是决定纳米粒子在蛋白网格中扩散行为的主要因素



一、粗粒化原理

二、耗散粒子动力学

三、模拟实例

- 棒状纳米粒子的入胞过程
- 细胞内化过程中的刚度效应
- 细胞膜介导的协同效应

四、加速分子动力学



二、DPD(耗散粒子动力学)

DPD发展历程

✓ 1992 年 Hoogerbrugge 和 Koelman 结合分子动力学和气体格子法发展出了一个能在介观时空尺度上模拟复杂流体的方法称为 DPD 方法

- 2001年Pagonabarraga提出多体DPD方法
- 2003年Groot将静电作用引入DPD模拟
- 2004年Groot由界面张力获取相互作用参数
- 2005年Eric将MD与DPD模拟相关联

基础理论

- 1995年Espanol和Warren提出了DPD中耗散力和随机力中权函数满足涨落耗散定理
- 1997年Groot和Warren通过自由能将高分子系统的 Flory-Huggins 理论与DPD相联
- 1999年Coveney和Fabritiis将DPD粒子质量和大小定义成可变



二、DPD(耗散粒子动力学)

DPD相互作用势

conservative forces

$$F_{ij}^C = \begin{cases} a_{ij}(1 - r_{ij})\hat{\mathbf{r}}_{ij} & r_{ij} < 1 \\ 0 & r_{ij} \geq 1 \end{cases}$$

用以描述DPD模拟系统中所有的分子内和分子间的物理非键作用力，其中作用参数 a_{ij} 可以通过Flory-Huggins理论或者界面张力求得

dissipative forces

$$F_{ij}^D = -\gamma \omega^D(r_{ij})(\hat{\mathbf{r}}_{ij} \cdot \mathbf{v}_{ij})\hat{\mathbf{r}}_{ij} \quad \sigma^2 = 2\gamma k_B T$$

random forces

$$F_{ij}^R = \sigma \omega^R(r_{ij}) \theta_{ij} \hat{\mathbf{r}}_{ij}$$

weighting factor

$$\omega^D(r) = [\omega^R(r)]^2 = \begin{cases} (1 - r)^2 & (r < 1) \\ 0 & (r \geq 1) \end{cases}$$

耗散力和随机力的值通过涨落-耗散定理相关联，两者之间只能任取其一，一般情况下只取耗散力参数

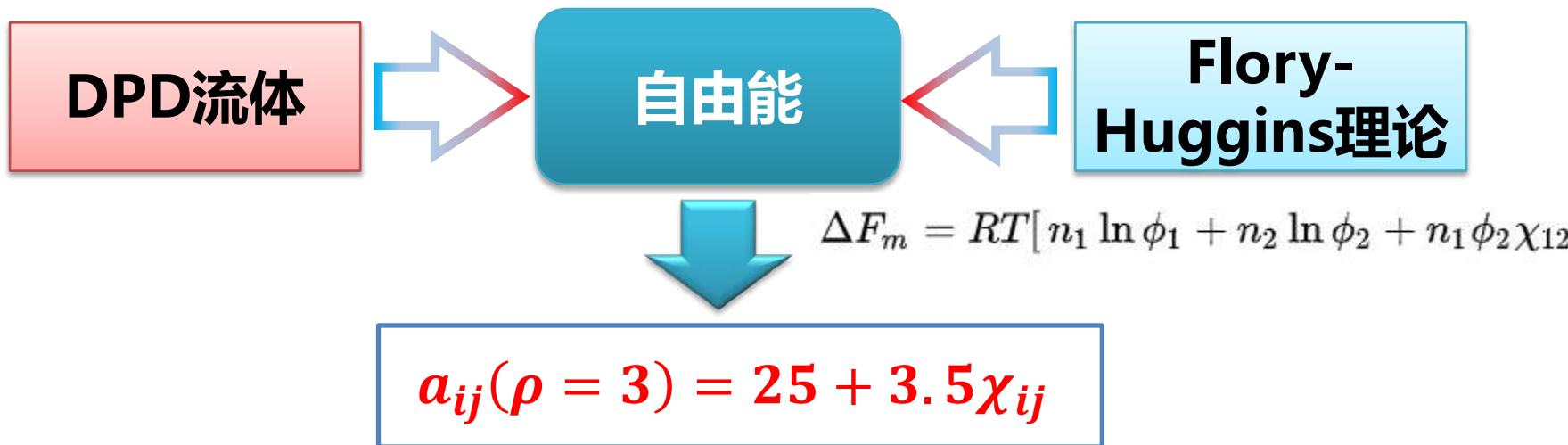


二、DPD(耗散粒子动力学)

DPD相互作用势

相互作用参数 a_{ij} 的确定

保守力相互排斥参数可由Flory-Huggins理论与DPD之间的映射关系求得



χ_{ij}

- 直接的方法是用Flory-Huggins模型关联高分子系统的相互平衡或其他热力学性质的实验结果求得
- 利用分子力学方法得到粗粒化粒子系统的混合能而求得
- 利用溶解度参数方法获得



二、DPD(耗散粒子动力学)

DPD特征概述

- ◆ In DPD, a particle represents a group of atoms
根据分子的实际结构需要合理的划分“组”
- ◆ The interactions between the coarse-grained particles should be “soft”, they can also be taken as carriers of the momentum of the fluid
与分子动力学不同，DPD粒子之间依靠软排斥势，因此允许粒子完全重叠
- ◆ Due to the integration of the degrees of freedom corresponding to the intra-structures of a DPD particle, we should add dissipationon each particle
耗散力主要用来描述体系能量的耗散
- ◆ To compensate heat sink, random force is needed.
额外施加的随机力调控模拟体系的温度
- ◆ The most important parameter in DPD is the a_{ij}
模拟结果对参数 a_{ij} 有一定的依赖性



二、DPD(耗散粒子动力学)

DPD计算流程

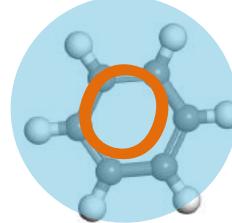
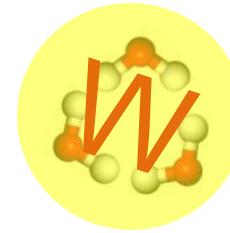
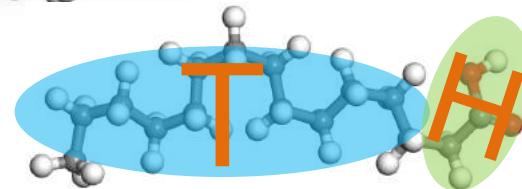
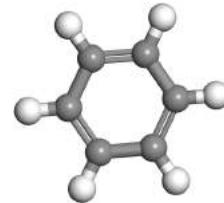
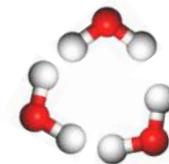
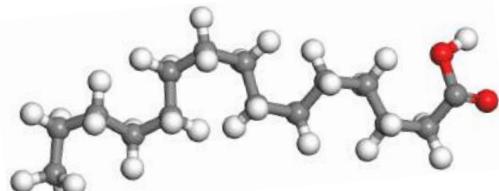
定义珠子



计算相互作用参数



设置初始构型及模拟环境进行模拟



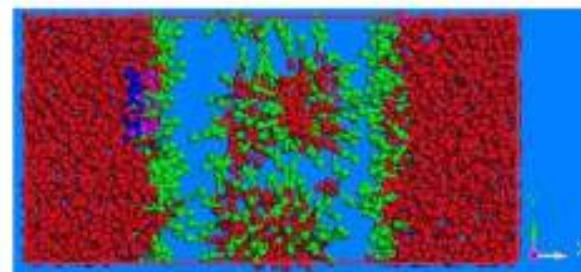
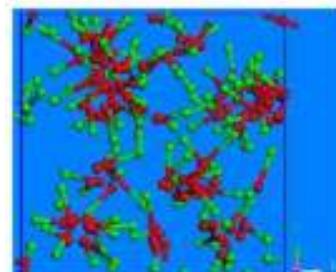
参数	H	T	O	W
H				
T	保守力作用参数a			
O				
W				

$$\mathbf{F}_{ij} = \mathbf{F}_{ij}^C + \mathbf{F}_{ij}^D + \mathbf{F}_{ij}^R$$

$$\mathbf{F}_{ij}^C = a_{ij} \omega(r_{ij}) \mathbf{n}_{ij}$$

$$\mathbf{F}_{ij}^D = -\gamma \omega^2(r_{ij}) (\mathbf{n}_{ij} \cdot \mathbf{v}_{ij}) \mathbf{n}_{ij}$$

$$\mathbf{F}_{ij}^R = \sigma \omega(r_{ij}) \theta_{ij} (\Delta t)^{-1/2} \mathbf{n}_{ij}$$





一、粗粒化原理

二、耗散粒子动力学

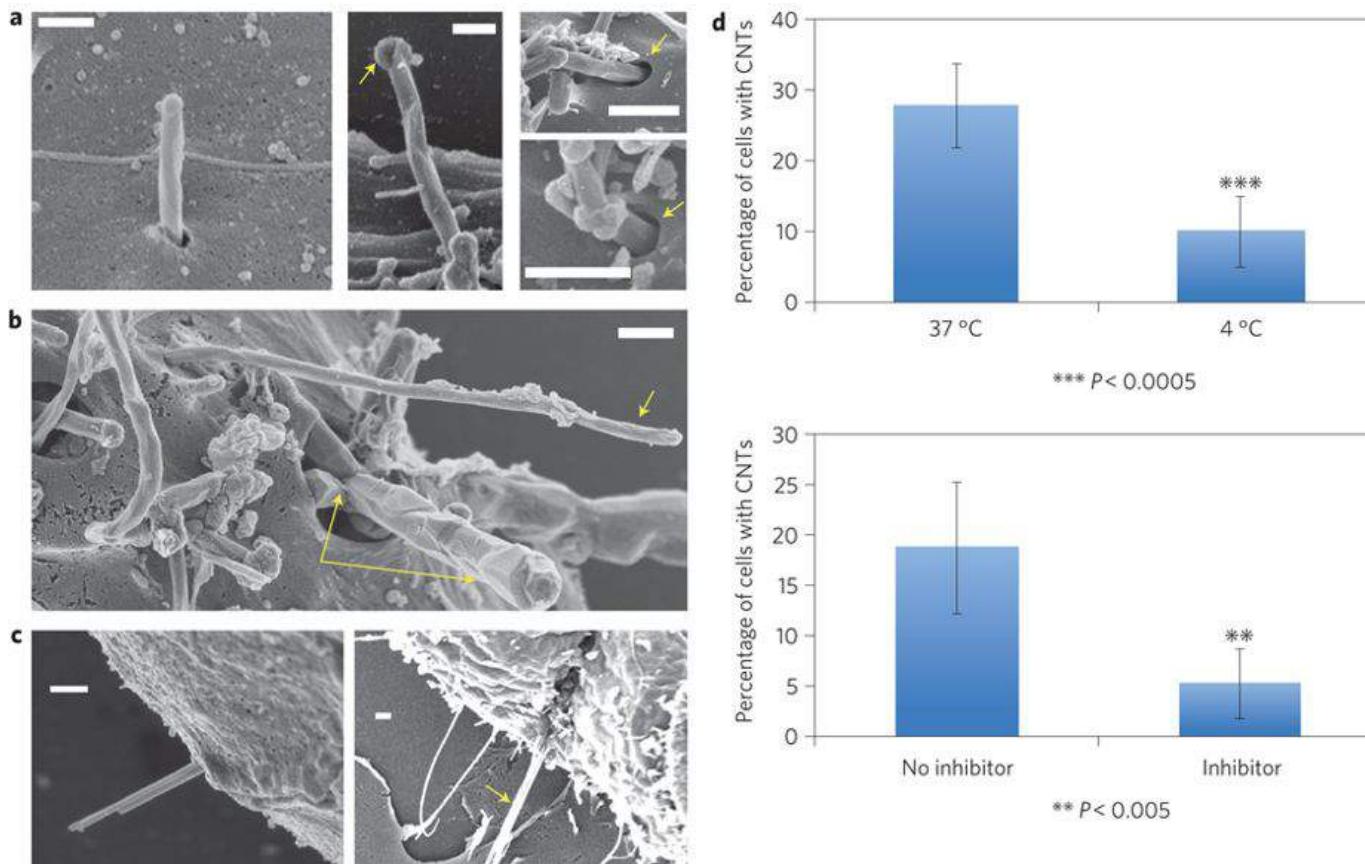
三、模拟实例

- 棒状纳米粒子的入胞过程
- 细胞内化过程中的刚度效应
- 细胞膜介导的协同效应

四、加速分子动力学

三、模拟实例-粗粒化分子动力学模拟

棒状纳米粒子的入胞过程



实验发现多壁碳纳米管、金纳米线、石棉纤维等棒状的纳米粒子
入胞时与细胞膜平面有一个夹角

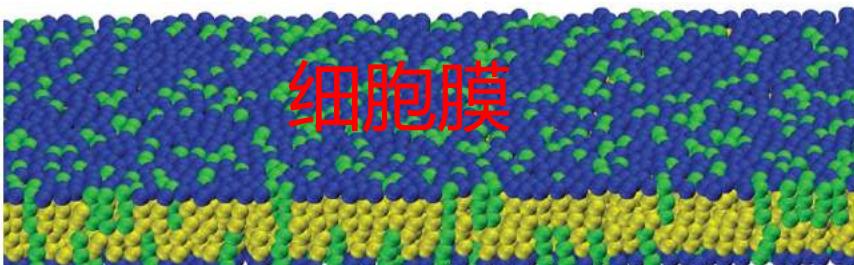
Why tip entry is the preferred mode of cellular uptake?



三、模拟实例-粗粒化分子动力学模拟

棒状纳米粒子的入胞过程

粗粒化模拟模型



多壁碳纳米管 模拟
中设为一个刚体

相互作用力场势

$$U_{lj}(r) = 4\epsilon_{ij} \left[\left(\frac{b}{r}\right)^{12} - \left(\frac{b}{r}\right)^6 \right] \quad 0 < r < r_{cut} = 2.5b$$

$$U_{WCA}(r) = 4\epsilon_{ij} \left[\left(\frac{b}{r}\right)^{12} - \left(\frac{b}{r}\right)^6 + 0.25 \right] \quad 0 < r < r_{cut} = 2.5b$$

$$U_{cos}(r) = \begin{cases} \epsilon_{ij} + U_{WCA}(r) & r < r_{cut} = 2^{1/6}b \\ -\epsilon_{ij} \cos^2 \left(\frac{\pi(r - r_{cut})}{2\omega} \right) & r_{cut} < r < r_{cut} + \omega \end{cases}$$

$$U_{FENE}(r) = -\frac{1}{2} k_{FENE} r_\infty^2 \ln \left(1 - \frac{r^2}{r_\infty^2} \right) \quad 0 < r < r_\infty = 1.5\sigma$$

$$U_{harmonic}(r) = \frac{1}{2} k_{harmonic} (r - r_0)^2 \quad 0 < r < r_0 = 4\sigma$$



三、模拟实例-粗粒化分子动力学模拟

棒状纳米粒子的入胞过程

各类粒子之间的相互作用

Type 1	Type 2	interaction	parameters
Lipid/receptor head	Lipid/receptor head	WCA	$b=0.95 \sigma$
Lipid/receptor head	Lipid/receptor tail	WCA	$b=0.95 \sigma$
Lipid/receptor tail	Lipid/receptor tail	COS	$b=\sigma$, $w=1.6\sigma$
Lipid/receptor tail	MWCNT	WCA	$b=0.95 \sigma$
Lipid/receptor tail	Ligand	WCA	$b=0.95 \sigma$
Lipid head	MWCNT	WCA	$b=0.95 \sigma$
Receptor head	MWCNT	WCA	$b=0.95 \sigma$
Lipid head	Ligand	WCA	$b=0.95 \sigma$
Receptor head	Ligand	LJ	$b=\sigma$, $\epsilon_{ij} = 2.5\epsilon$



三、模拟实例-粗粒化分子动力学模拟

棒状纳米粒子的入胞过程

Lammps输入文件 (in文件)

```
# Deserno lipids
units          lj
dimension     3
boundary      p p p
atom_style    bond
read_data     readdat.dat

group bilayer type 1 2 3 4
group lipid   type 1 2 3
group receptor type 2 3 4
group MWCNT   type 5 6
group ligand   type 6

#-----definition the interaction-----
pair_style hybrid/overlay table linear 600 1j/cut 2.5 &
dpd/tstat 1.1 1.1 3.0 34387
pair_coeff * * dpd/tstat 1.0
pair_coeff 1 1 table tabulated_potential.dat HEAD_HEAD
pair_coeff 1 2*3 table tabulated_potential.dat HEAD_TAIL
pair_coeff 1 4*6 table tabulated_potential.dat HEAD_HEAD
pair_coeff 2*3 2*3 table tabulated_potential.dat TAIL_TAIL_Wc_1.6
pair_coeff 2*3 4*6 table tabulated_potential.dat HEAD_TAIL
pair_coeff 4 4 table tabulated_potential.dat HEAD_HEAD
pair_coeff 4 5 table tabulated_potential.dat HEAD_HEAD
pair_coeff 4 6 1j/cut 2.5 1.0 2.5
pair_coeff 5*6 5*6 1j/cut 0.0 1.0 1.122462
pair_modify shift yes
comm_modify vel yes
special_bonds fene
neighbor 1.0 bin
neigh_modify delay 2 every 2 check yes
#####
```

} 体系中的组份

} 相互作用势



三、模拟实例-粗粒化分子动力学模拟

棒状纳米粒子的入胞过程

Lammps输入文件 (in文件)

```
#####
mass * 1.0
timestep 0.01
bond_style hybrid fene harmonic
bond_coeff 1 fene 30 1.5 1.0 1
bond_coeff 2 fene 30 1.5 1.0 1.0
bond_coeff 3 harmonic 10 4
thermo 1000
thermo_style custom step temp etotal lx ly press ebond bonds
velocity bilayer create 1.1 12345
dump 1 all custom 5000 traj.lammpstrj id mol type x y z ix iy iz
```

```
fix 1 MWCNT rigid single
fix 2 MWCNT setforce 0.0 0.0 0.0
min_style cg
minimize 1.0e-8 1.0e-8 100000 100000
```

```
unfix 1
unfix 2
fix 1 MWCNT rigid/nve langevin 1.1 1.1 1.0 123456
fix 2 bilayer press/berendsen x 0 0 100 y 0 0 100 couple xy
fix 3 bilayer nve
run 5000000
```

相互作用键势

能量最小化

系统控制



三、模拟实例-粗粒化分子动力学模拟

棒状纳米粒子的入胞过程

Lammps输入文件（结构文件）

LAMMPS simulation

139702 atoms
133047 bonds

6 atom types
3 bond types

0.000 160.000 xlo xhi
0.000 160.000 ylo yhi
0.000 100.000 zlo zhi

Atoms

1	1	1	0.1590090000E+01	0.3048620000E+01	0.5030510000E+02
2	1	2	0.1610340000E+01	0.2691100000E+01	0.4937140000E+02
3	1	3	0.1373590000E+01	0.2150480000E+01	0.4853970000E+02
4	2	1	0.1567760000E+03	0.1498490000E+03	0.5092700000E+02
5	2	2	0.1568850000E+03	0.1494430000E+03	0.5005890000E+02
6	2	3	0.1571850000E+03	0.1490510000E+03	0.4915340000E+02
7	3	4	0.1544670000E+03	0.1481840000E+03	0.5067570000E+02
8	3	2	0.1547090000E+03	0.1481850000E+03	0.4973090000E+02
9	3	3	0.1548490000E+03	0.1479780000E+03	0.4869760000E+02
10	4	1	0.1444880000E+01	0.1522530000E+03	0.5104860000E+02
11	4	2	0.1451190000E+01	0.1524790000E+03	0.5008580000E+02
12	4	3	0.1567830000E+01	0.1531060000E+03	0.4926730000E+02
13	5	1	0.3451720000E+01	0.2114480000E+01	0.4751750000E+02
14	5	2	0.2745410000E+01	0.2527520000E+01	0.4800520000E+02
15	5	3	0.1885660000E+01	0.2972140000E+01	0.4827610000E+02
16	6	1	0.1559150000E+03	0.1546470000E+01	0.5133320000E+02
17	6	2	0.1558100000E+03	0.1674630000E+01	0.5029440000E+02
18	6	3	0.1556390000E+03	0.1350070000E+01	0.4931600000E+02

Bonds

1	1	1	2
2	2	2	3
3	3	1	3
4	1	4	5
5	2	5	6
6	3	4	6
7	1	7	8
8	2	8	9
9	3	7	9
10	1	10	11
11	2	11	12
12	3	10	12

粒子和键信息

模拟盒子信息

各个原子的详细信息

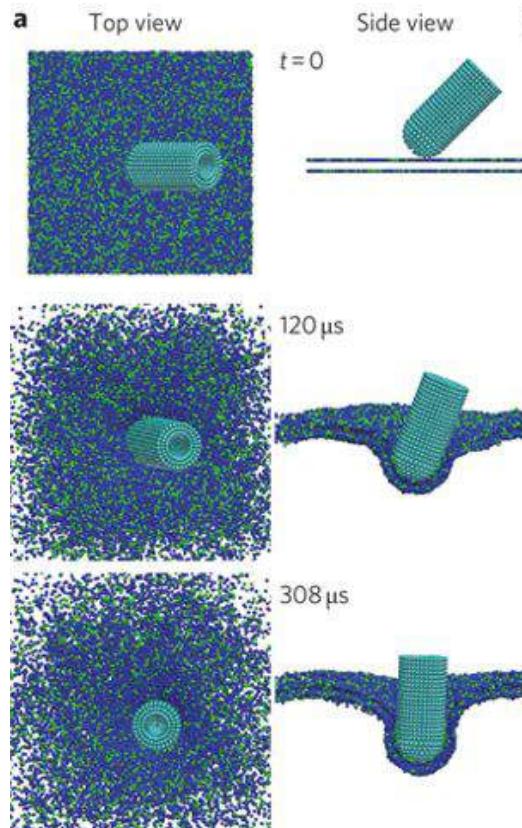
脂质分子和受体分子之间的连键信息

三、模拟实例-粗粒化分子动力学模拟

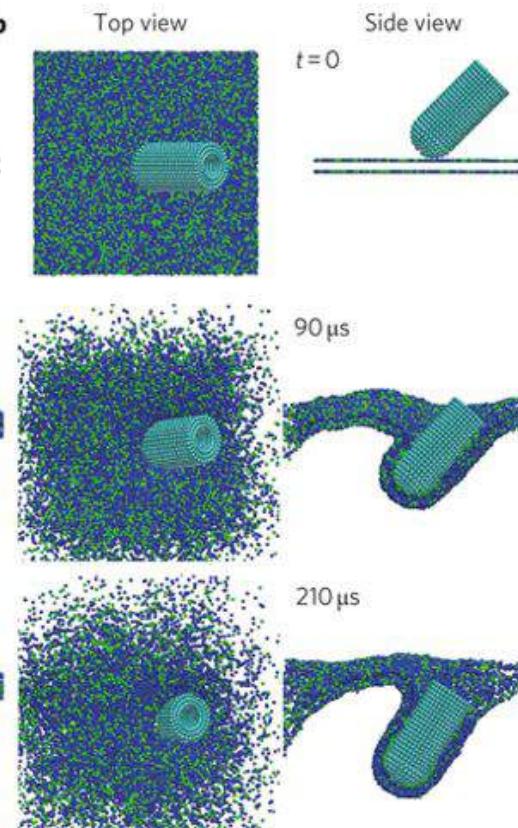
棒状纳米粒子的入胞过程

模拟结果

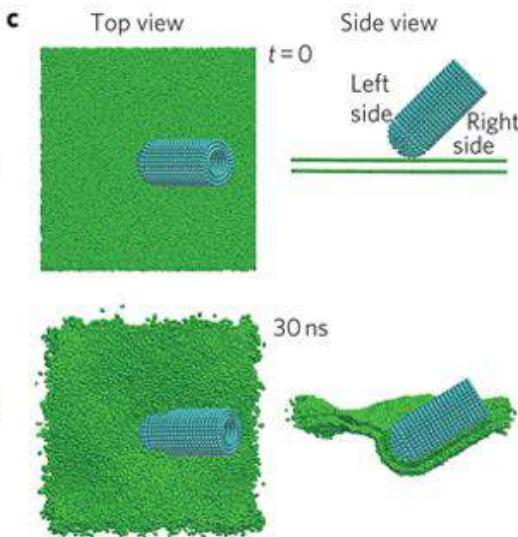
受体占比25%



受体占比33%



受体占比100%



棒状纳米粒子的入胞角度随着受体分子的增加而逐渐变平

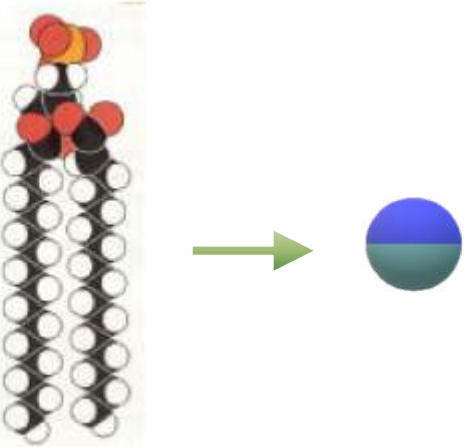


三、模拟实例-粗粒化分子动力学模拟

棒状纳米粒子的入胞过程

One-particle-thick model

粒子间的相互作用势函数



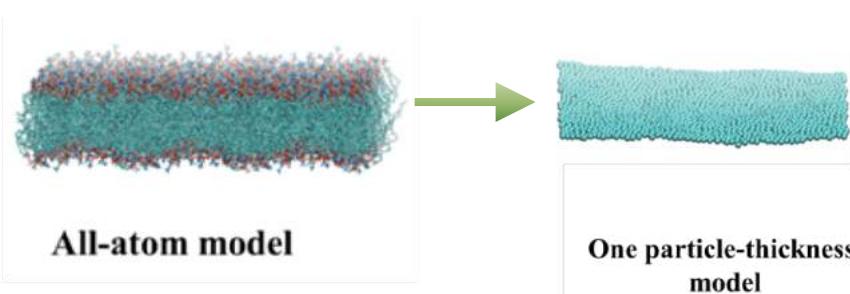
$$U(\mathbf{r}_{ij}, \mathbf{n}_i, \mathbf{n}_j) = \begin{cases} u_R(r) + \varepsilon_{beads-beads} [1 - \phi(\hat{\mathbf{r}}_{ij}, \mathbf{n}_i, \mathbf{n}_j)] & r < r_{min} \\ u_A(r)\phi(\hat{\mathbf{r}}_{ij}, \mathbf{n}_i, \mathbf{n}_j) & r_{min} < r < r_c \end{cases}$$

$$u_A(r) = -\varepsilon_{beads-beads} \cos^{2\zeta} \left(\frac{\pi}{2} \frac{r - r_{min}}{r_c - r_{min}} \right) \quad r_{min} < r < r_c$$

$$u_R(r) = \varepsilon_{beads-beads} \left[\left(\frac{r_{min}}{r} \right)^4 - 2 \left(\frac{r_{min}}{r} \right)^2 \right] \quad r < r_{min}$$

$$\phi(\hat{\mathbf{r}}_{ij}, \mathbf{n}_i, \mathbf{n}_j) = 1 + \mu(a(\hat{\mathbf{r}}_{ij}, \mathbf{n}_i, \mathbf{n}_j) - 1)$$

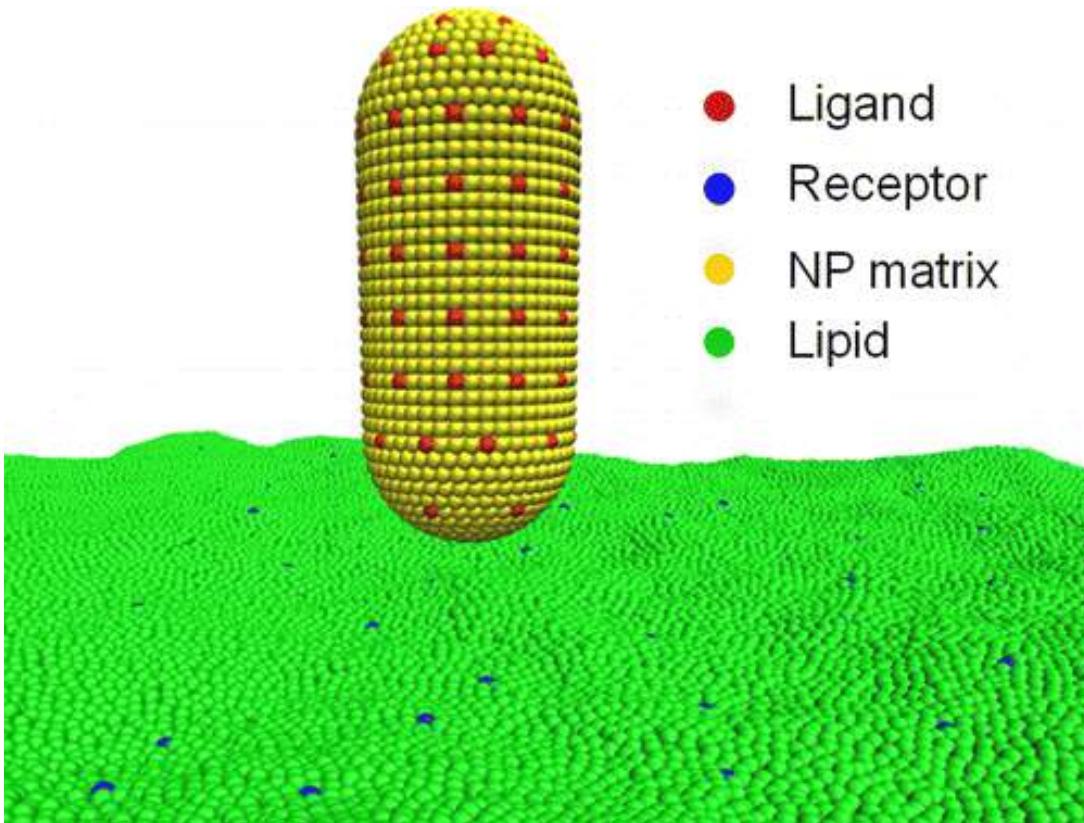
$$a(\hat{\mathbf{r}}_{ij}, \mathbf{n}_i, \mathbf{n}_j) = (\mathbf{n}_i \times \hat{\mathbf{r}}_{ij}) \cdot (\mathbf{n}_j \times \hat{\mathbf{r}}_{ij}) + \sin\theta_0 (\mathbf{n}_i - \mathbf{n}_j) \cdot \hat{\mathbf{r}}_{ij} - \sin^2\theta_0$$



高效简单，能够捕捉到介观层面的信息

三、模拟实例-粗粒化分子动力学模拟

棒状纳米粒子的入胞过程



纳米粒子的尺寸接近真实实验上的尺寸

配体和受体的密度分别为

$$\xi_l = 0.059/\sigma^2$$

$$\xi_R = 0.0038/\sigma^2$$

和真实状态相符



三、模拟实例-粗粒化分子动力学模拟

棒状纳米粒子的入胞过程

Lammps输入文件 (in文件)

```
units lj
dimension 3
boundary p p p
atom_style hybrid ellipsoid molecular
read_data readdat.dat
group bilayer type 1 2
group receptor type 2
group NP type 3 4
group ligand type 4
}
#-----nonbond interactions-----
pair_style hybrid lj/expand 5 fluidmembrane 2.6
pair_coeff 1*2 1*2 fluidmembrane 1.0 1.0 2.6 4 3 0
pair_coeff 1 3*4 lj/expand 1.0 1.0 1.0 1.122462
pair_coeff 2 3 lj/expand 1.0 1.0 1.0 1.122462
pair_coeff 2 4 lj/expand 5.0 1.0 1.0 5.0
pair_coeff 3*4 3*4 lj/expand 0.0 1.0 0.0 1.122462
pair_modify shift yes
comm_modify vel yes
neighbor 1.0 bin
neigh_modify delay 4 every 2 check yes one 1000
mass 1*2 1.0
mass 3*5 2.0
set type 1*2 shape 1 1 1
thermo 5000
thermo_style custom step temp etotal lx ly press ebond bonds
timestep 0.005
dump 1 all xyz 5000 dump.xyz
velocity bilayer create 0.2 87273 dist gaussian
# production run
fix 1 NP rigid single
fix 2 NP setforce 0.0 0.0 0.0
fix 3 bilayer langevin 0.2 0.2 0.1 12109 zero yes angmom 3.333 gjf no
fix 4 bilayer press/berendsen x 0 0 10 y 0 0 10 couple xy
fix 5 bilayer nve/asphere
run 100000
unfix 1
unfix 2
fix 1 NP langevin 0.2 0.2 0.1 123456 zero yes
fix 2 NP rigid/nve single
unfix 4
fix 4 bilayer press/berendsen x 0 0.0001 10 y 0 0.0001 10 couple xy
run 50000000
```

体系中的组份

相互作用势

系统控制



三、模拟实例-粗粒化分子动力学模拟

棒状纳米粒子的入胞过程

Lammps输入文件（结构文件）

LAMMPS simulation

```
16771    atoms
          5 atom types
15876    ellipsoids
```

} 粒子信息

```
0.000 120.000    xlo xhi
0.000 120.000    ylo yhi
0.000 100.000    zlo zhi
```

} 模拟盒子信息

Atoms

1	1	0.9499999881E+00	0.9499999881E+00	0.5000000000E+02	1	0.2387319952E+00	0		
2	1	0.9499999881E+00	0.1899999976E+01	0.5000000000E+02	1	0.2387319952E+00	0		
3	1	0.9499999881E+00	0.2849999964E+01	0.5000000000E+02	1	0.2387319952E+00	0		
4	1	0.9499999881E+00	0.3799999952E+01	0.5000000000E+02	1	0.2387319952E+00	0		
5	1	0.9499999881E+00	0.4749999940E+01	0.5000000000E+02	1	0.2387319952E+00	0		
6	1	0.9499999881E+00	0.5699999928E+01	0.5000000000E+02	1	0.2387319952E+00	0		
7	1	0.9499999881E+00	0.6649999917E+01	0.5000000000E+02	1	0.2387319952E+00	0		
8	1	0.9499999881E+00	0.7599999905E+01	0.5000000000E+02	1	0.2387319952E+00	0		
9	1	0.9499999881E+00	0.8549999893E+01	0.5000000000E+02	1	0.2387319952E+00	0		
10	1	0.9499999881E+00	0.9499999881E+01	0.5000000000E+02	1	0.2387319952E+00	0		

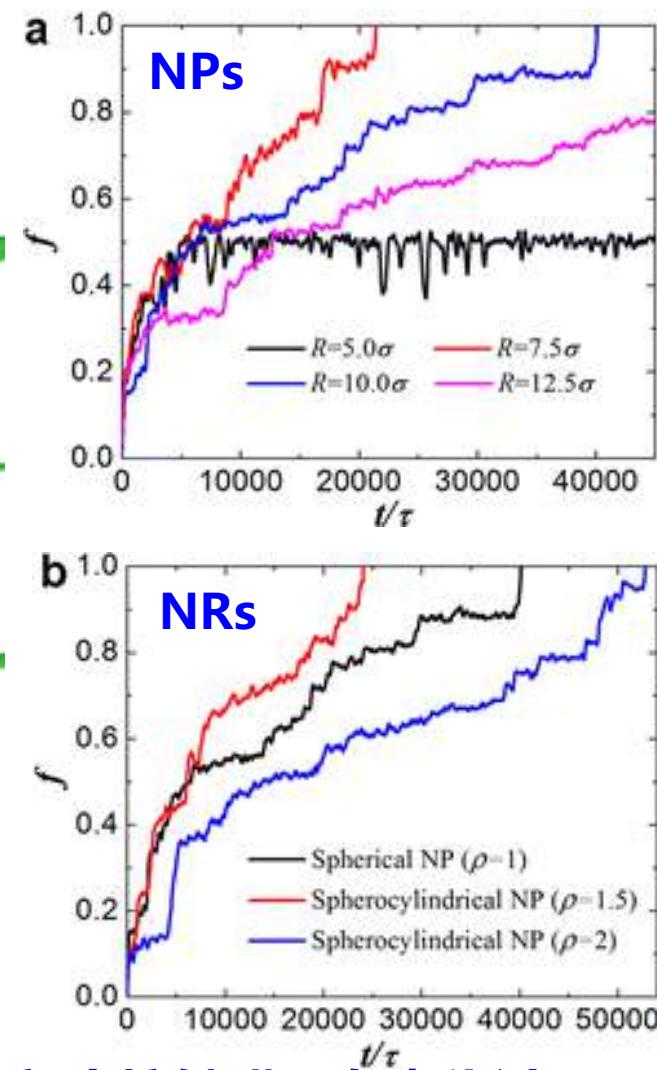
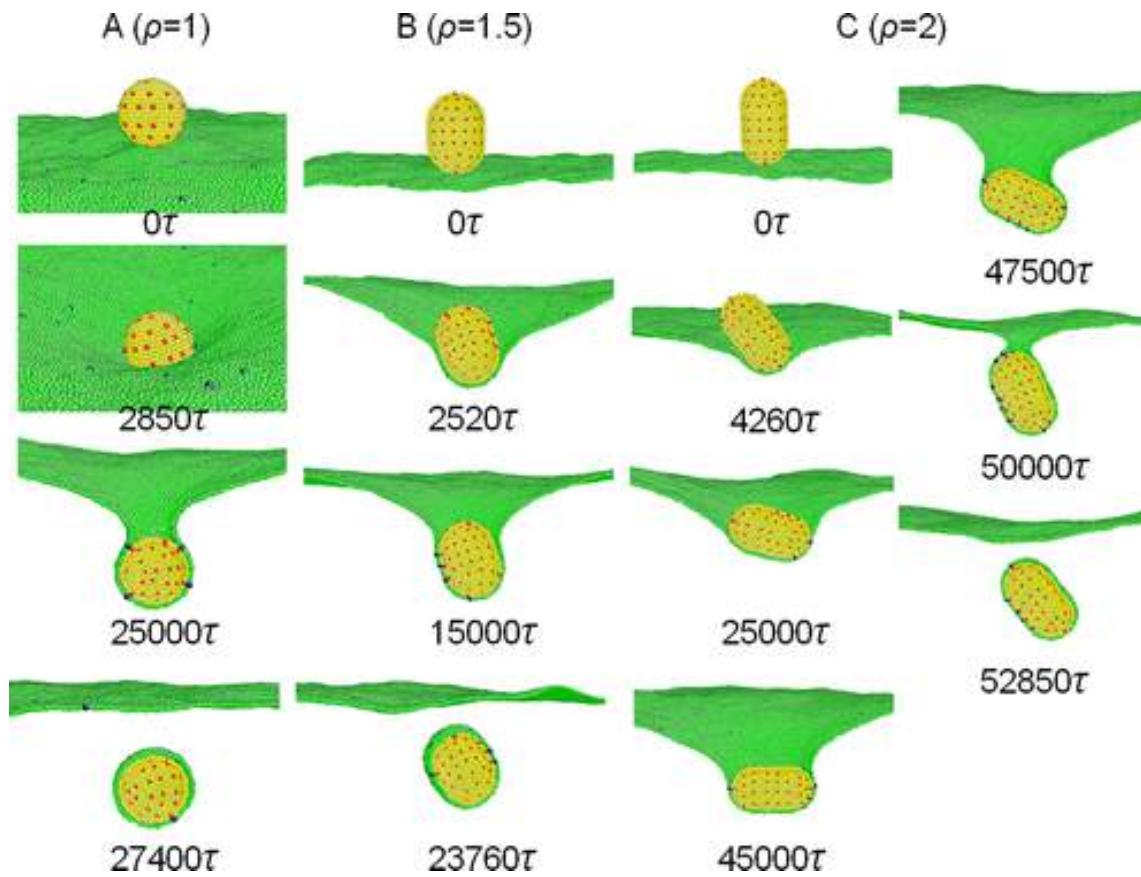
各个原子
的详细信
息



三、模拟实例-粗粒化分子动力学模拟

棒状纳米粒子的入胞过程

模拟结果



一般情况下，棒状纳米粒子在内化中的端部先接触膜，在内化过程中伴随着明显旋转过程



三、模拟实例-粗粒化分子动力学模拟

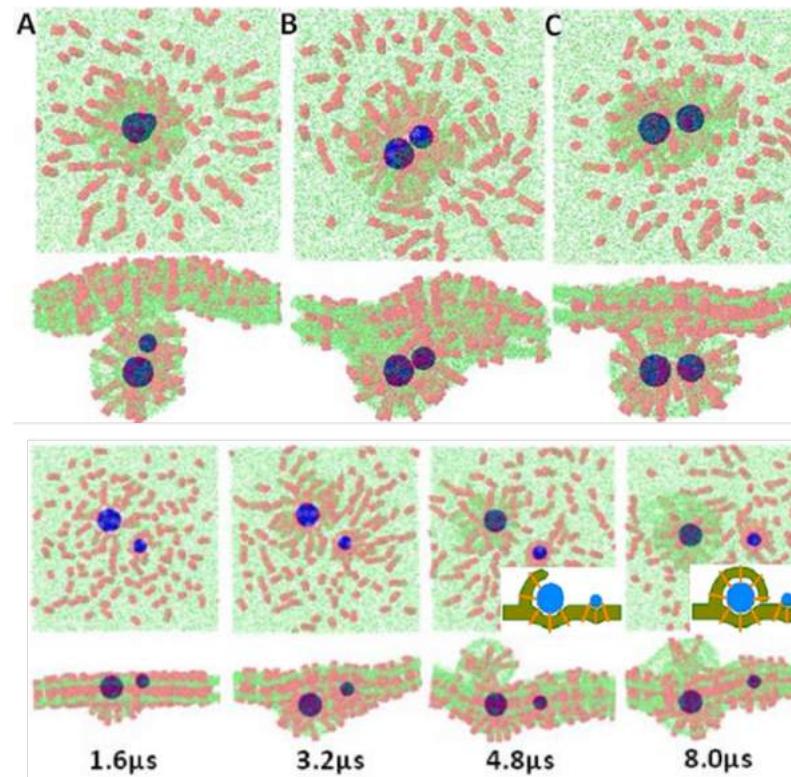
棒状纳米粒子的入胞过程

1. 实验发现一般情况下一维纳米粒子入胞时端部首先会接触，导致纳米粒子与细胞膜之间有夹角
2. 分子模拟证实了实验发现，并进一步发现了一维纳米粒子内化过程中的旋转现象。
3. 理论分析指出了旋转出现的作用机理，并预测了影响旋转的主要因素
4. 分子模拟验证证实了理论模型的预测，表明棒状纳米粒子的旋转主要受膜表面张力的影响

三、模拟实例

(DPD) 耗散粒子动力学模拟

细胞膜介导的协同效应

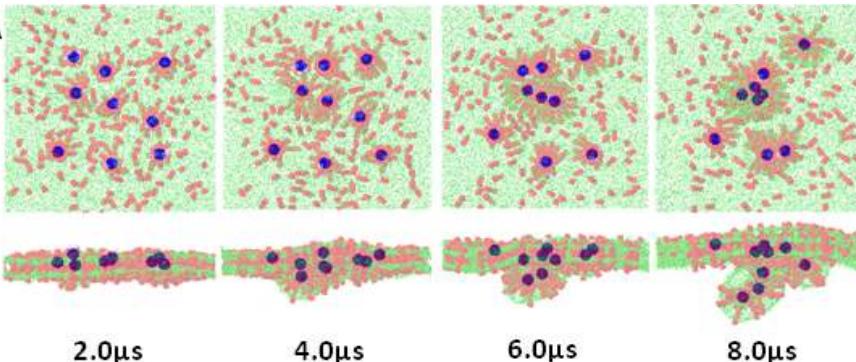


三、模拟实例-DPD

细胞膜介导的协同效应

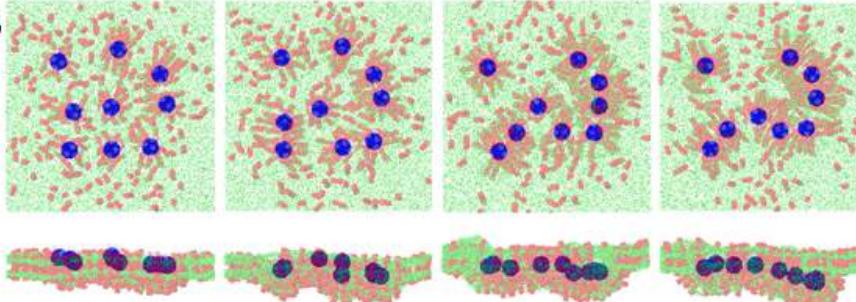
模拟结果

A



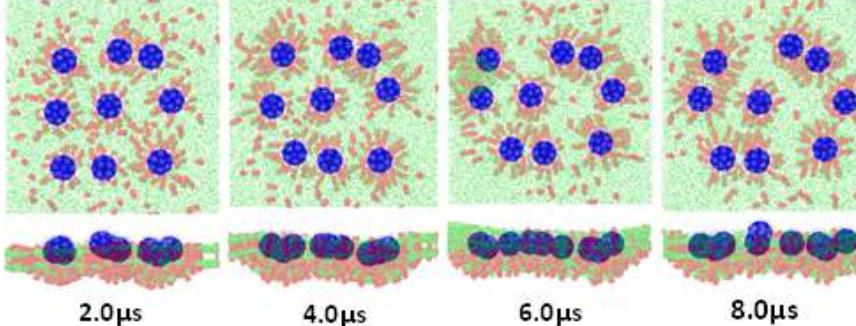
直径为2.5 nm的纳米粒子
在内吞之前形成紧密堆积
的团簇。

B



直径为4.0 nm的纳米粒子
在磷脂膜表面形成珍珠状
的线形排列

C

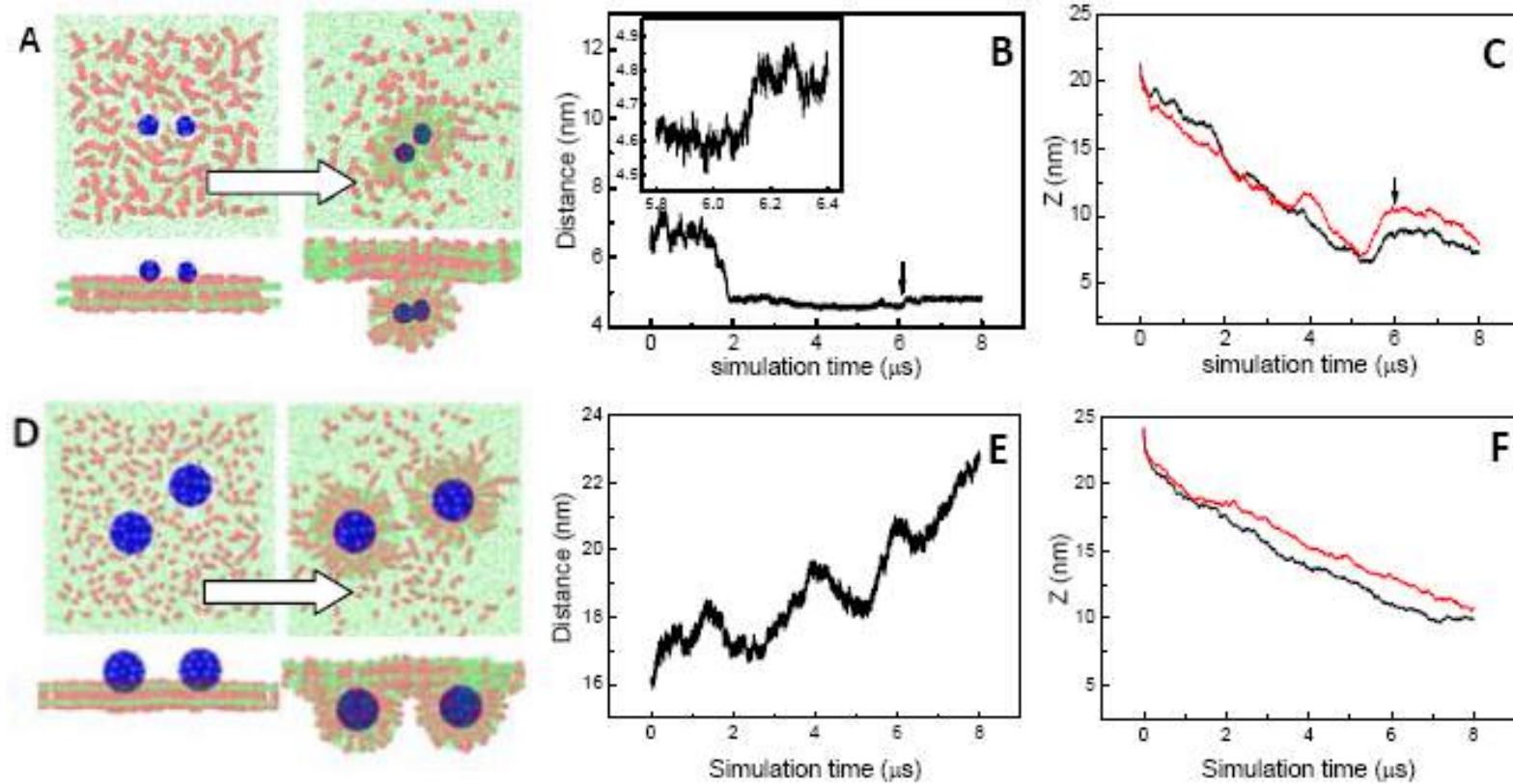


直径为6.0 nm的纳米粒子
在磷脂膜上相互远离并单
独完成内吞过程

三、模拟实例-DPD

细胞膜介导的协同效应

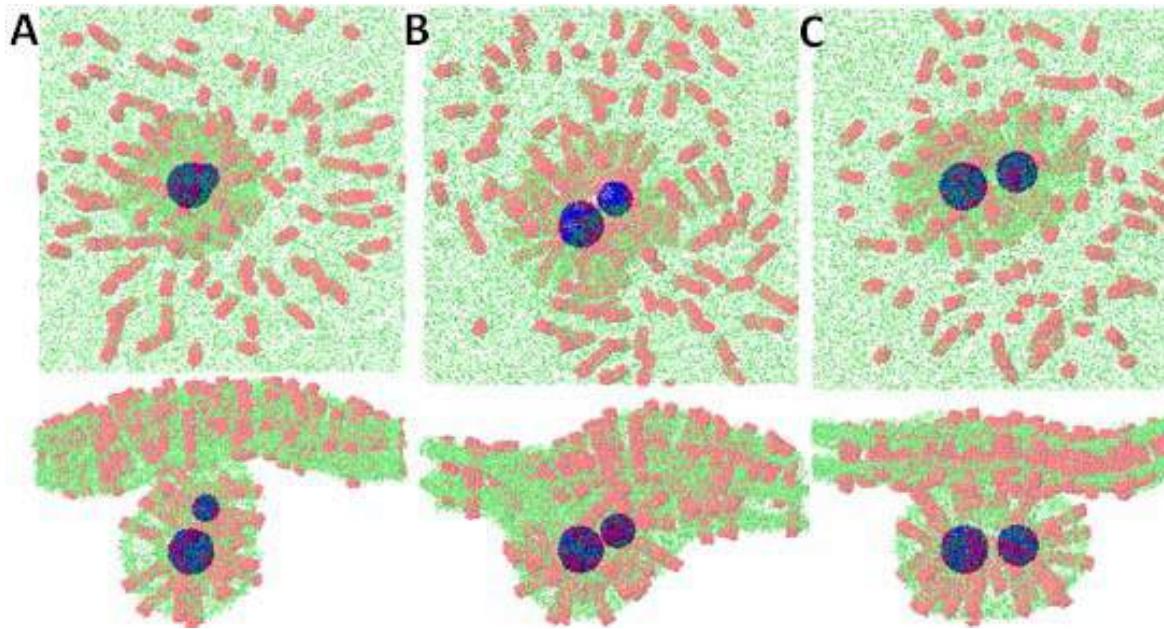
模拟结果



较小尺寸的两个纳米粒子协同内吞说明两者之间为相互吸引；
较大尺寸的两个纳米粒子单独内吞说明两者之间为相互排斥。

三、模拟实例-DPD

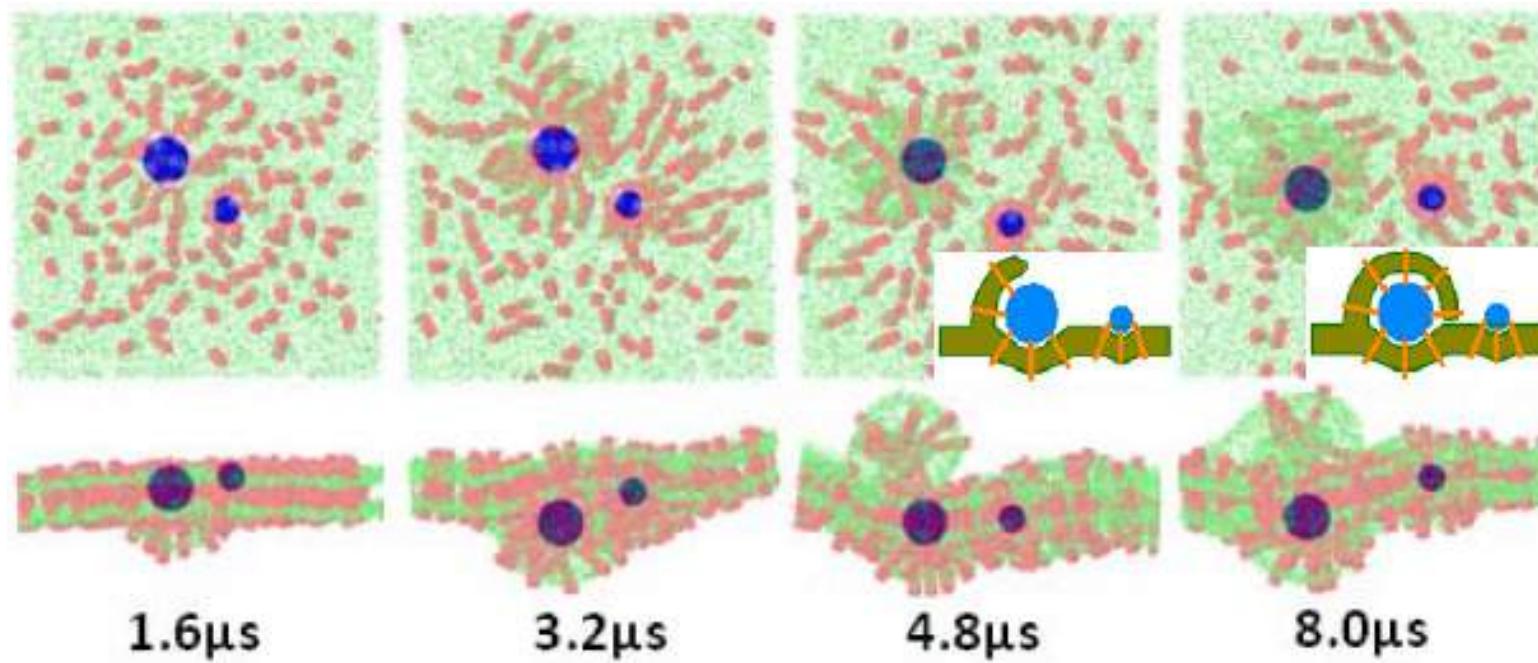
细胞膜介导的协同效应 模拟结果



随着两个纳米粒子尺寸区别的增大，其内吞路径逐渐由同步内
吞向不同步内吞转变

三、模拟实例-DPD

细胞膜介导的协同效应 模拟结果



在中等初始距离下，两个尺寸区别较大的纳米粒子倾向于按照类胞饮的方式进行内吞



一、粗粒化原理

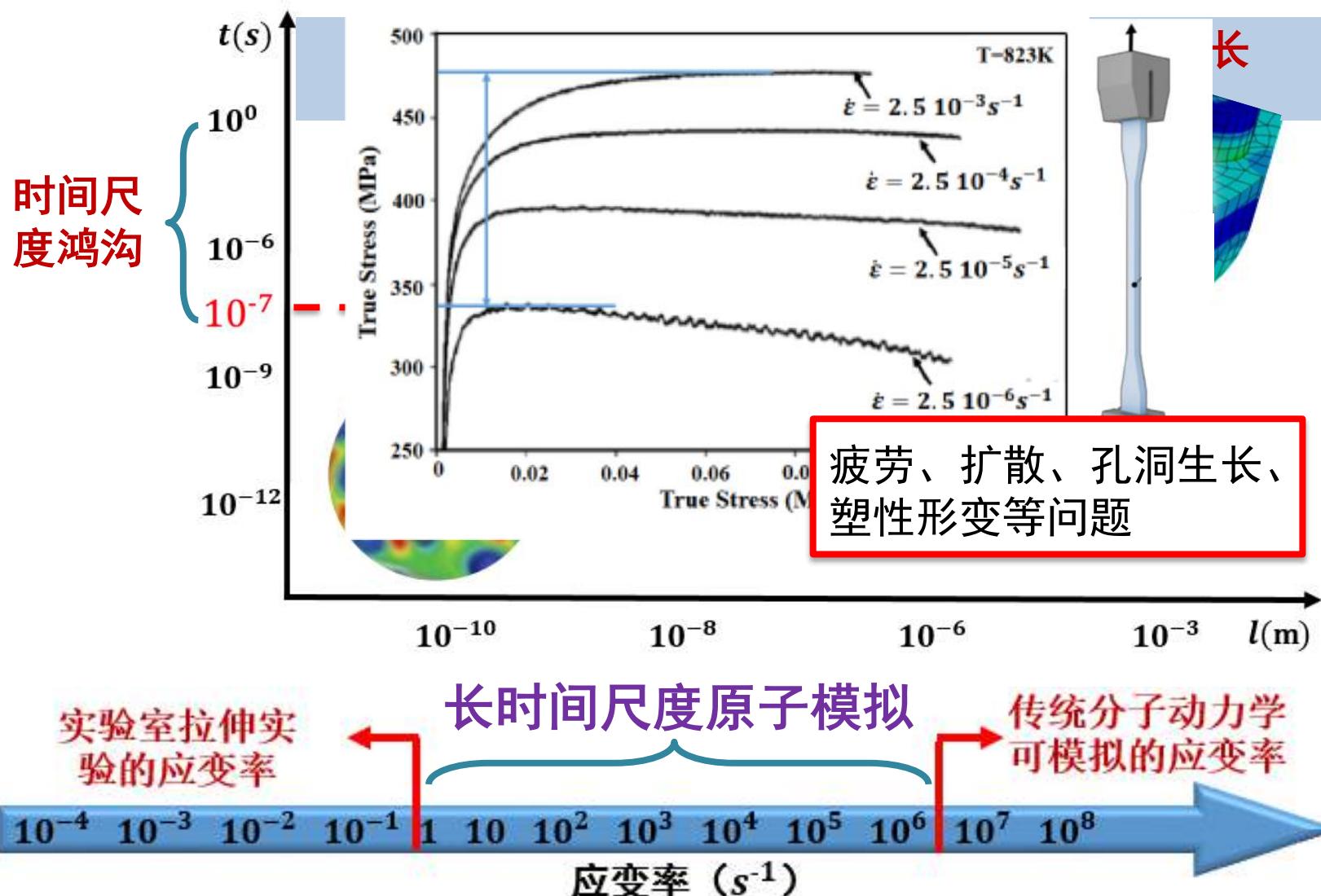
二、耗散粒子动力学

三、模拟实例

- 棒状纳米粒子的入胞过程
- 细胞内化过程中的刚度效应
- 细胞膜介导的协同效应

四、加速分子动力学

分子动力学在时间尺度的差异





四、加速分子动力学

Key bottlenecks of MD limitation

Regular time step: 1fs

Regular strain rate in MD: 10^8 1/s

Regular strain rate in experiments: 10^{-3} 1/s

Why?

For example: 10^5 atoms,

100 ps \rightarrow 1 hour of computing time

If the system is loading for 1s

1s = 10^{15} fs \rightarrow 10^{15} timesteps

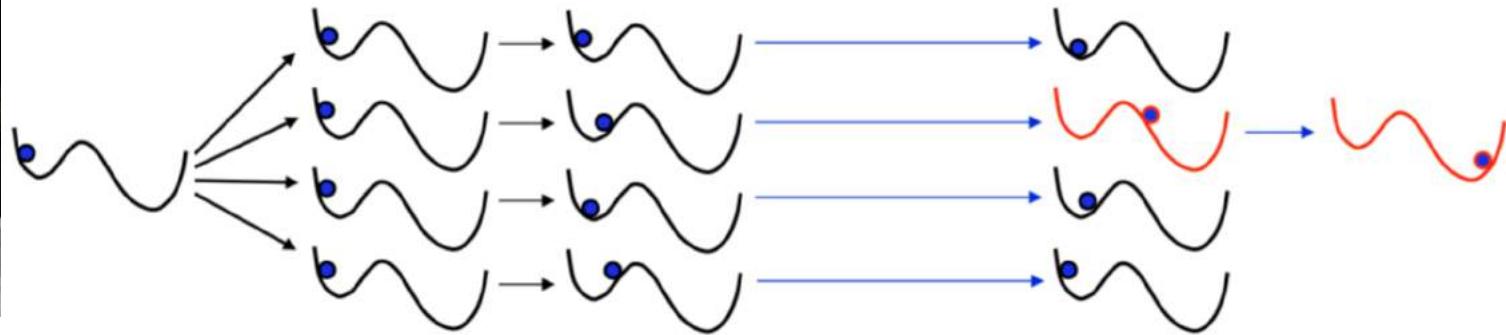
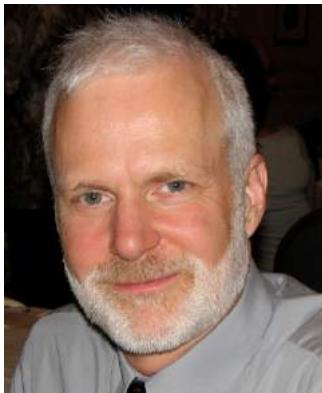
10^{10} hour of computing time

What does that mean?

1year = $365 \times 24 \sim 10^4$ hours $\Rightarrow 10^{10}$ hour $\sim 10^6$ years

四、加速分子动力学

Parallel replica dynamics



Arthur Voter

PRD is described in by Art Voter by performing accelerated dynamics that is suitable for infrequent-event systems that obey first-order kinetics. It is using multiple replicas of a system.

Each replica runs on a partition of one or more processors.

When a PRD simulation is performed, it is assumed that each replica is running the same model.

<https://lammps.sandia.gov/doc/prd.html>

Examples/prd



四、加速分子动力学

Temperature-accelerated dynamics

Higher temperature gives faster processes. But, one can not simply do MD at higher temperature, since high T and low T may have different processes and equilibrium states

IDEA of TAD

Use Higher temperature to find (sample) possible transitions, but execute them with their correct low-T probability

PROCEDURE

- Run at high-T until transition occurs
- Find E_a for the transition
- Reverse transition and run again at high-T



Leads to a catalogue of transitions and their activation barriers

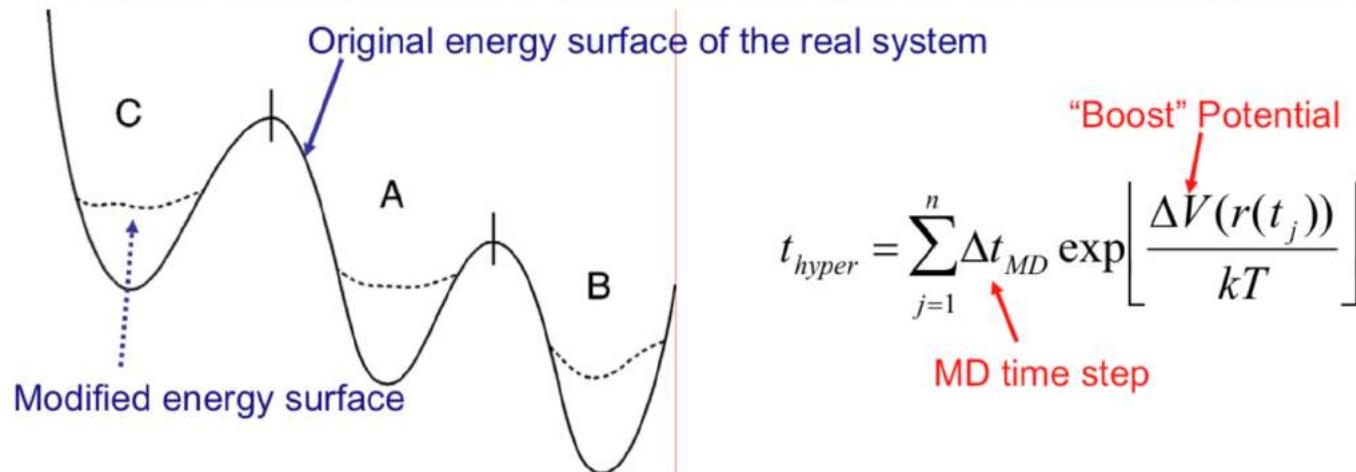
<https://lammps.sandia.gov/doc/tad.html>

Examples/tad

四、加速分子动力学

Hyperdynamics

Elevate the potential wells to make system transition out faster



- design bias potential ΔV (zero at dividing surfaces)
- run thermostatted trajectory on the biased surface ($V + \Delta V$)
- accumulate hypertime as

$$t_{\text{hyper}} = \sum \Delta t_{\text{MD}} \exp[\Delta V(R(t))/k_B T]$$

- time converges on correct value in long-time limit (w/ vanishing relative error)

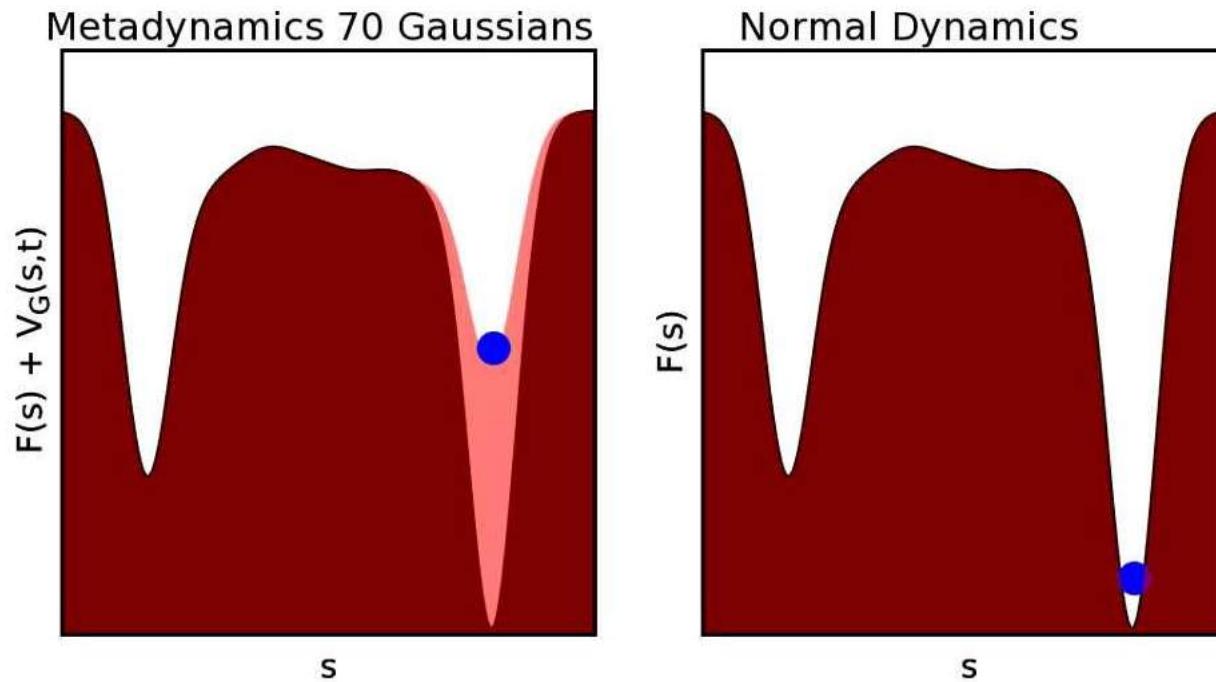
https://lammps.sandia.gov/doc/fix_hyper_local.html

Examples/hyper

四、加速分子动力学

Metadynamics

Laio, Alessandro, and Michele Parrinello. "Escaping free-energy minima." *Proceedings of the National Academy of Sciences* 99.20 (2002): 12562-12566.



$F(s)$ =Free energy along s

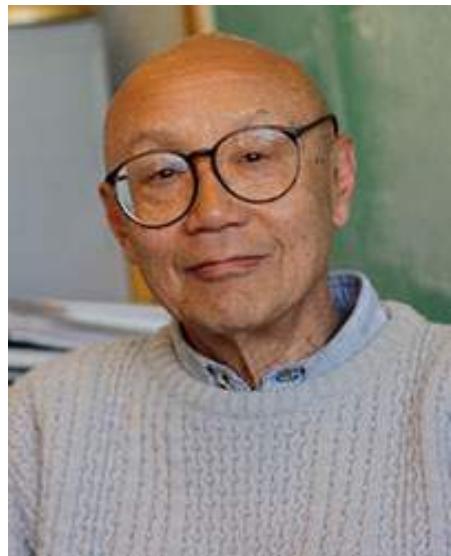
$V_G(s,t)=\sum_{i=1,2,\dots,N} h e^{[-(s-s_i)^2/2\sigma^2]}$ where h, σ =Gaussian height and width

<https://lammps.sandia.gov/doc/PDF/colvars-refman-lammps.pdf>

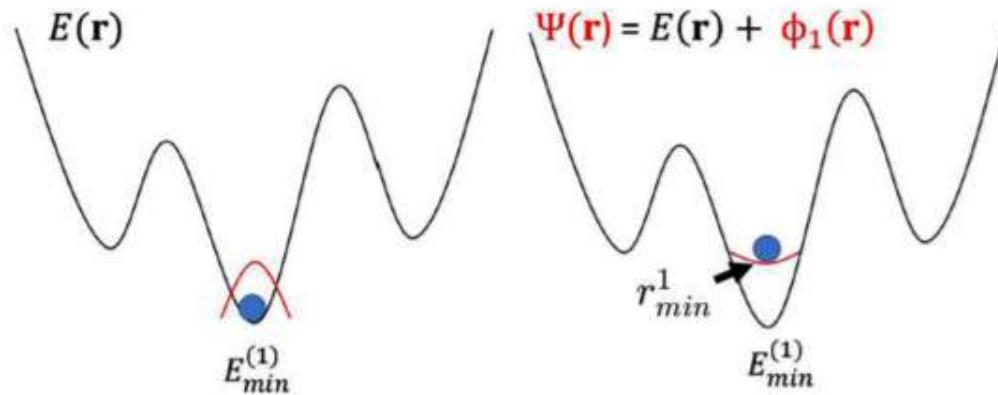
examples/USER/colvars

四、加速分子动力学

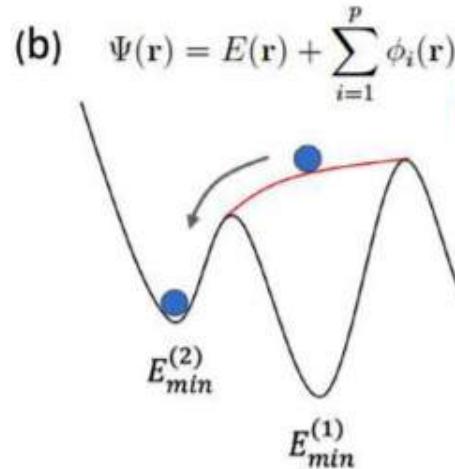
Autonomous Basin Climbing (ABC)



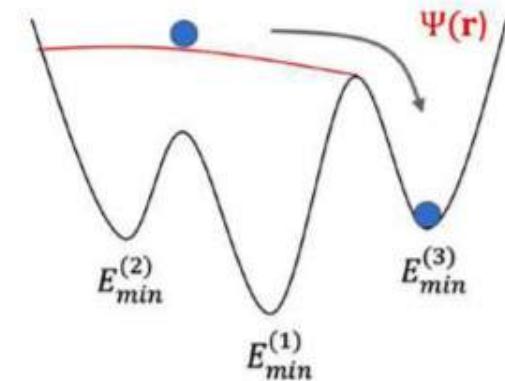
(a)



(b)



(c)



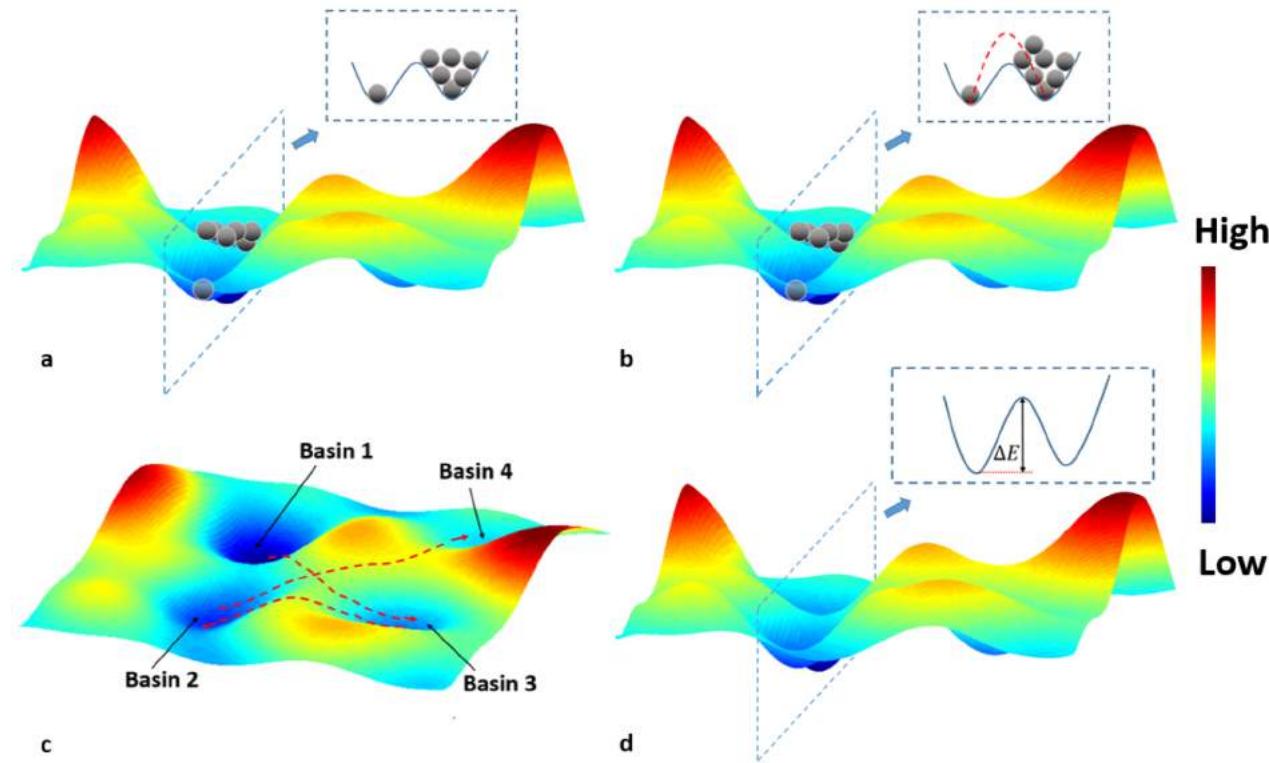
Sidney Yip

@ MIT

Typical application: solid materials, mechanical deformation

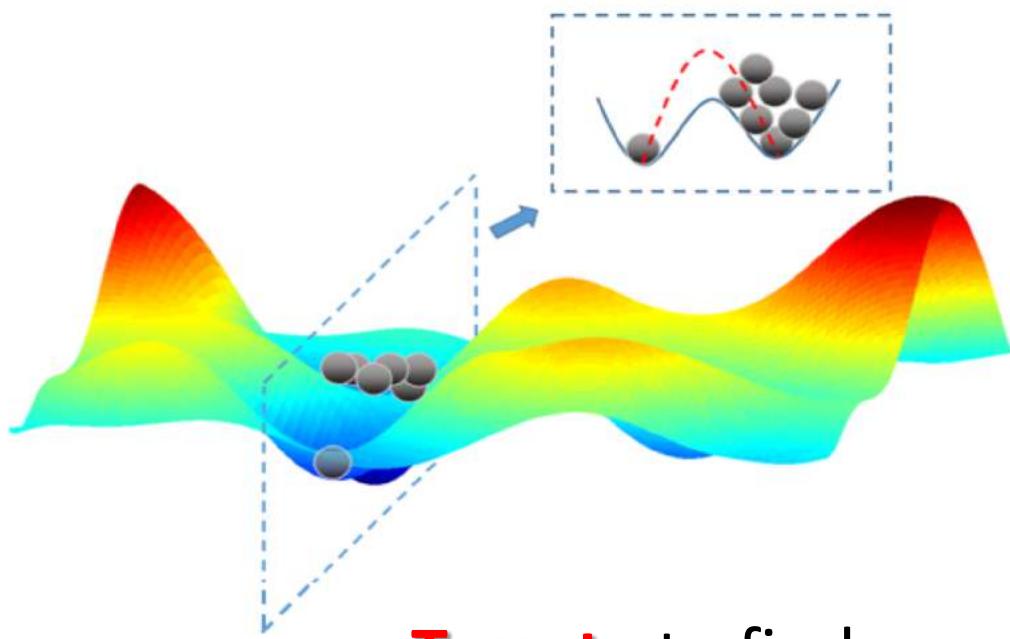
四、加速分子动力学

- a) Autonomous Basin Climbing (ABC).
- b) Nudged Elastic Band (NEB).
- c) Kinetic Monte Carlo (KMC).
- d) Transition State Theory (TST).



四、加速分子动力学

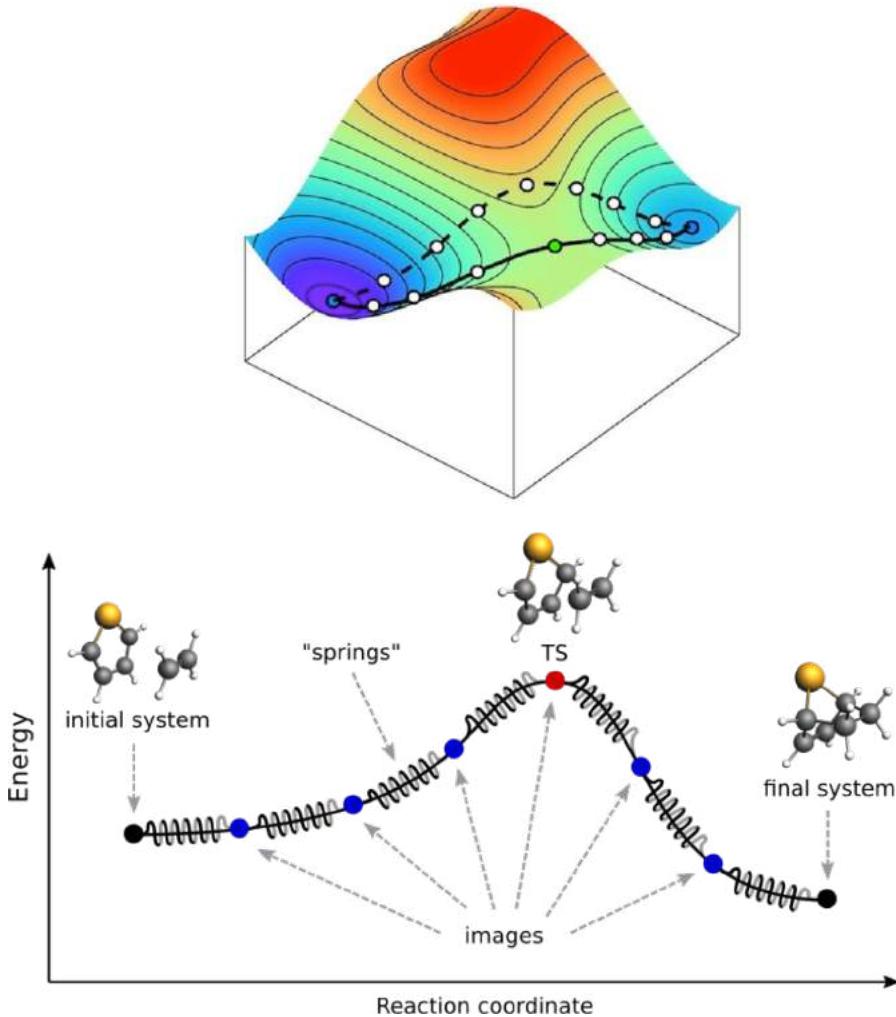
Nudged Elastic Band (NEB)



The barrier from ABC is not accurate. It usually over estimates the barriers.

Target : to find accurate energy barriers from pre-identified minimum, as well as reaction path and the transition state.

四、加速分子动力学



Construct n replica of system

Position of replica is interpolated between initial and final state

Trajectory is obtained by minimizing

$$\sum_{i=1}^n H_i + \sum_{i=2}^n k (\vec{r}_{i-1} - \vec{r}_i)^2$$

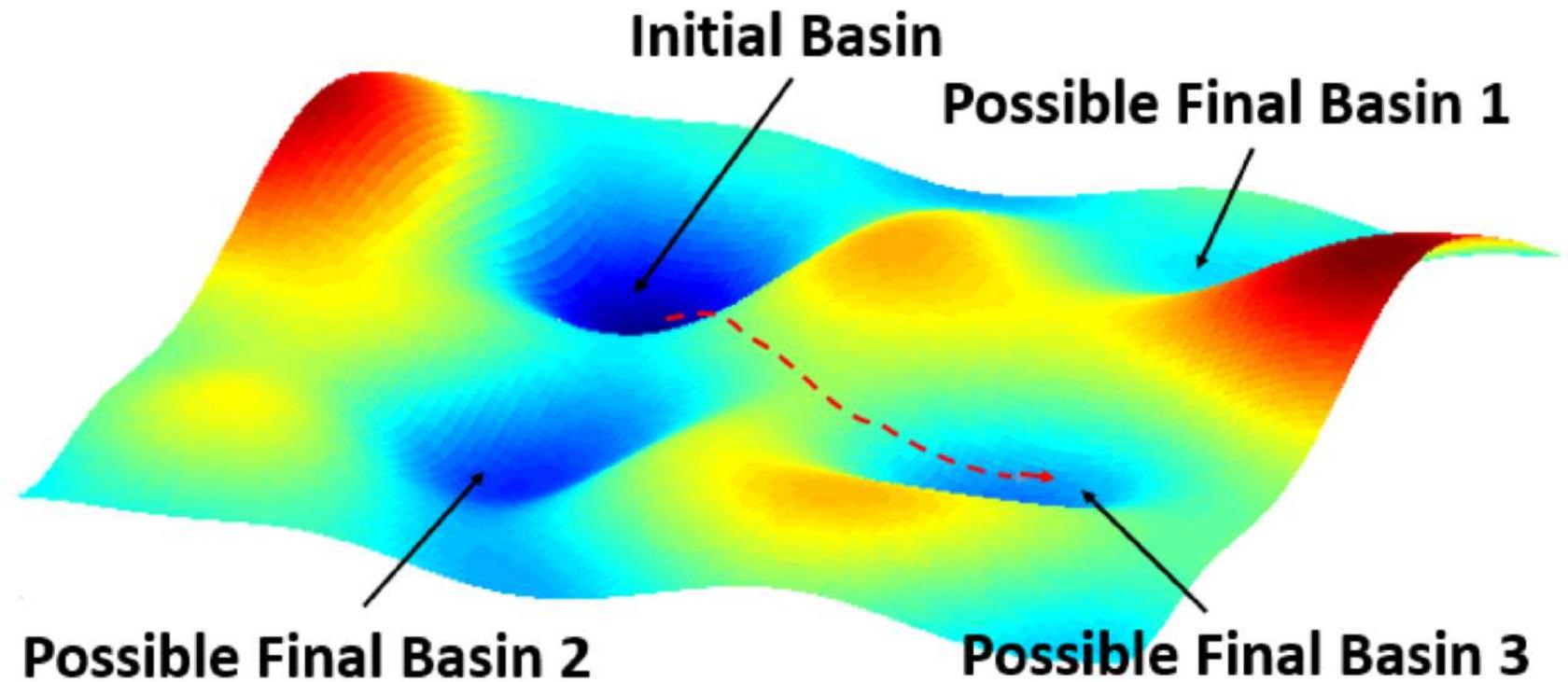
r_i is generalized coordinate vector

https://lammps.sandia.gov/doc/fix_neb.html
<https://lammps.sandia.gov/doc/neb.html>

Examples/neb

四、加速分子动力学

Kinetic Monte Carlo (KMC)



Target : to find the most probable final state.

四、加速分子动力学

Monte Carlo Algorithm

Generate initial structure \tilde{R} . Calculate $V(\tilde{R})$.

Modify structure to \tilde{R}' . Calculate $V' = V(\tilde{R}')$.

If $V' < V$ then

$\tilde{R} \leftarrow \tilde{R}'$, $V \leftarrow V'$

else

Generate random number RAND:

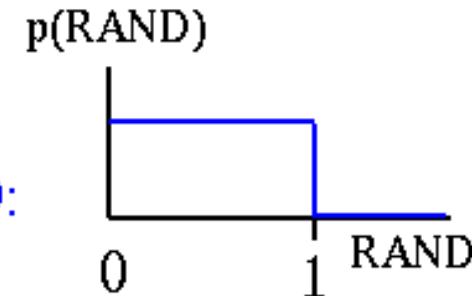
If $e^{-(V'-V)/kT} > \text{RAND}$

$\tilde{R} \leftarrow \tilde{R}'$, $V \leftarrow V'$

End if

End if

Repeat for N steps.



Metropolis Monte Carlo.

https://lammps.sandia.gov/doc/fix_gcmc.html

Examples/gcmc
Examples/MC

The Paper (>20000 citations)

THE JOURNAL OF CHEMICAL PHYSICS

VOLUME 21, NUMBER 6

JUNE, 1953

Equation of State Calculations by Fast Computing Machines

NICHOLAS METROPOLIS, ARIANNA W. ROSENBLUTH, MARSHALL N. ROSENBLUTH, AND AUGUSTA H. TELLER,

Los Alamos Scientific Laboratory, Los Alamos, New Mexico

AND

EDWARD TELLER, * Department of Physics, University of Chicago, Chicago, Illinois

(Received March 6, 1953)

A general method, suitable for fast computing machines, for investigating such properties as equations of state for substances consisting of interacting individual molecules is described. The method consists of a modified Monte Carlo integration over configuration space. Results for the two-dimensional rigid-sphere system have been obtained on the Los Alamos MANIAC and are presented here. These results are compared to the free volume equation of state and to a four-term virial coefficient expansion.

奇怪的是，此算法用了20到25年才
被广泛的接受并运用！



四、加速分子动力学

Monte Carlo

Advantages

- Conceptually simple
- Easy to implement
- Can Equilibrate any degree of freedom/No Dynamics needed
- Accurate Statistical Mechanics

Disadvantages

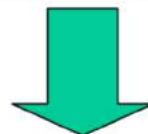
- No Kinetic Information
- Requires many Energy Evaluations
- Stochastic nature gives noise in data
- Not easy to get entropy/free energy

四、加速分子动力学

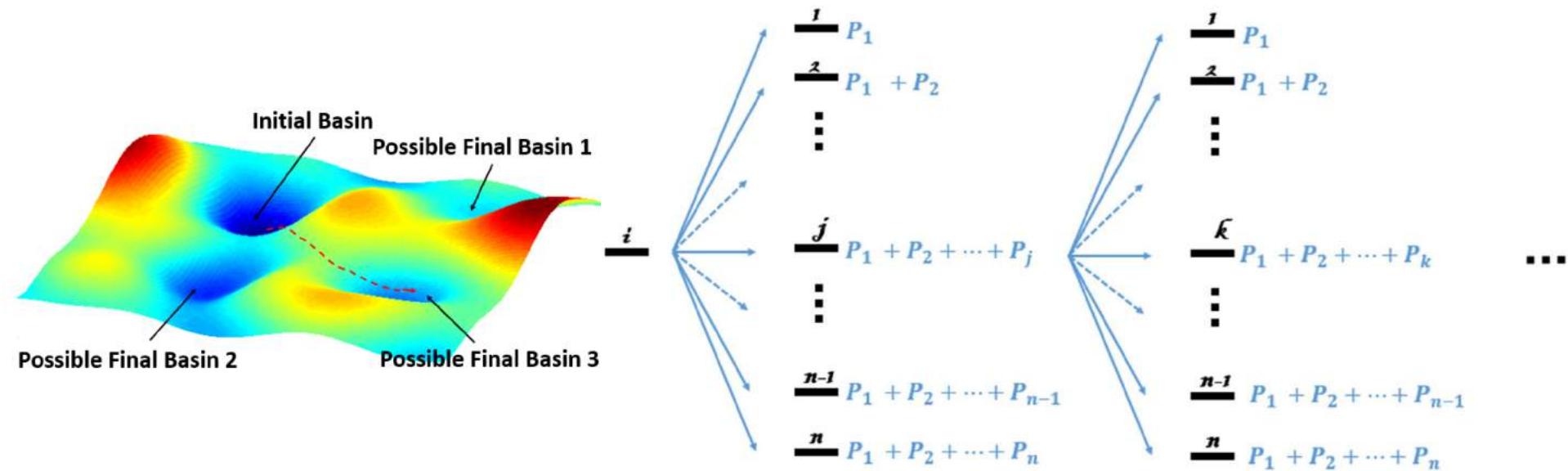
Kinetic Monte Carlo

Know locally stable states of a system

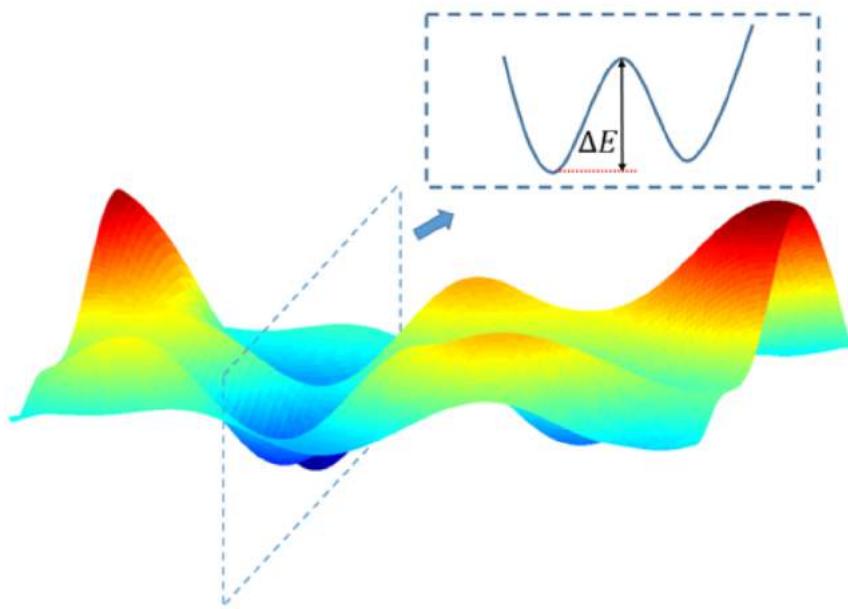
Know kinetic mechanism to move between different states (e.g. hopping of atoms along a particular trajectory)



Perform Monte Carlo simulation over possible states with transition rates similar to the “real” transition rates



Transition State Theory (TST)

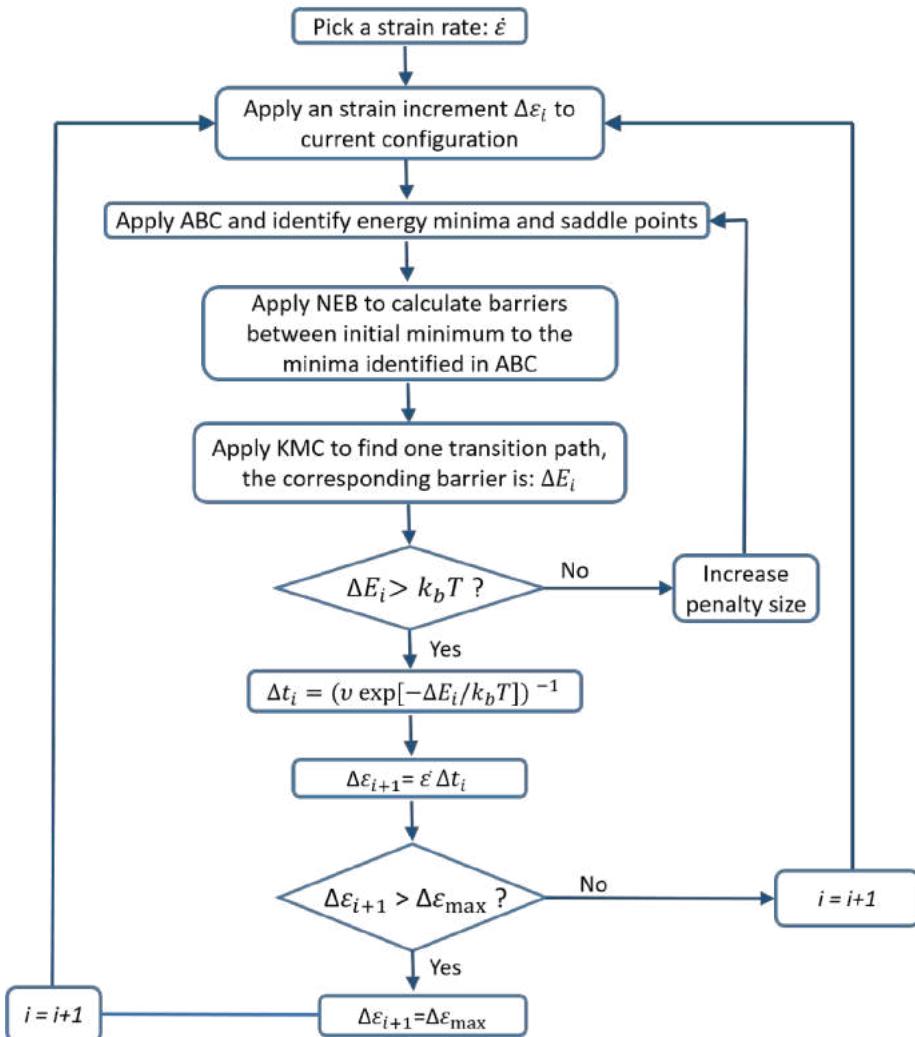
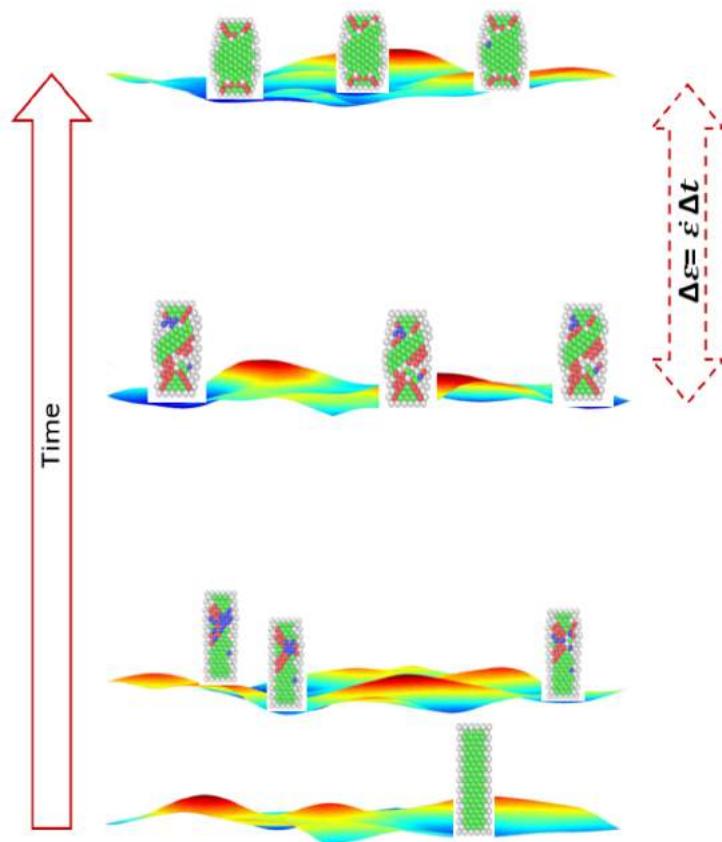


- ΔE : Barrier from NEB calculation;
- ν_0 : Characteristic frequency factor;
- k : Boltzmann constant;
- T : Temperature ;
- Δt : Macro time scale.

$$\Delta t = \left[\nu_0 \exp\left(-\frac{\Delta E}{k_B T}\right) \right]^{-1}$$

四、加速分子动力学

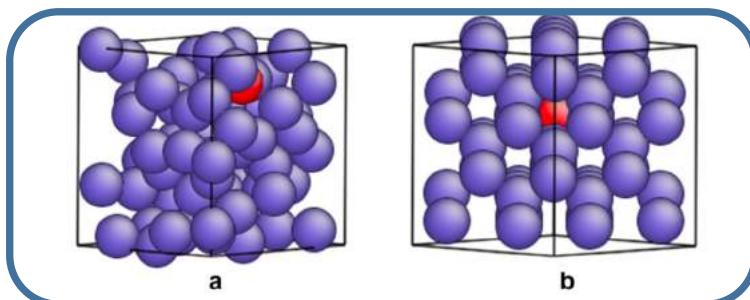
恒定（缓慢）应变率加载过程的实现



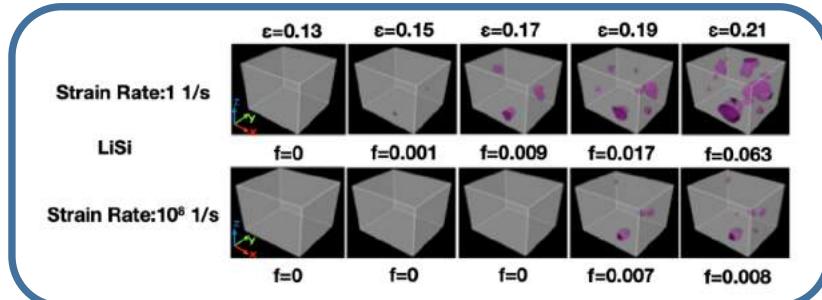
Xin Yan and Pradeep Sharma. Nano Letters. 16(2016)3487

四、加速分子动力学

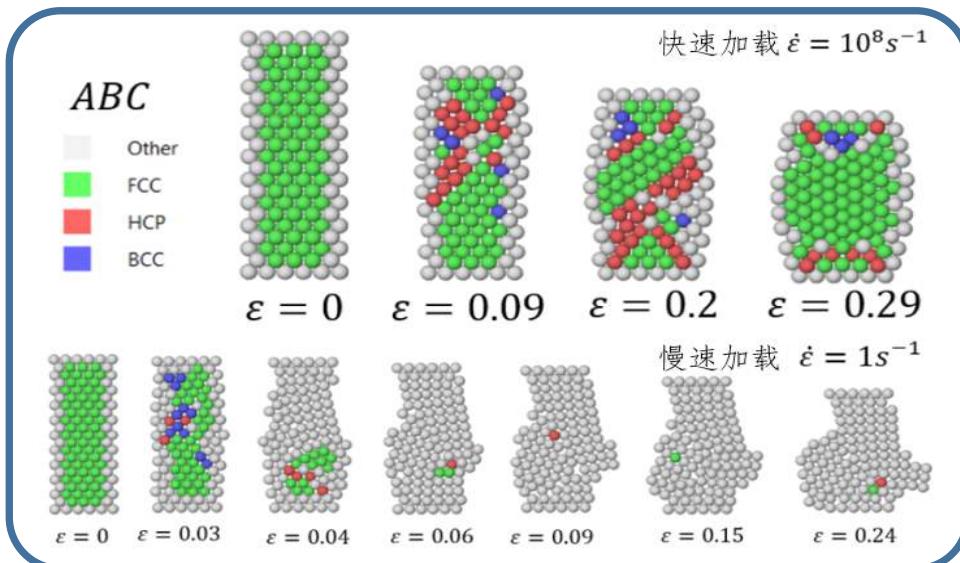
扩散过程



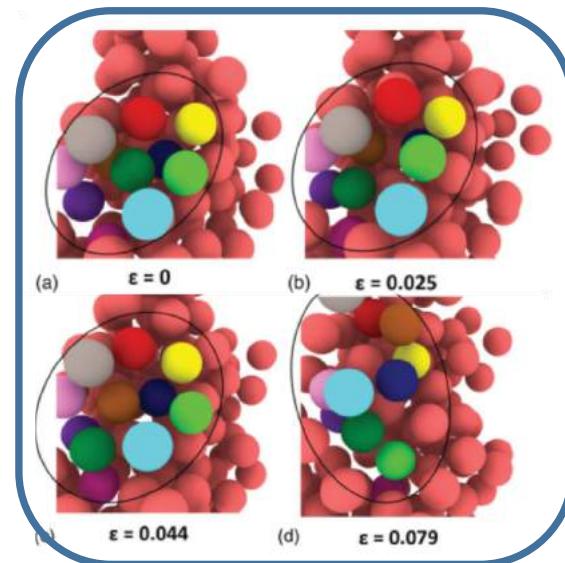
微观孔洞形成



低应变率加载



塑性机理





谢谢！