

## Control of crystal nucleation: insights from molecular simulation

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## Control of crystal nucleation: insights from molecular simulation

- Significance of solid state & crystal engineering
- Molecular simulations
  - Interaction potential
  - Molecular dynamics
- Simulation of crystallisation from solution
- Uncovering the mode of action of additives that determine and modulate crystal nucleation
- Concluding remarks

## Acknowledgements

- Papa K. Boateng
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- Jittima Chatchawalsaisin, Thailand
- John Kendrick, IPI

## Significance of the solid state

> 85% of dosage forms contain drug in solid form  
Stability & unit dose (ease of manufacture & compliance)



Structure  
crystalline (polymorphic), amorphous)  
Particle morphology  
Particle size & distribution  
nanoparticles



### Properties influenced



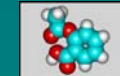
Dissolution rate/  
bioavailability



Mechanical/  
Compactability



Surface/interface  
Film coating, Granulation



Chemical stability



Powder flow

## Crystal engineering

### Structure

crystalline (polymorphic), amorphous

### Particle morphology

Particle size & distribution nanoparticles



### Factors at our disposal

Mechanical: T, p, stirring, spray conditions  
 Chemical: chemical potential (vapour pressure, supercooling, supersaturation), seeding, solvent, additives

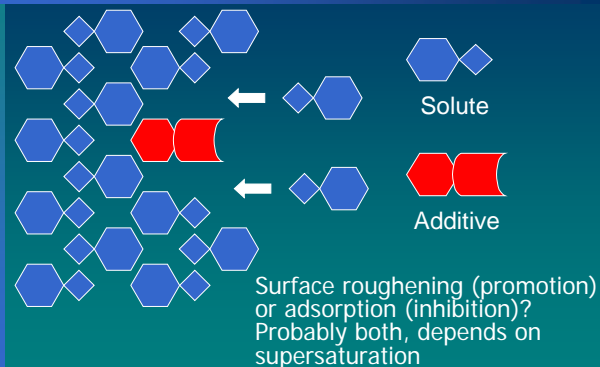
## Effect of additives on crystal nucleation/growth

Offer considerable scope with respect to degree of control  
 Promote, retard, or inhibit crystal nucleation/growth (e.g. stabilisation of amorphous form or nanocrystals)  
 Obtain desired habit, enantiomer or polymorph of drug

### Wider significance and applications

- Control nucleation of proteins
- Inhibition of urinary stone formation
- Inhibition of ice formation during cryoprotection
- Prevention of pipe blockages (inhibition of wax precipitation, inhibition of gas hydrates)
- Anti-freeze agents in Arctic fish

## Modulation/inhibition of crystal growth by additives (solvent)

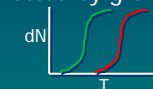


e.g. Weissbuch et al (1995) Acta Cryst. B51 115-148  
 Also polymers modify transport properties

## Modulation/inhibition of crystal nucleation by additives

### Effect of additive on crystal nucleation or growth?

Measurement of metastable zone width (MZW) (linked to lag time)  
 Nucleation inhibitors widen it; not affected by growth



### Mechanism

Disruption of nucleation within emerging aggregate??  
 Surface type mechanism as for crystal growth modifiers??

Need molecular level understanding but no suitable experimental methodology

→ Molecular simulation

## Interaction potential (molecular mechanics)

$$U = \sum_{i < j} \sum 4\epsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] + \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}}$$

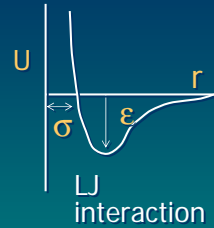
$$+ \sum_{bonds} \frac{1}{2} k_b (r - r_0)^2$$

$$+ \sum_{angles} \frac{1}{2} k_a (\theta - \theta_0)^2$$

$$+ \sum_{torsions} k_\phi [1 + \cos(n\phi - \delta)]$$



Ball & spring



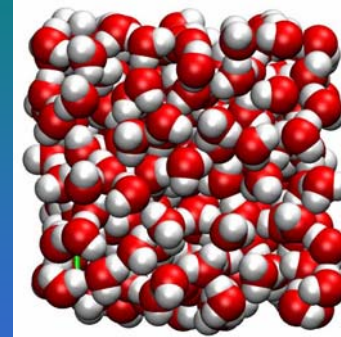
LJ interaction

Pair-interactions  
 $N(N-1)/2$

LJ: short ranged  $R_c$   
 qq: long-ranged  
 (Ewald summation)

Parameters empirical;  
 from experiment and optimised

## Molecular dynamics simulation



Simulate time evolution of a system of atoms/molecules

$$\mathbf{f}_i = -\sum_j \nabla_{\mathbf{r}_i} U(\mathbf{r}_i, \mathbf{r}_j)$$

$$\mathbf{r}_i(t + \Delta t) = 2\mathbf{r}_i(t) - \mathbf{r}_i(t - \Delta t) + \frac{\mathbf{f}_i(t)}{m_i} \Delta t$$

Periodic boundaries &  
 minimum image convention

NVE, NVT, NPT & NoT  
 Employ extended Lagrangian  
 e.g. L(r,p,H,s)

### Limitations

Limited system size  
 Cpu time (1ns -> 100ns)  
 Accuracy of interaction potential

1. Initial configuration
2. Equilibration
3. Production (averages)

NPT ↓ G

## Limitations of molecular dynamics: limited accessible timescale

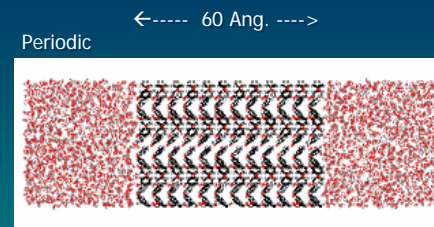
Simulation time scales ~ns-μs;  
 Nucleation & crystallisation > μs

Crystal growth (& dissolution) processes are becoming accessible to MD

## Effect of water on crystal growth of resorcinol

432 Resorcinol  
 2117 Water

Crystal minimised  
 in H<sub>2</sub>O and then  
 Kept static

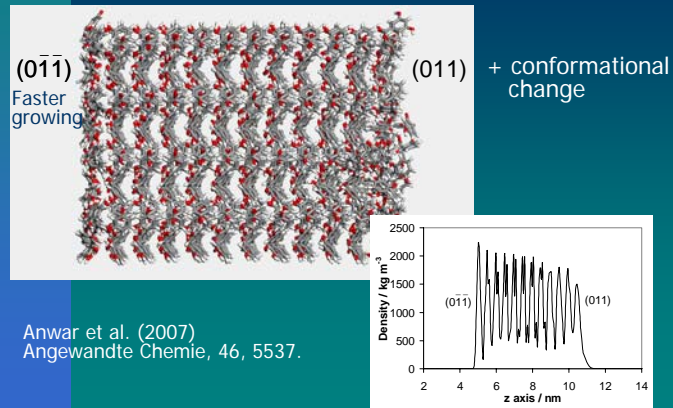


Faster  
 growing  
 face {0-1-1}

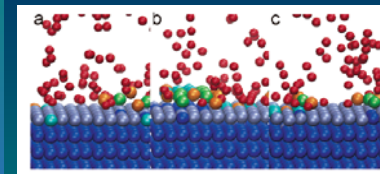
Slower  
 growing  
 face {011}

Hussain & Anwar\* (1999)  
 JACS 121, 8583-8591

## Resorcinol crystal growth from vapour: surface reconstruction



## Crystal growth and dissolution rate



MD + potential of mean force  
+ kinetic Monte carlo  
→ Rate constants for crystal growth & dissolution

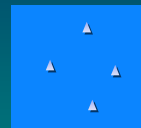
S. Piana & J. Gale (2005) JACS 127, 1975

## Limitations of molecular dynamics: limited accessible timescale

Simulation time scales ~ns- $\mu$ s;  
Nucleation & crystallisation >  $\mu$ s

Crystal growth (& dissolution) processes are becoming accessible to MD

Nucleation is a 'rare event'  
& in general inaccessible



Approach:

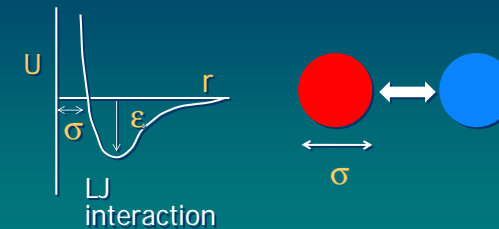
Identify model with fast nucleation kinetics  
(= material whose liquid state **cannot** be supercooled)  
Simplify, simplify ..

Lennard Jones model

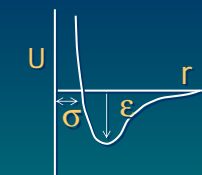
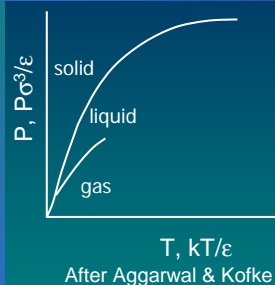
Physical analogue is one noble gas dissolved in another

## Lennard Jones model (weak van der Waals forces)

analogue of inert (noble) gases



## Lennard-Jones phase diagram



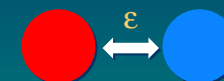
● Solid  
 $\sigma=4.48 \text{ \AA}$   
 $\epsilon=8.3 \text{ kJmol}^{-1}$

● Liquid  
 $\sigma=3.00 \text{ \AA}$   
 $\epsilon=2.5 \text{ kJmol}^{-1}$

## Onset of crystallization

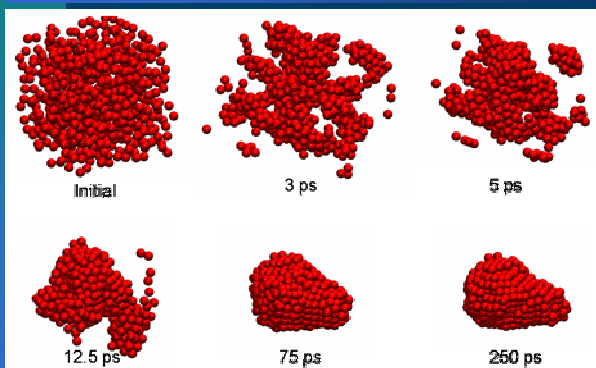
LJ $\epsilon_{\text{solute-solvent}}$ (kJmol <sup>-1</sup> )	Onset (ps)
4.0	No Crystallisation
3.0	No Crystallisation
2.0	No Crystallisation
1.0	73.6
0.5	57.6
0.1	61.6
0.05	39.6
0.01	31.6
0.005	47.6

Fix ratio of solute:solvent, vary solute-solvent affinity  $\epsilon$



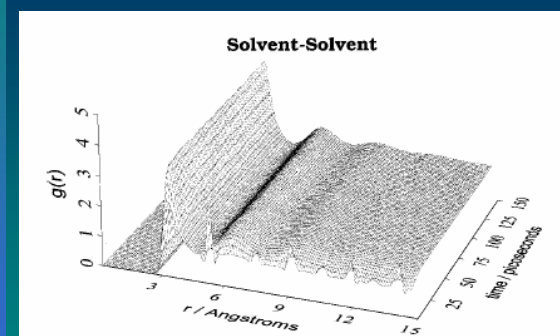
Determined by the time of appearance of the second peak (at 7.1Å) in the radial distribution function for the solute-solute interaction as a function of LJ  $\epsilon_{\text{solute-solvent}}$ \*

## Nucleation from solvent

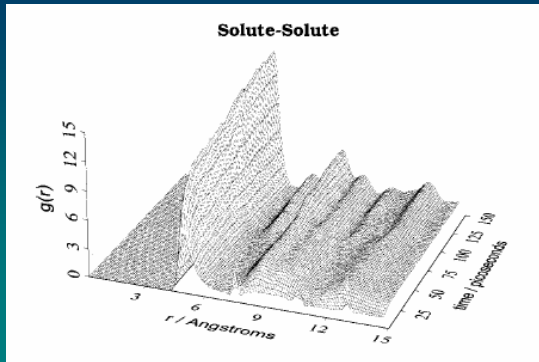


Anwar & Boateng (1999) JACS

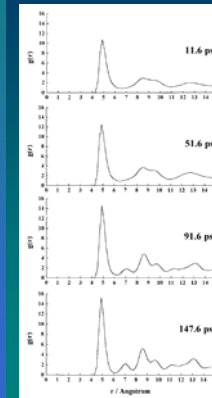
## Solvent-solvent $g(r)$ as a function time



## Solute-solute $g(r)$ as a function time



## Characterisation of nucleus structure: solute-solute $g(r)$



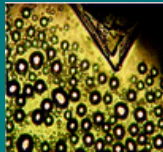
Initial liquid-like structure  
 → BCC/FCC → FCC  
 Oswald's rule of stages!

Peaks for both FCC & BCC

FCC structure; known stable phase for chosen LJ system

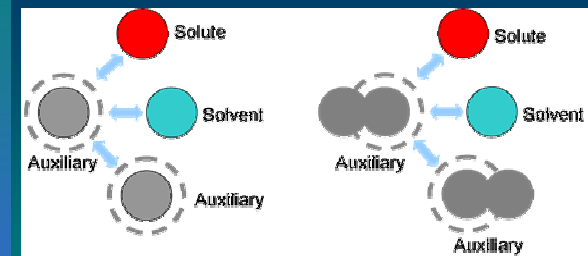
## Inferences from the LJ simulations

- Nucleation from solvent can be simulated, albeit for high supersaturations
- Pre-nucleation clustering & phase separation (concentration gradients & massive instantaneous crystallisation in supersaturated columns)
- Amorphous liquid-like phase, which subsequently becomes crystalline; now a widely accepted phenomenon



Alison et al(2003) (SAXS/WAXD) PCCP  
 Bonnet et al (2003) Chem Comm  
 Galkin & Vekilov (proteins) (2000) JACS

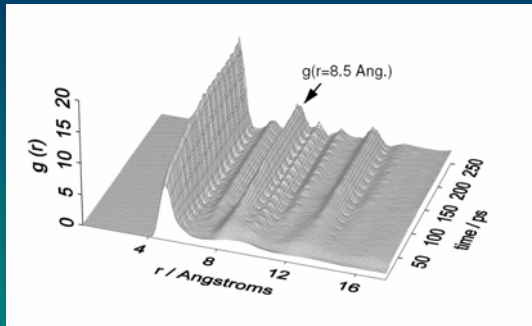
## Designer additives



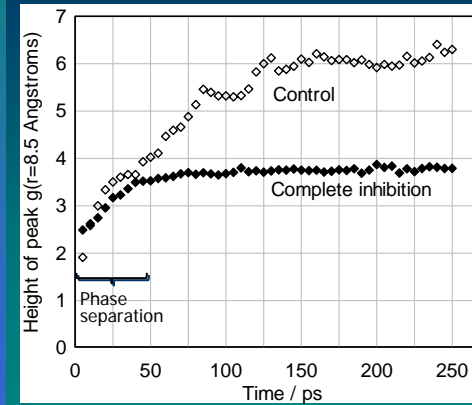
Single particle additives    Dimer structure additives

Change particle character at will

## Solute-solute $g(r)$ as a function time Reference system



## Nucleation kinetics



## Single particle additives



Particle of varying size and interaction

**Size**  
 > solute  
 = solute  
 < solute

**Affinity for solute**  
 add-solute > solute-solute  
 add-solute = solute-solute  
 add-solute < solute-solute

**Affinity for solvent**  
 as solute-solvent  
 as solvent-solvent

**Affinity for itself**  
 Lorentz-Berthelot rules

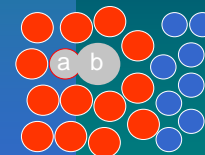
**Solute-phillic [incorporated]**  
 Inhibition for sizes > solute  
 High affinity for solute enhances inhibition; effect significant for sizes < solute

**amphi-phillic [at interface]**  
 Does not cause inhibition, merely retards; effect marked when affinity for solute high.

## Dimer additives: solute-philic



a : = solute  
 b : affinity (varied) for solute;  
 not much affinity for solvent



Dimer located within cluster

**Inhibitor**; effect particularly strong when size of b < / > solute

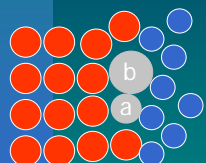
With b=a=solute expected promotion as dimer could act as template; Kinetically easier for individual atoms with freedom; Also interference from neighbouring dimers

Increased affinity of b for solute plays a role but is secondary; important when steric disruption minimal

## Dimer additives: weakly amphi-philic



a : = solute  
b : affinity (varied) for solute;  
affinity for solvent (LB rule)



Dimer located at  
interface, in plane

### Inhibiter & promoter

Inhibitor when size of b > solute

Size of b = solute, little effect

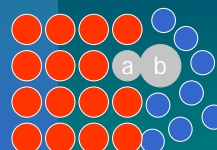
Size of b < solute, nucleation promoter

Increased affinity of b for solute retards  
nucleation but is secondary; makes interface  
rigid

## Dimer additives: amphi-philic



a : = solute  
b : not much affinity for solute;  
affinity(varied) for solvent



Dimer located at  
interface,  
perpendicularly

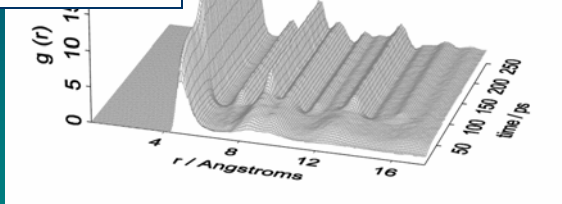
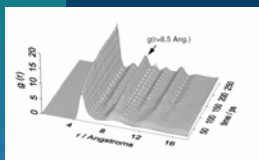
### Promoter (or slight retarder)

Slight retardation when size of b > solute

Promotion (spectacular!)  
when size of b = / < solute

Increased affinity of b for solvent  
-> slight retardation

## Solute-solute $g(r)$ as a function time Surfactant-type dimer additive



## The design rules that determine the effect of a nucleation additive

- Strong affinity just for solvent → ineffective, since not incorporated
- For inhibition  
Strong interaction with solute; Disrupts lattice (differences in structure, strong interaction with solute, many degrees of freedom [entropic effect])
- Promotion  
surface-active molecules (effect dependent on supersaturation; expect inhibition at high supersatn.)

### Laboratory

Relative affinity for solute/solvent  
= solubility in solute/solvent  
Disruption = molecular dissimilarity with solute  
Interfacial molecular characteristics

## Concluding remarks

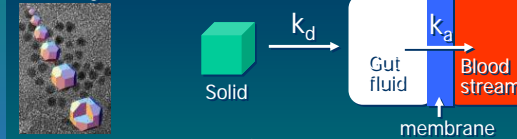
- **Nucleation from solution** can be simulated using molecular dynamics
- **Model consistent with experimental observations**; predicted phase separation into liquid-like clusters, now widely accepted by experimentalists
- **Derived design rules for nucleation inhibitors/promoters**: affinity for solute/solvent, molecular dissimilarity, interfacial properties

### Future

**Rationalise** mechanisms of action of known nucleation inhibitors and modulators; **Develop framework** for rationally identifying or designing additive molecules for either inhibiting or promoting nucleation in a specific system

## Surface free energy and nanocrystals

Nanocrystals ~100-600nm



High surface area  $\rightarrow$   $\uparrow$  Dissolution rate (& solubility)  
Immense potential for delivery to lung e.g. of peptides/proteins

1 cm<sup>3</sup> NaCl cube successively subdivided

Cube side / m	Total area/ m <sup>2</sup>	$\gamma_{sv}$ / J
1 cm	$6 \times 10^{-4}$	$1.2 \times 10^{-4}$
0.1 cm	$6 \times 10^{-3}$	$1.2 \times 10^{-3}$
1 mm	6	1.2
100 nm	60	12

Unstable:  $\uparrow$  surface area  $\rightarrow$  aggregate/fuse  
Need surfactant

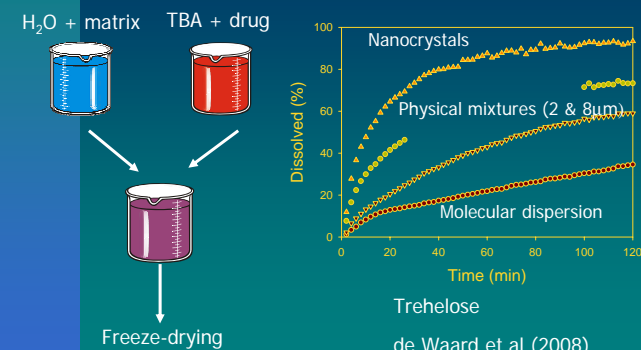
## Nanoparticles of pharmaceuticals

Promise to solve problem of poorly soluble drugs (?)

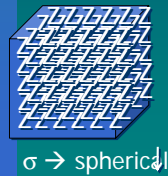
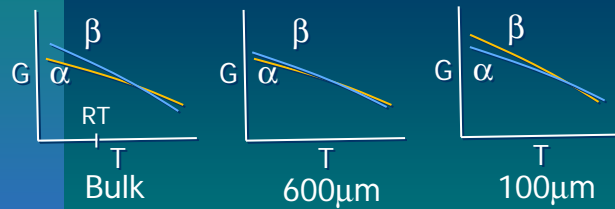
Nanoparticles: 'stand-alone' or confined

- **Wet milling** (Liversidge et al)  
NanoCrystal®  
Products: Rapamune (immuno-supp); Emend  
Batch process, inefficient; contamination
- **High pressure homogenisation** (Muller et al)  
DissoCubes®
- **Precipitation** (incl. sc-CO<sub>2</sub>)  
into polymer/surfactant containing media  
into matrices

## Controlled crystallisation: Solid dispersion technology



## Phase stability as a function of length scale



Phase diagram  $G(T,P,\sigma,\gamma)$   
 $\sigma$  Particle size  
 $\gamma$  Interfacial free energy

## Interfacial free energy calculation: Stability of nanocrystals

### Thermodynamics

Drug  
 Crystalline  
 (polymorphic)  
 amorphous



Matrix  
 Crystalline  
 (polymorphic)  
 amorphous



$\gamma$  dependent on crystal faces (need to average)

$$G = 4/3 \cdot \pi r^3 \cdot G_B + 4 \pi r^2 \cdot \gamma \quad \downarrow \gamma \text{ for stability}$$

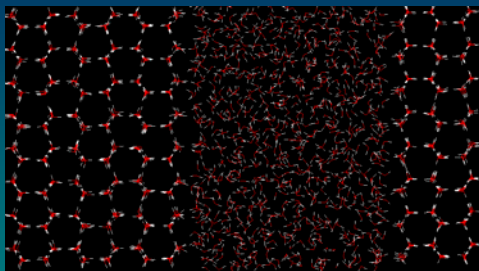
### Kinetics

Mobility of molecules in matrix (T, T<sub>g</sub>, humidity)

### Systems

Drug: Fenofibrate  
 Matrix: Mannitol, sorbitol, inulin

## Solid-liquid interfacial free energy: Ice-water interface



Thermodynamic integration with cleaving potentials  
 Handel et al. (2008) Phys. Rev. Lett. **100**, 036104

Applications to heterogeneous solid-liquid interfaces  
 expected to be easier (water freezes at interface!)

## Potential energy calculations

### Prediction of morphology

$\begin{array}{c} ZZZZZ \\ ZZZZZ \\ ZZZZZ \end{array} \Big| \begin{array}{c} Z \\ Z \\ Z \end{array}$ 
 Rate of growth  $k^{HKL} \propto E_{att}^{HKL}$   
 Works well for growth from  
 vapour Clydesdale et al. 1991

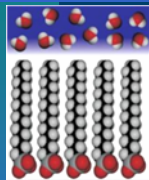
### Effect of additives

$\begin{array}{c} ZZZZZ \\ ZZZZZ \\ ZZZZZ \end{array} \Big| \begin{array}{c} Z \\ Z \\ Z \end{array}$ 
 (i) Binding of additive  
 (ii)  $E_{att}$  with additive  
 (iii)  $E_{att}$  without additive  
 Docherty et al. 1991

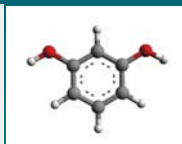
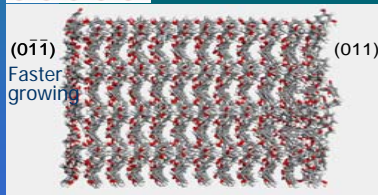
### Effect of solvent

Not so successful, Khoshkhoo & Anwar 1996

## Potential or free energy?



Structuring of H<sub>2</sub>O close hydrophobic surfaces  
→ loss in entropy



Conformational changes  
→ increase in entropy

Anwar et al. (2007)  
Angewandte Chemie, 46, 5537

## Essential statistical mechanics

Partition function

$$Q(N, V, T) = \frac{1}{N!} \frac{1}{h^{3N}} \int d\mathbf{p}^N \exp[-p^2/2mkT] \int d\mathbf{r}^N \exp[-\beta U(\mathbf{r}^N)]$$

$$Q(N, V, T) = \frac{1}{\Lambda^{3N} N!} \int d\mathbf{r}^N \exp[-\beta U(\mathbf{r}^N)] \quad \text{where} \quad \beta = 1/kT \quad \Lambda = (h^2/2\pi mkT)^{1/2}$$

Macroscopic thermodynamic properties

$$F = -kT \ln Q \quad S = kT \frac{\partial \ln Q}{\partial T} + k \ln Q \quad U = kT^2 \frac{\partial \ln Q}{\partial T}$$

Direct integration (sample entire phase space)  
not feasible

In general, cannot calculate absolute F but can  $\Delta F$

## Thermodynamic integration

Free energy *difference*

$$F_{II} - F_I = \int_{\lambda=0}^{\lambda=1} d\lambda \left( \frac{\partial F}{\partial \lambda} \right)_{N, V, T}$$

Integrate the derivative of the free energy with respect to a thermodynamic variable that links the two states by a reversible path

$$\begin{aligned} \left( \frac{\partial F(\lambda)}{\partial \lambda} \right)_{N, V, T} &= -\frac{1}{\beta} \frac{\partial}{\partial \lambda} \ln Q(N, V, T, \lambda) \\ &= -\frac{1}{\beta Q(N, V, T, \lambda)} \frac{\partial Q(N, V, T, \lambda)}{\partial \lambda} \\ &= \frac{\int d\mathbf{r}^N \frac{\partial H(\lambda)}{\partial \lambda} \exp[-\beta H(\lambda)]}{\int d\mathbf{r}^N \exp[-\beta H(\lambda)]} \\ &= \left\langle \frac{\partial H(\lambda)}{\partial \lambda} \right\rangle_{\lambda} \end{aligned}$$

$$H(\lambda) = H_I(1-\lambda) + H_{II}\lambda$$

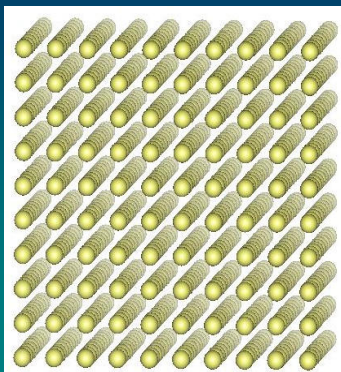
$$F_{\lambda=1} - F_{\lambda=0} = \int_{\lambda=0}^{\lambda=1} d\lambda \left\langle \frac{\partial H(\lambda)}{\partial \lambda} \right\rangle_{\lambda}$$

$$F_{\lambda=1} - F_{\lambda=0} = \int_{\lambda=0}^{\lambda=1} d\lambda \langle H_{II} - H_I \rangle_{\lambda}$$

## Lennard-Jones parameters for solute and solvent

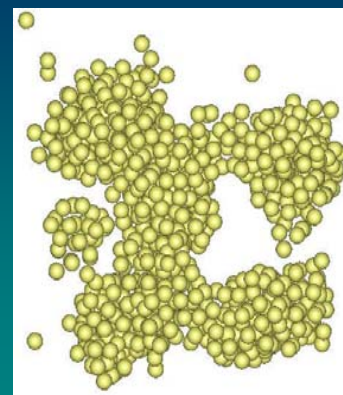
Interaction	$\epsilon$ / kJmol <sup>-1</sup>	$\sigma$ / Å
Solute - Solute	8.314	4.48
Solvent - Solvent	2.494	3.00
Solute - Solvent	4.0 - 0.01	3.74

Snapshot of LJ crystallization  
System size: 1000 solute and 16384 solvent



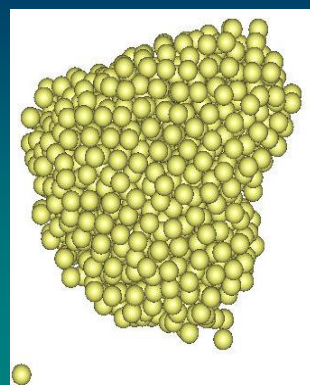
Initial configuration

Snapshot of LJ crystallization  
System size: 1000 solute and 16384 solvent



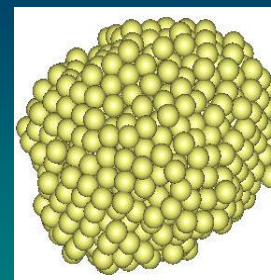
6 ps

Snapshot of LJ crystallization  
System size: 1000 solute and 16384 solvent



16 ps

Snapshot of LJ crystallization  
System size: 1000 solute and 16384 solvent



140 ps

Anwar & Boateng (1998)  
J. Am. Chem. Soc. 120, 9600-9604