Small Molecule Crystallization

Jessica K. Liang

Department of Chemical Engineering

Illinois Institute of Technology

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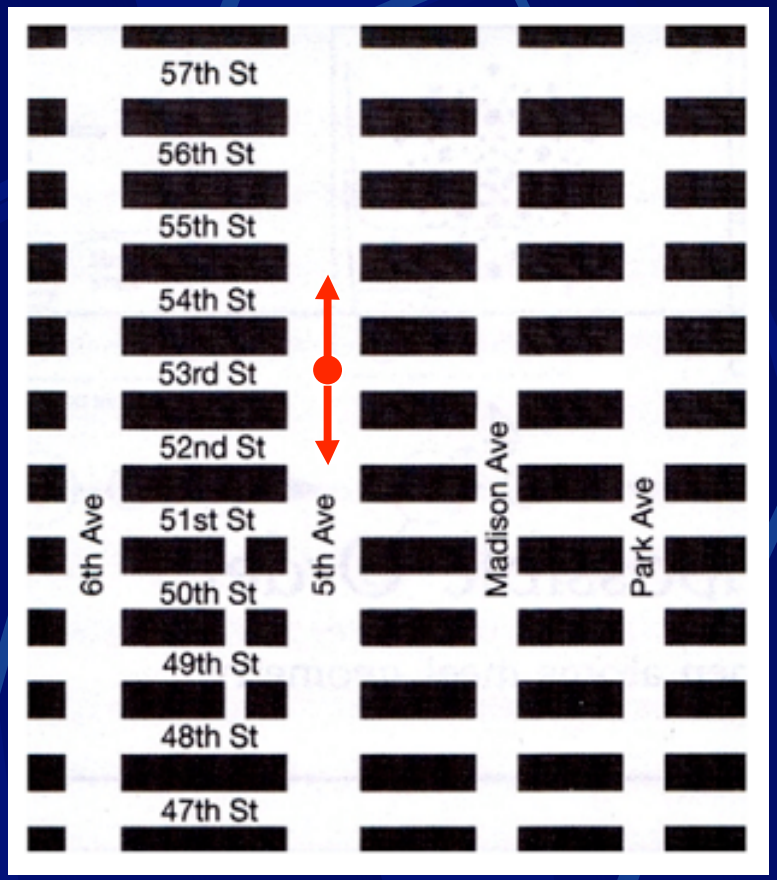
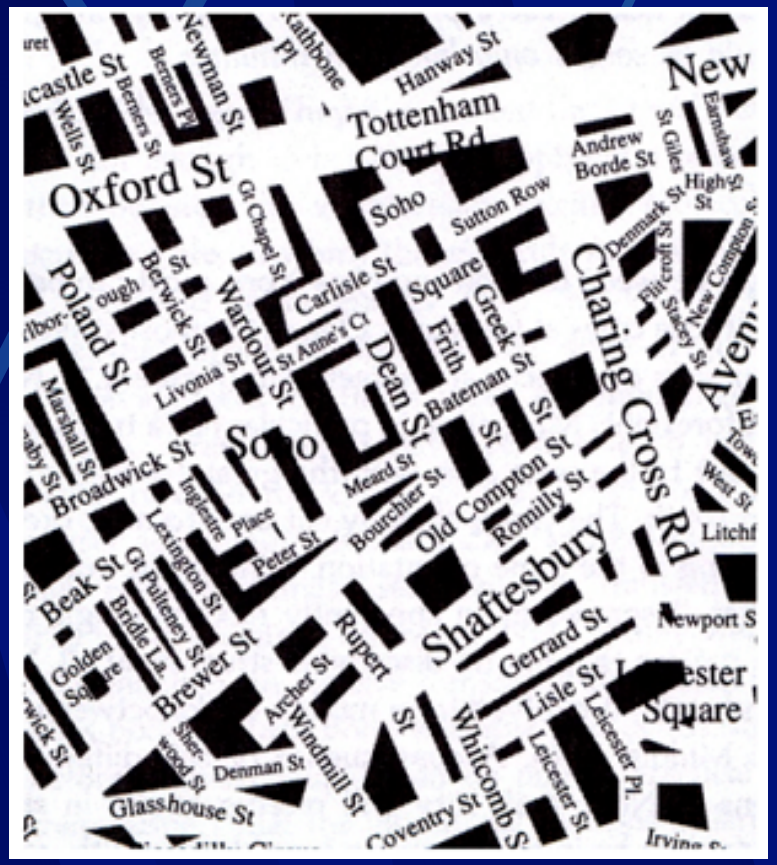
Overview

- Basic Crystal Science
- Crystallization Process
- Our Research Projects
- Lab Tour

What is a Crystal?



New York



London

Crystal

Amorphous

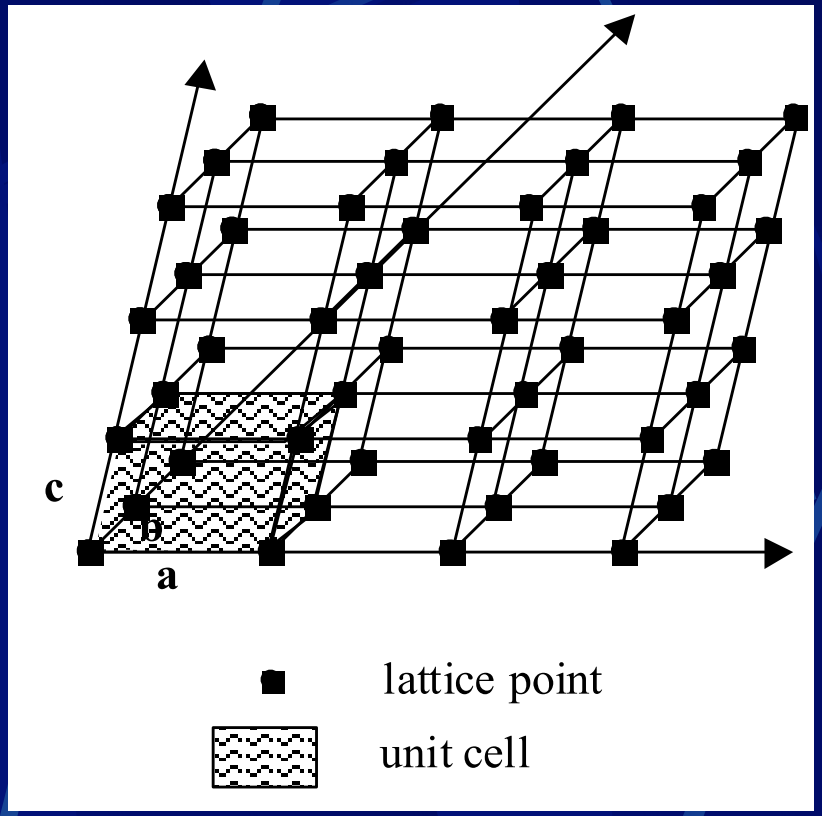
Definition of Crystal

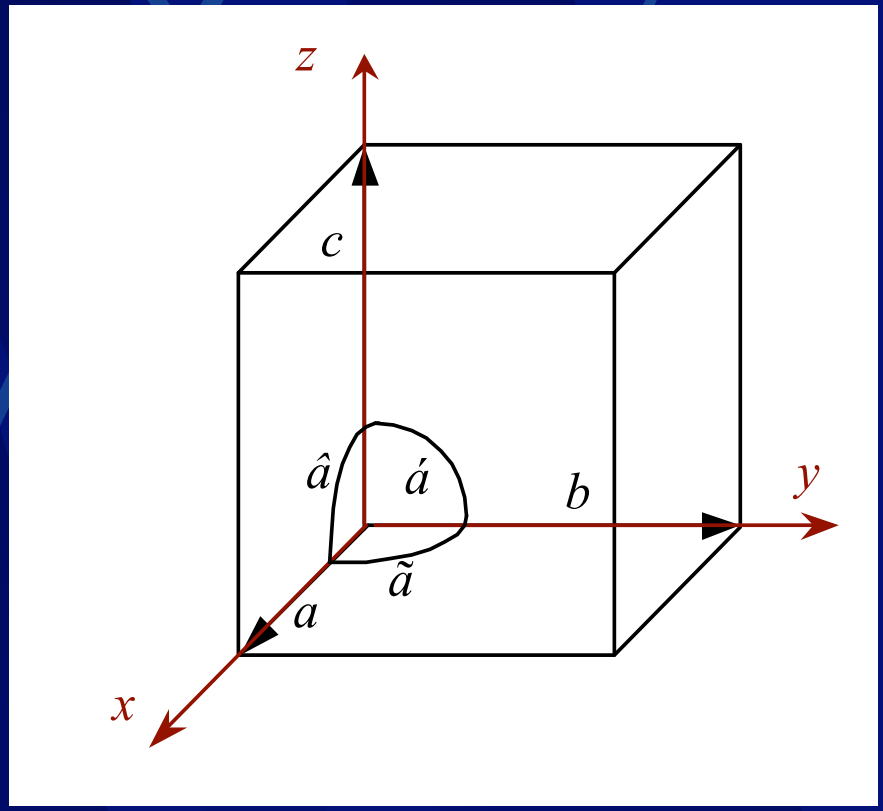
Ø Solid with short and long range order with atoms or molecules in a fixed lattice arrangement

Ø The distinction between a crystal and an amorphous solid is that between order and disorder over large distances

Ø Internal structure of crystals accessible by x-ray diffraction analysis

Crystal Structure





Unit cell parameters: a, b, c, α, β, γ

Seven Crystal Systems

Crystal system	Unit cell dimensions
Cubic	$\alpha = \beta = \gamma = 90°; a = b = c$
Tetragonal	$\alpha = \beta = \gamma = 90°; a = b \neq c$
Orthorhombic	$\alpha = \beta = \gamma = 90°; a \neq b \neq c$
Monoclinic	$\alpha = \gamma \neq 90° \quad \beta; a \neq b \neq c$
Triclinic	$\alpha \neq \beta \neq \gamma; a \neq b \neq c$
Trigonal	$\alpha = \beta = \gamma \neq 90°; \quad a = b = c$
Hexagonal	$\alpha = \beta = 90°; \gamma = 120°; a = b = d \neq c$

Space Groups

Ø 230 space groups

Ø For organic molecules, statistics shows that 95% of all compounds crystallize out in these 16 space groups

- P21/c monoclinic
- P21 monoclinic
- P21/m monoclinic
- P2/c monoclinic
- C2/c monoclinic
- C2/m monoclinic
- Cc monoclinic
- C2 monoclinic
- P-1 triclinic
- P1 triclinic
- P212121 orthorhombic
- Pbca orthorhombic
- Pnma orthorhombic
- Pna21 orthorhombic
- Pbcn orthorhombic
- Pca21 orthorhombic
- P21212 orthorhombic

X-Ray Diffraction

Structure Determination

- Need good quality single crystal

Send to Crystallographer.

- They determine lattice type, parameters i.e. a, b, c, α, β, γ atom positions and space group
- Space groups relate crystal symmetry on an atomic scale to possible arrangement of atom which possess that symmetry.
- Given systems and space group you can calculate all possible arrangement of atoms which meet this

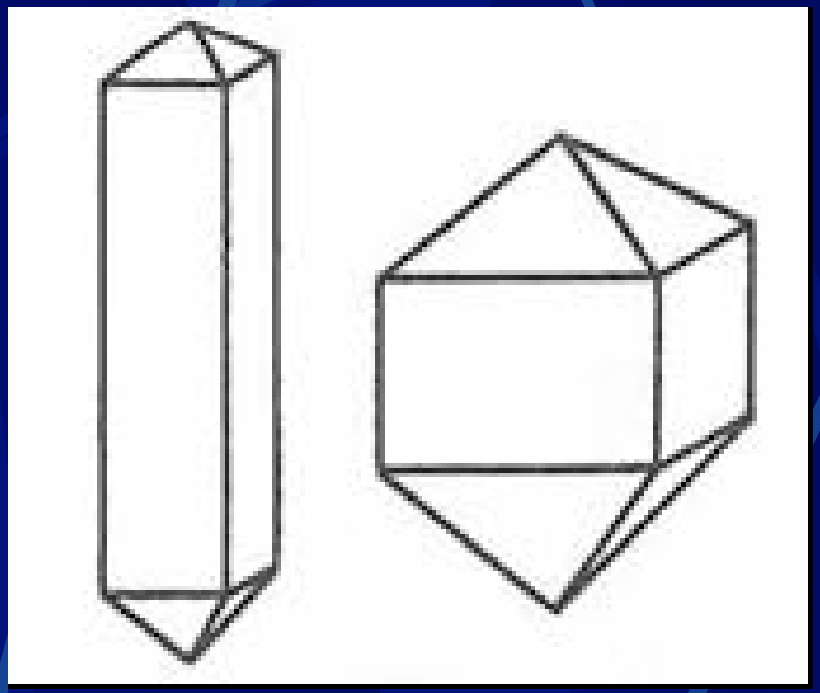
Types of Crystals

Ø Ionic – Charged ions held in place on lattice by electrostatic forces (NaCl)
Ø Covalent – Atoms connected by framework of covalent bonds (Diamond)
Ø Molecular Crystals – Usually organic, composed of discrete molecules held together by weak attractive forces (Urea)
Ø Metallic Crystals – Ordered arrays of identical cations (Copper)

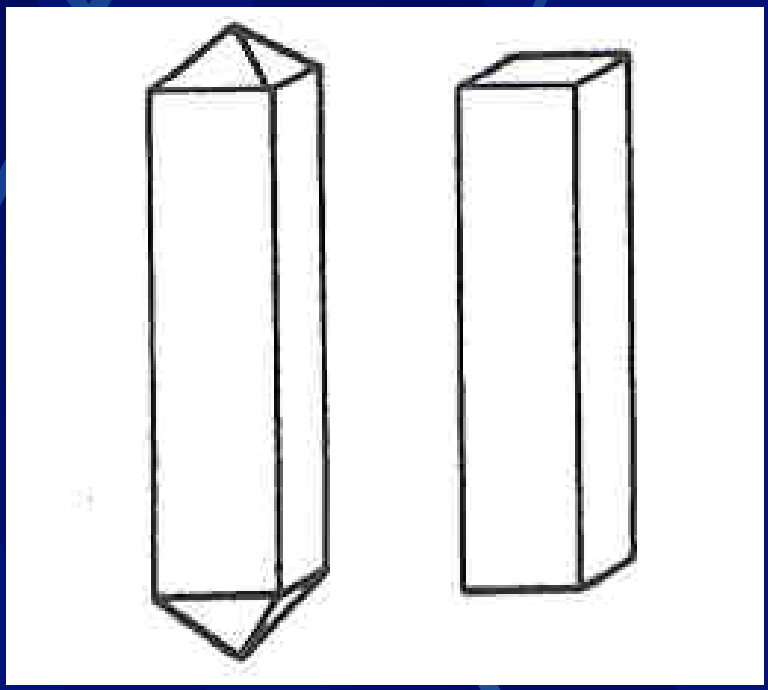
Morphology and Habit

- Crystal morphology is defined as the general appearance of crystals described by the Miller indices of the faces that show and give the crystals their characteristic shape
- Crystal habit means the general shape of a crystal as given by the relative length of the various major axes.
- Both morphology and habit depend on growth conditions and can vary under different process conditions.

Morphology and Habit



Same morphological form but different habit



Different morphological form but same habit

Crystal Size Distribution

μ

- Ø CSD: the most widely applied quality test of a crystalline product
- Ø Many industrial processes demand a narrow range of particle size as this results in good filtering, drying and free-flow ability

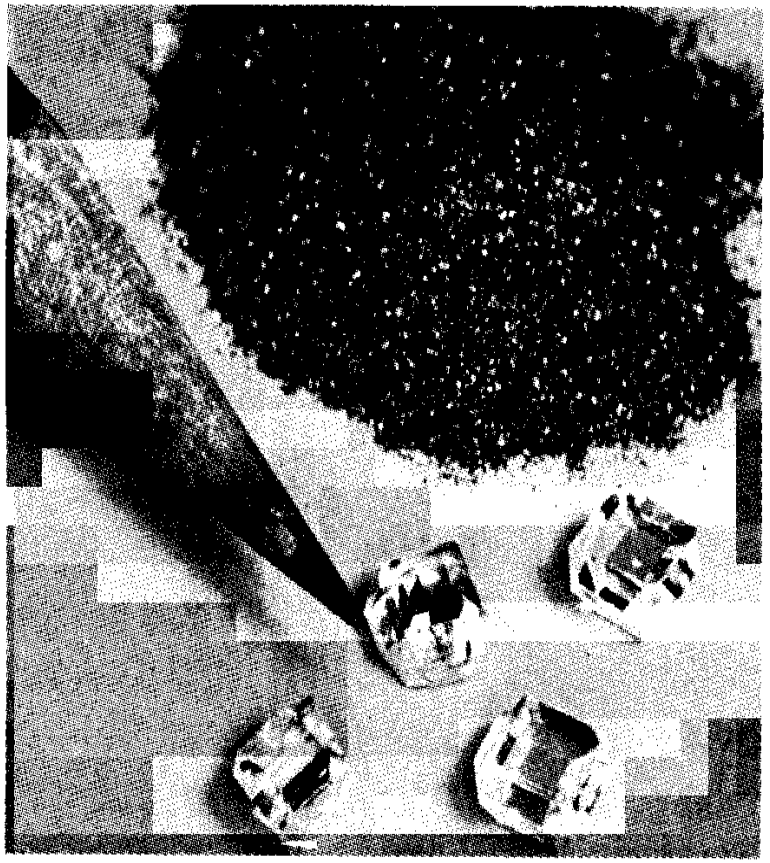
Sizing Method

Techniques	Size Range [μ m]	Size Parameter	Solid Content Range [Vol %]
Sieving	5 - 125000	Sieve aperture diameter $d_{s,a}$ of a sphere that would just pass through the aperture	-
Microscopy	0.5 - 150	Projected area diameter $d_{p,a}$ of a circle that has the same area as the projected image	-
Laser Diffraction	0.1 – 1000	Number/ volume size distribution	< 1
Focus Beam Reflectance Measurement (LASENTEC)	1 - 1000	Chord Length distribution	-
Ultrasonic spectroscopy	0.01 - 1000	Number/ volume size distribution	< 50

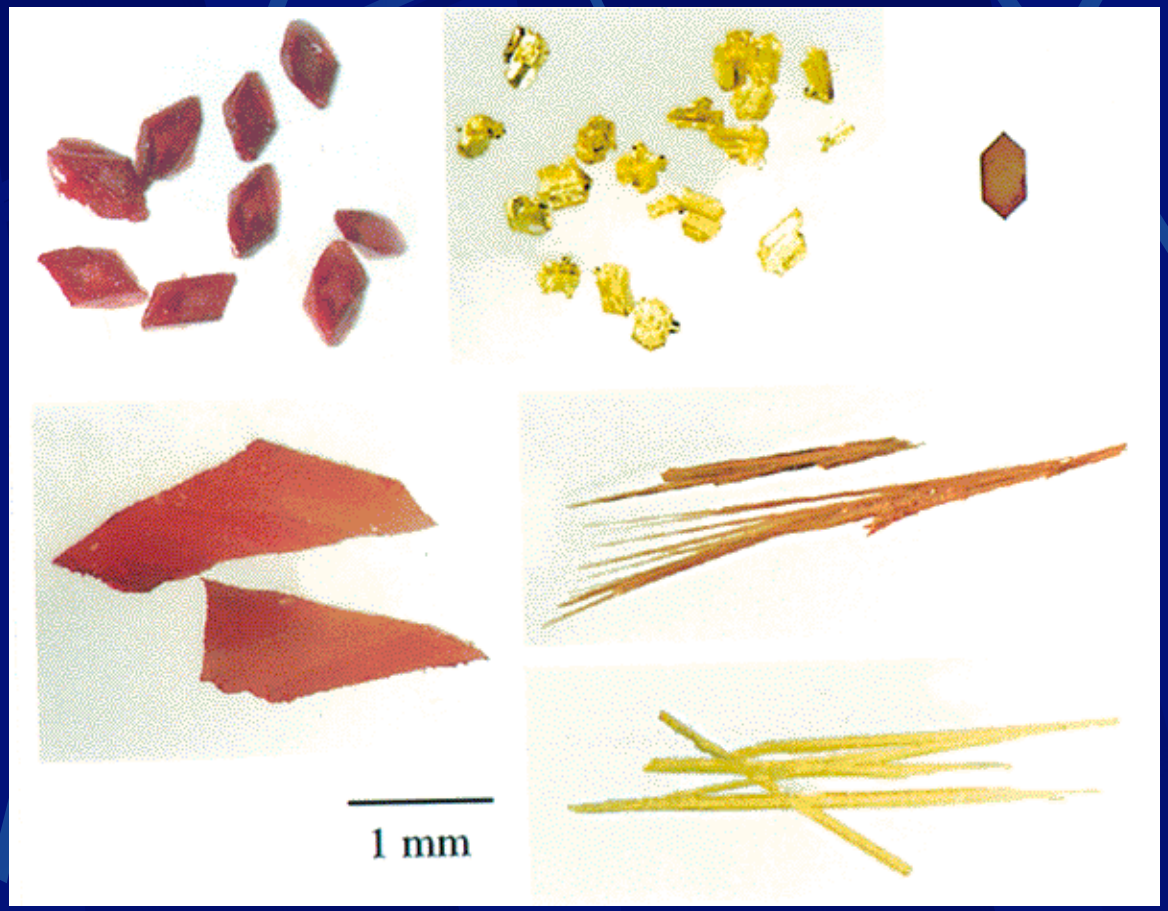
On-lined sizing

Polymorphism

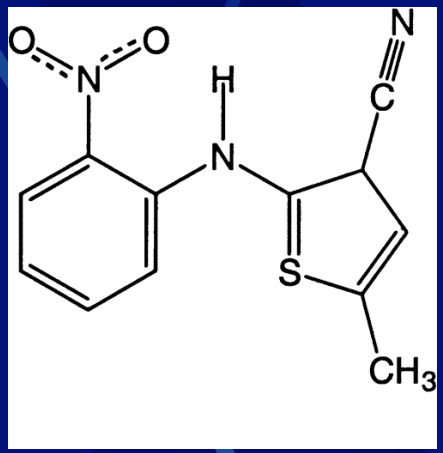
- The phenomenon of a chemical species having more than one possible crystal form e.g. Carbon (graphite: top and pencil and diamond: bottom) whilst remaining chemically identical
- Different forms maybe significantly different in terms of both their structures and physical & chemical properties



5-Methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile



"ROY"



6 Polymorph Forms

Reference: Yu, L.; Stephenson, G. A.; Mitchell, C. A.; Bunnell, C. A.; Snorek, S. V.; Bowyer, J. J.; Borchardt, T. B.; Stowell, J. G; Byrn, S. R. ***J. Am. Chem. Soc*. 2000, 122, 585**.

McCrone's Law

'Every compound has different polymorphic forms, and that, in general,the number of forms known for a given compound is proportional to the time and money spent in research on that compound.'

McCrone, W.C. **Polymorphism in Physics and Chemistry of the Organic Solid State**, Ed. by Fox D, Labes MM, Weissberger A1965, Vol. II, **pp. 726-767**, Wiley Interscience New York.

Types of Polymorphism

Packing Polymorphism

Ø Packing and bonding arrangement of the structure in its different forms are significantly different

Conformational Polymorphism

Ø The existence of different conformers of the same molecule in different polymorphic modifications

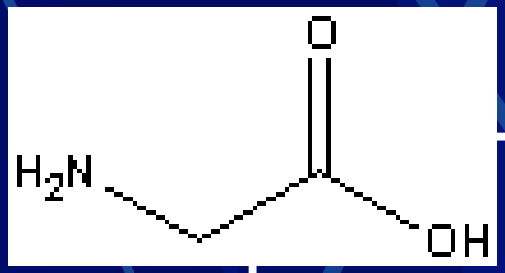
Ø Low energy difference between various conformations

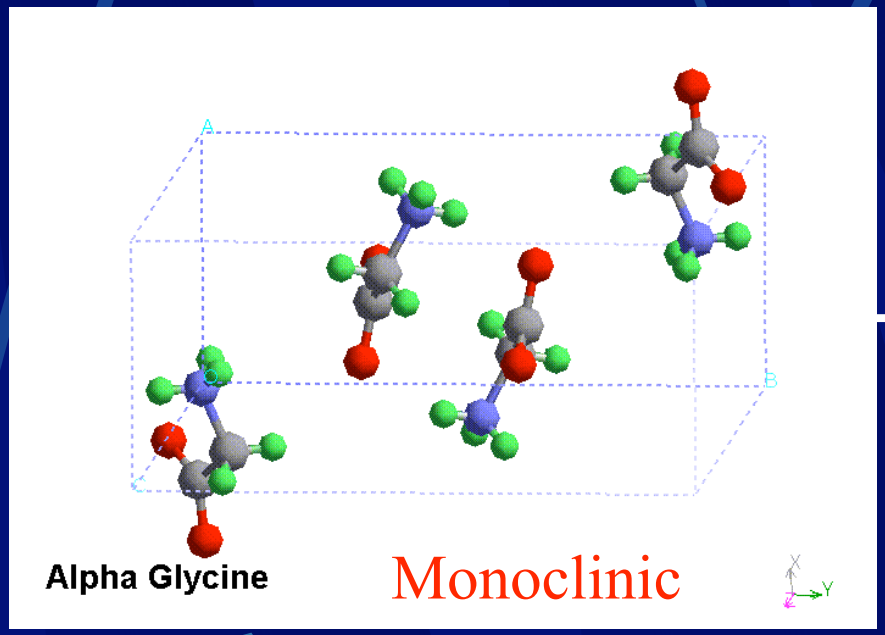
Pseudopolymorphism

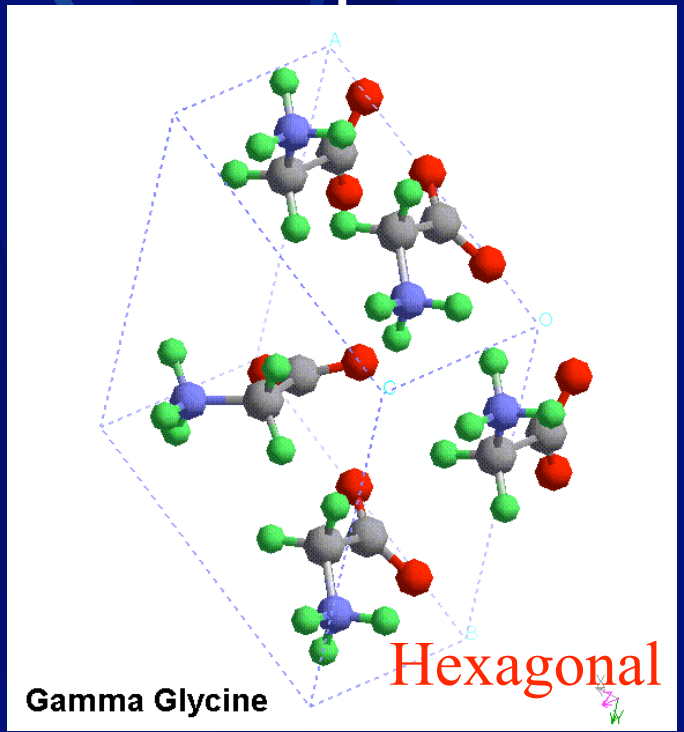
Ø A new structure of a compound that is hydrated or solvated

Packing Polymorphism

Glycine
($C_2H_5NO_2$)

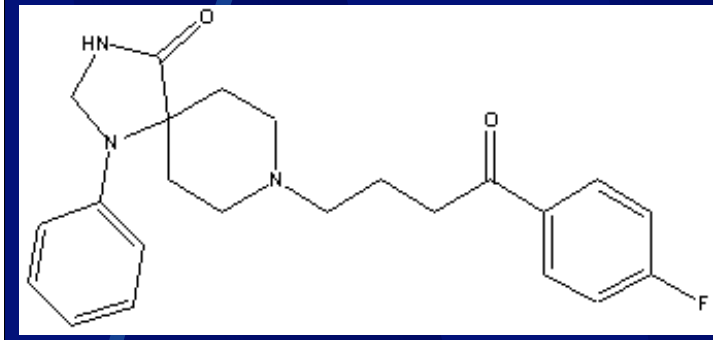




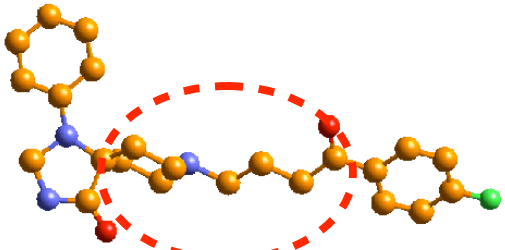


Albrecht G and Corey RB *J. Am. Chem. Soc.*, **1931**, 61, 1037.
Y. Iitaka, *Proc. Jap. Acad.* **1954**; Vol. 30,109-112

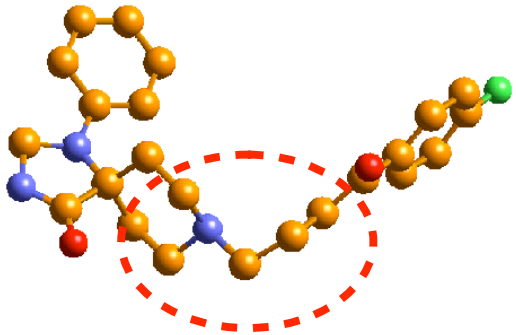
Conformational Polymorphism



Spiperone ($C_{23}H_{26}FN_3O_2$)



Form I



Form II

Koch MH, *Acta Cryst* B29, **1973**, 379.
Azibi M et al., *J. Pharm Sci*., 72, **1983**, 232.

Polymorphic Properties

Packing Properties

Ø Molar volume, density, refractive index, conductivity, hygroscopicity

Thermodynamic Properties

Ø Melting and sublimation temperature, structural energy, Enthalpy, Heat capacity, Entropy, Free energy and chemical potential, Thermodynamic activity, Vapor pressure, Solubility

Kinetic Properties

Ø Dissolution rates, rates of solid state reactions, stability

Spectroscopic Properties

Surface Properties

Ø Surface free energy, interfacial tension, morphology

Mechanical Properties

Ø Hardness, tensile strength, compactability, handling, flow

Bioavailability

Characterization Methods

Crystallography: X-Ray Diffraction

- Ø Single Crystal X-Ray Diffraction
- Ø X-Ray Powder Diffraction

Morphology: Microscopy ←

- Ø Polarizing Optical Microscopy
- Ø Thermal Microscopy

Phase Transitions: Thermal Methods of Analysis

- Ø Thermogravimetry
- Ø Differential Thermal Analysis
- Ø Differential Scanning Calorimetry

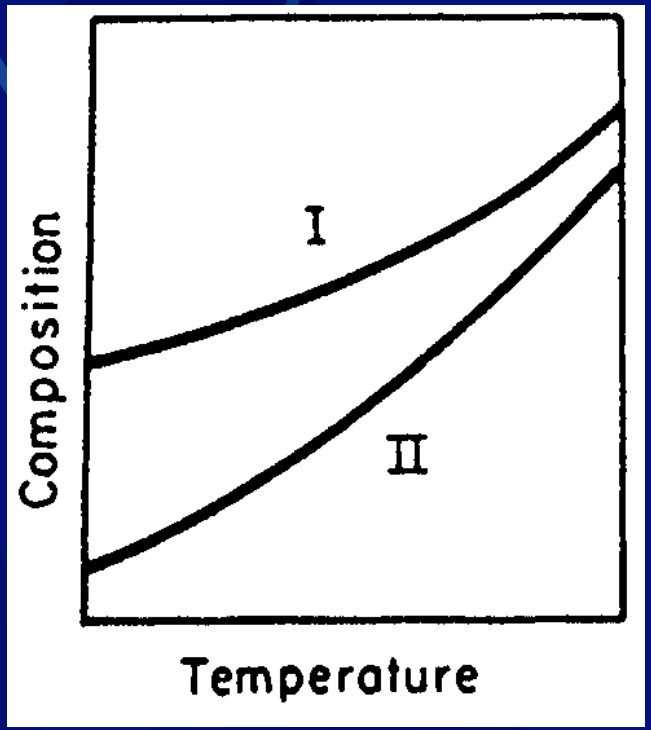
Molecular Motion: Vibrational Spectroscopy

- Ø Infrared Absorption Spectroscopy
- Ø Raman Spectroscopy ← **On-lined**

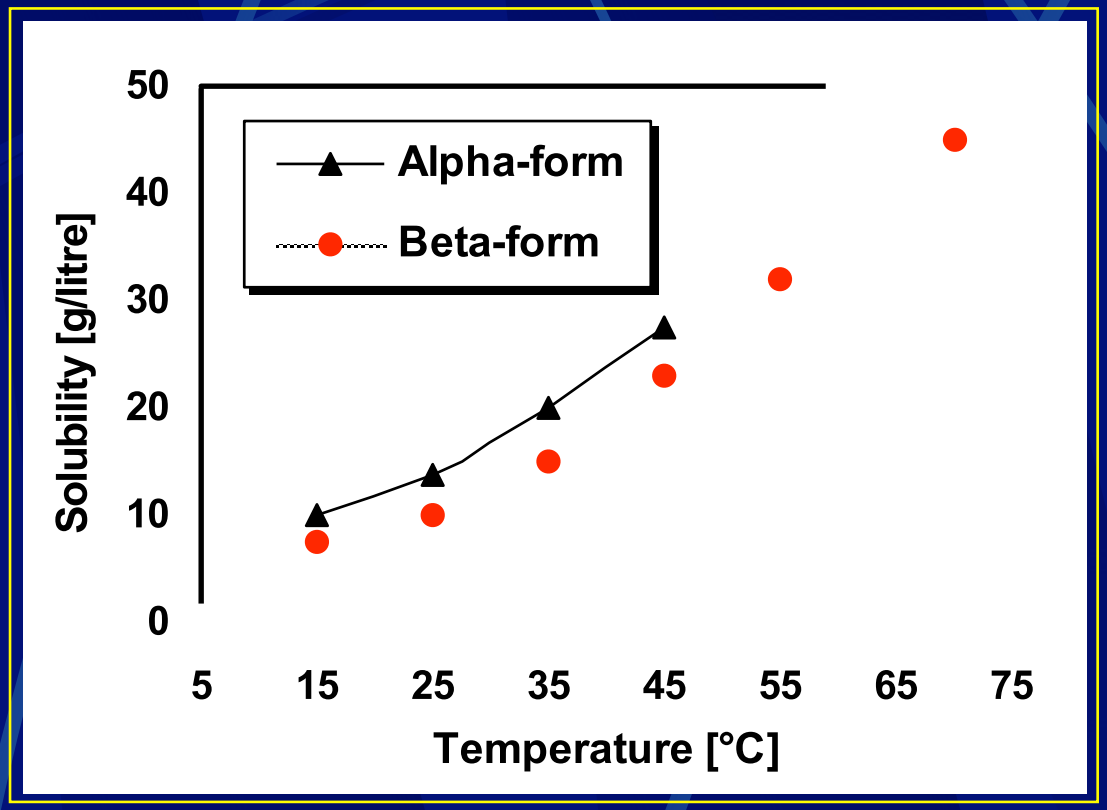
Chemical Environment: Nuclear Magnetic Resonance Spectrometry

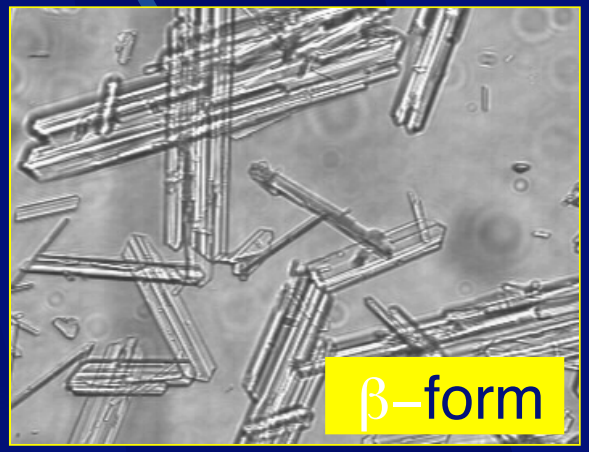
Monotropic System

- One form is metastable relative to the other at all temperatures below the melting point
- Polymorphs are not interconvertible
- Solubility of the stable form is always lower than the metastable form



Monotropic System

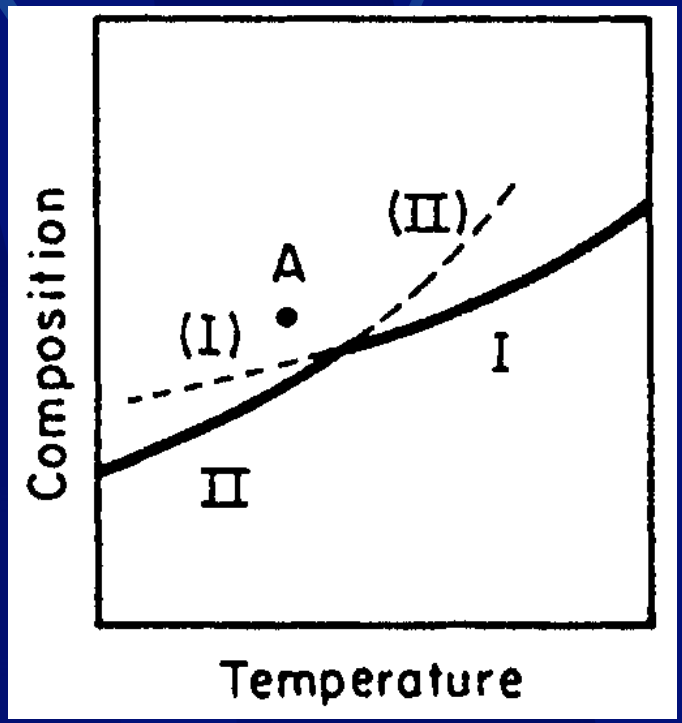




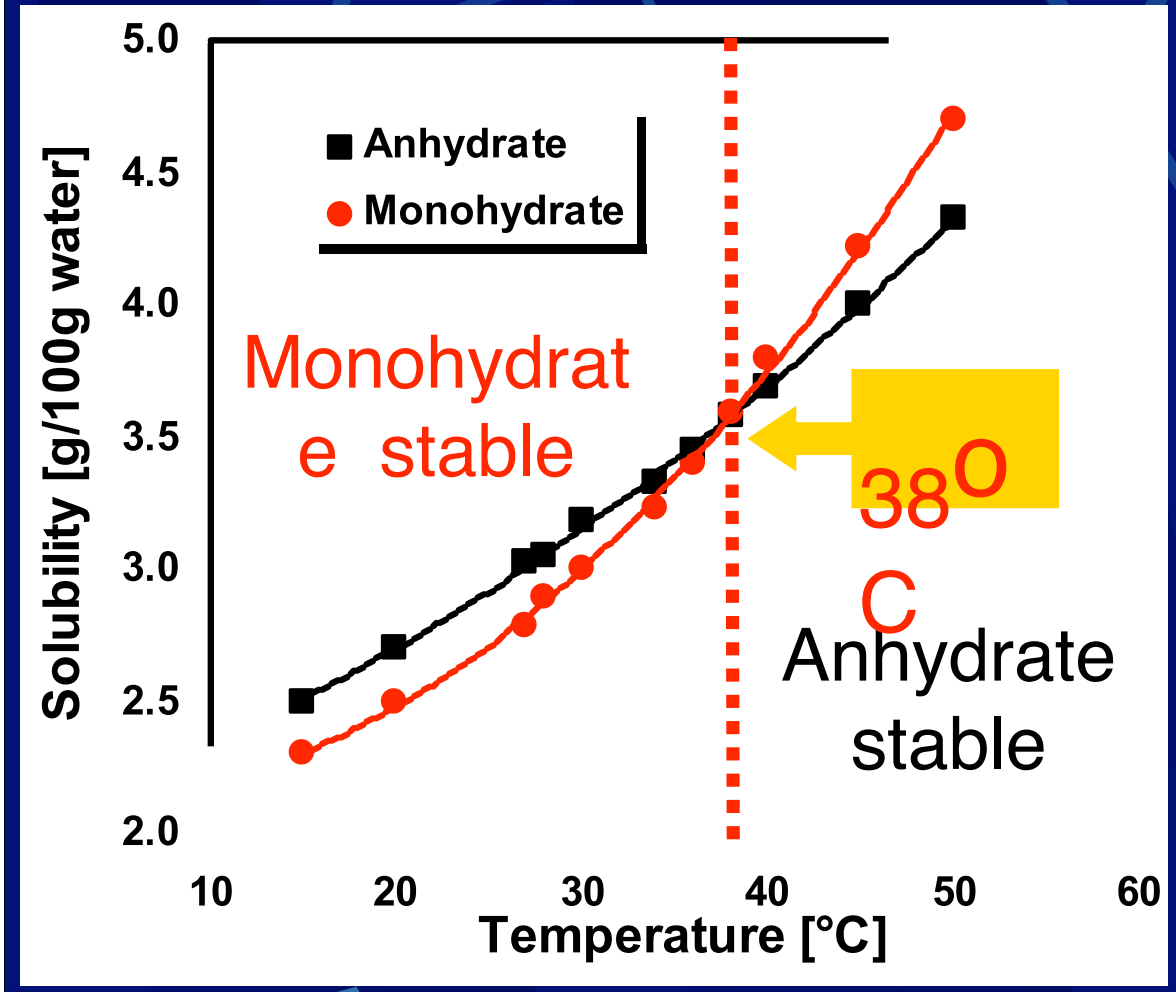
L-glutamic acid $C_5H_9NO_4$

Enantiotropic System

- Polymorphic form dependent upon the temperature and pressure of the system
- Reversible transition point where relative thermodynamic stabilities change
- Transition point below melting point for any of the solid phase



L-Phenylalanine



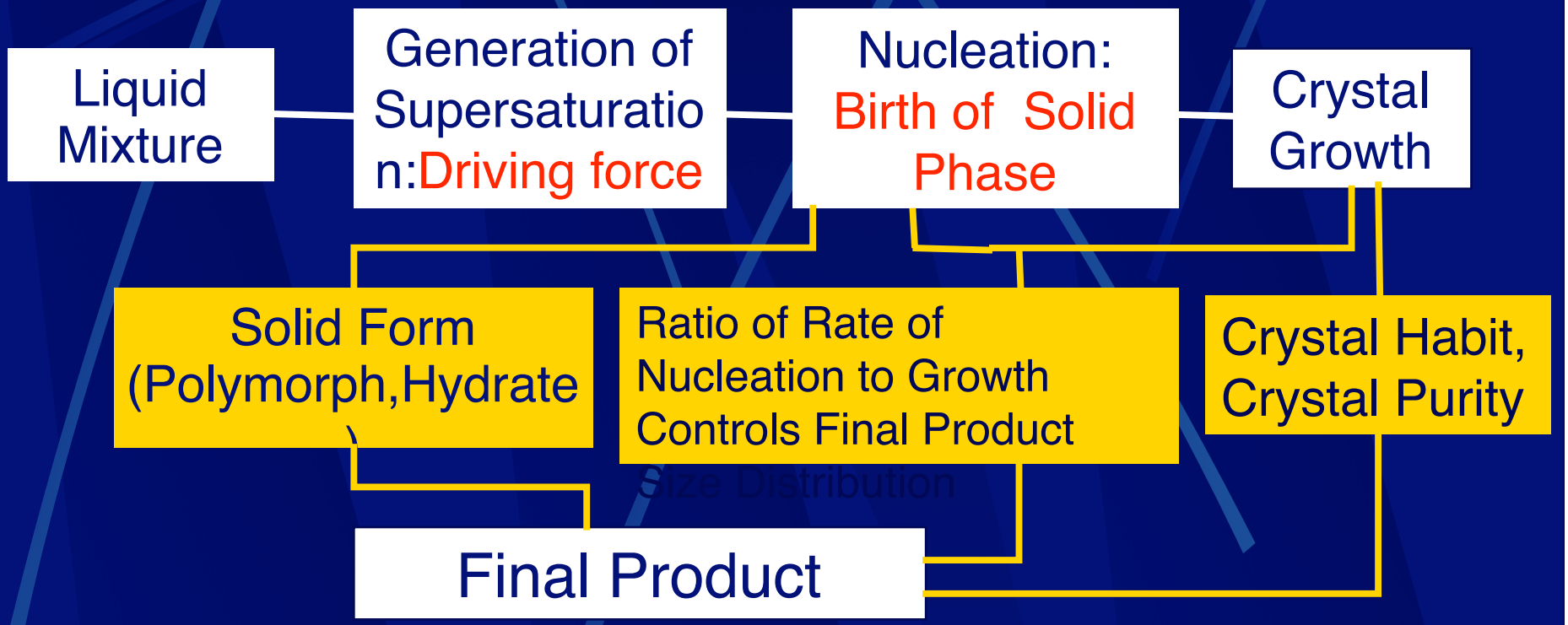
Ø Metastable form may exist for a long time;

Ø Presence of the stable form results in solvent mediated phase transformation

Crystallization

- Formation of a crystalline phase from a parent phase, e.g. solution
- One of the oldest and most important unit operations, e.g. extracting salt crystals from sea water
- Over 90% of all pharmaceutical products contain drug substances

Crystallization Process



Definition of Supersaturation

$$\Delta c = c - c^*$$

$$S = \frac{c}{c^*}$$

$$\sigma = \frac{\Delta c}{c^*} = S - 1$$

Supercooling

$$\Delta T = T^* - T_{cry}$$

C* : equilibrium concentration for a given temperature

C : solution concentration; T*: saturated temperature;

Tcry: Crystallization temperature

Generation of Supersaturation

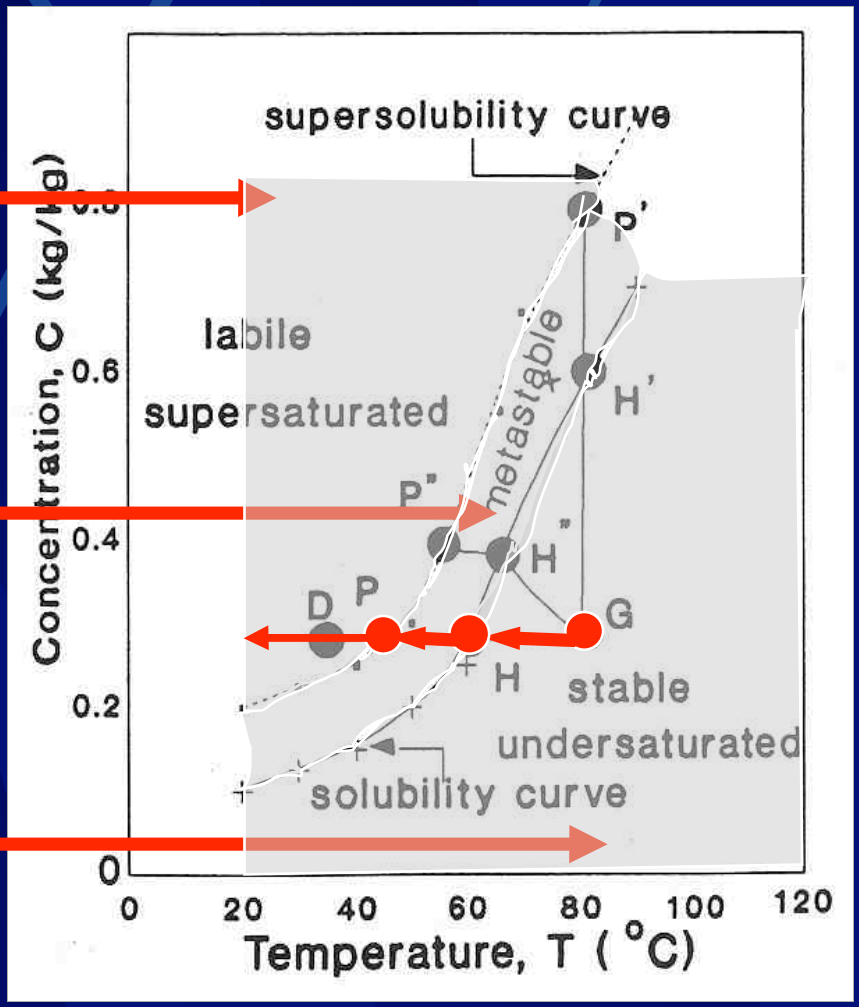
Mode	Supersaturation generation method
Cooling	Reduction in temperature
Evaporation	Lost of solvent
Dilution	Adding anti-solvent
Reaction	Generation of solute
Vacuum	Cooling, flashing evaporation

Metastable Zone

Ø Supersaturated zone:
Spontaneous nucleation is expected

Ø Metastable zone:
Spontaneous nucleation is impossible

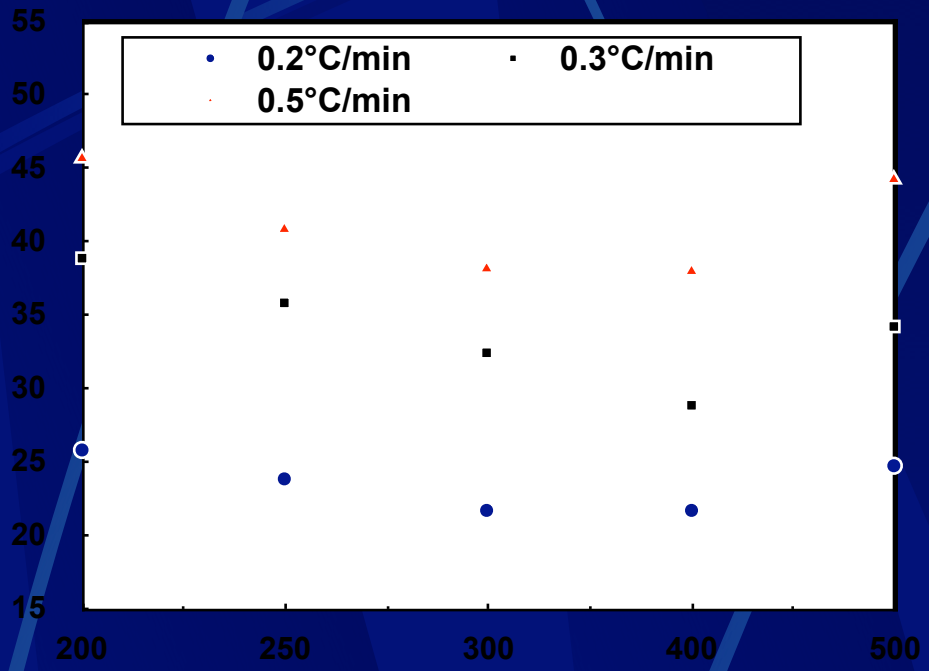
Ø Stable zone:
Nucleation is impossible



Metastable Zone Width

- Ø Metastable zone width (MSZW) is a critical parameter in the crystallisation process as it reveals the nucleation behaviour of the system
- Ø MSZW is a nucleation kinetic-limited parameter that is highly dependent on process conditions
- Ø Many factors may influence the value of MSZW, e.g. rate of cooling, agitation, the presence of foreign particles and impurities

Effects of Cooling Rate & Agitation



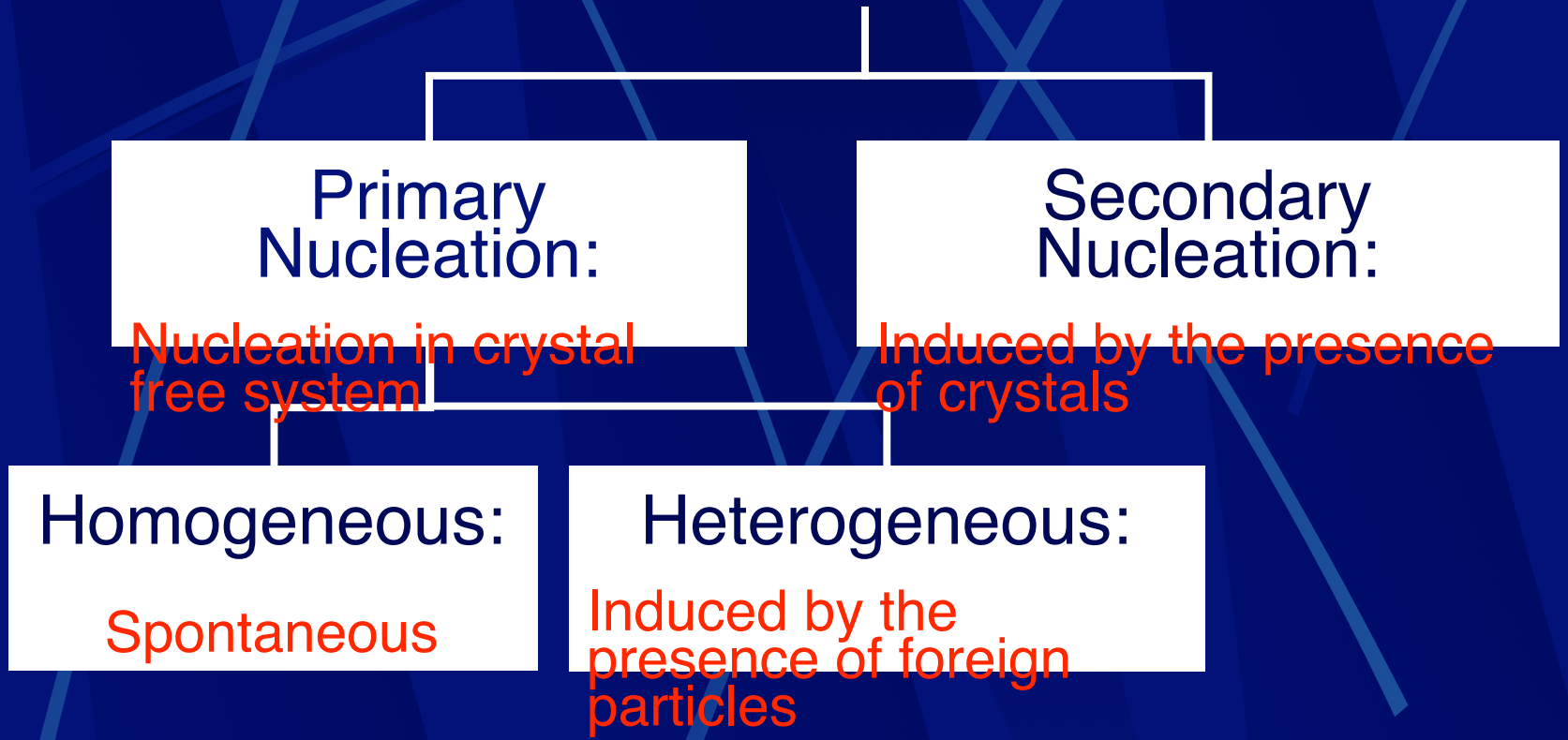
Ø MSZW decreases as stirrer speed increases

Ø MSZW widens at N>400rpm

Ø MSZW widens as cooling rate rises

Cooling crystallization of aqueous L-glutamic acid solutions

Nucleation


Primary Nucleation:
Nucleation in crystal free system
Secondary Nucleation:
Induced by the presence of crystals
Homogeneous:
Spontaneous
Heterogeneous:
Induced by the presence of foreign particles

Homogenous Nucleation

Gibbs Free Energy Change

$$\Delta G = \Delta G_s + \Delta G_v$$

$$\Delta G_s = 4\pi r^2 \gamma$$

$$\Delta G_v = -\left(\frac{4\pi r^3}{3v_m}\right) RT \ln(1 + S_B)$$

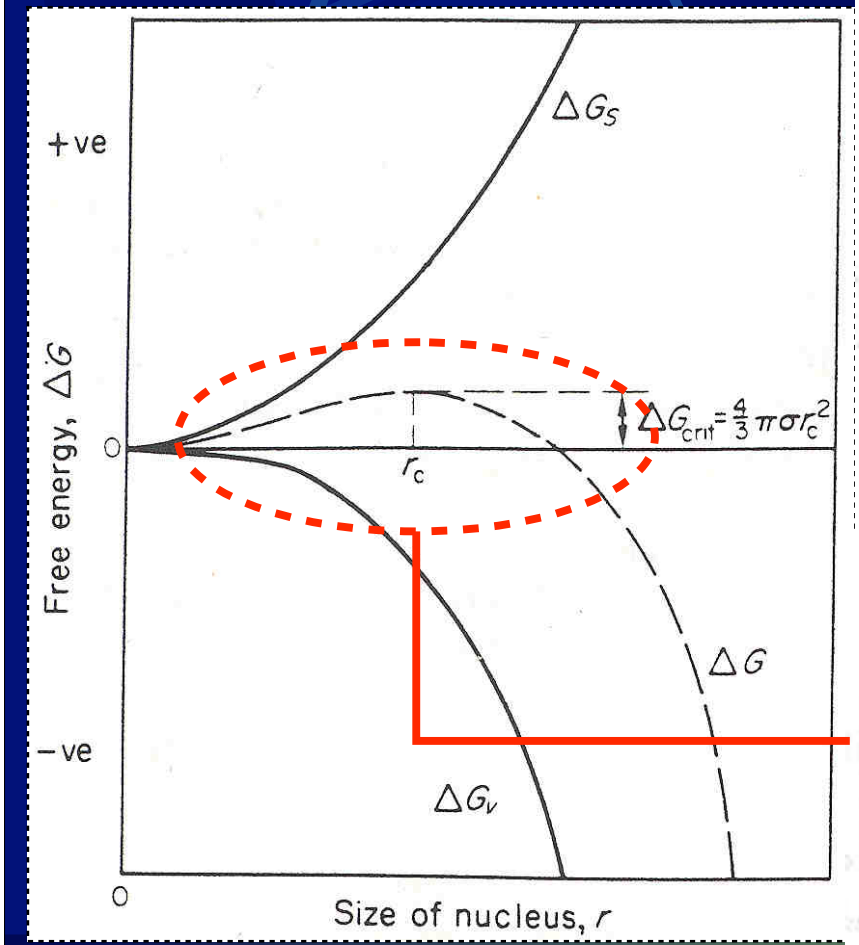
r: radius of cluster

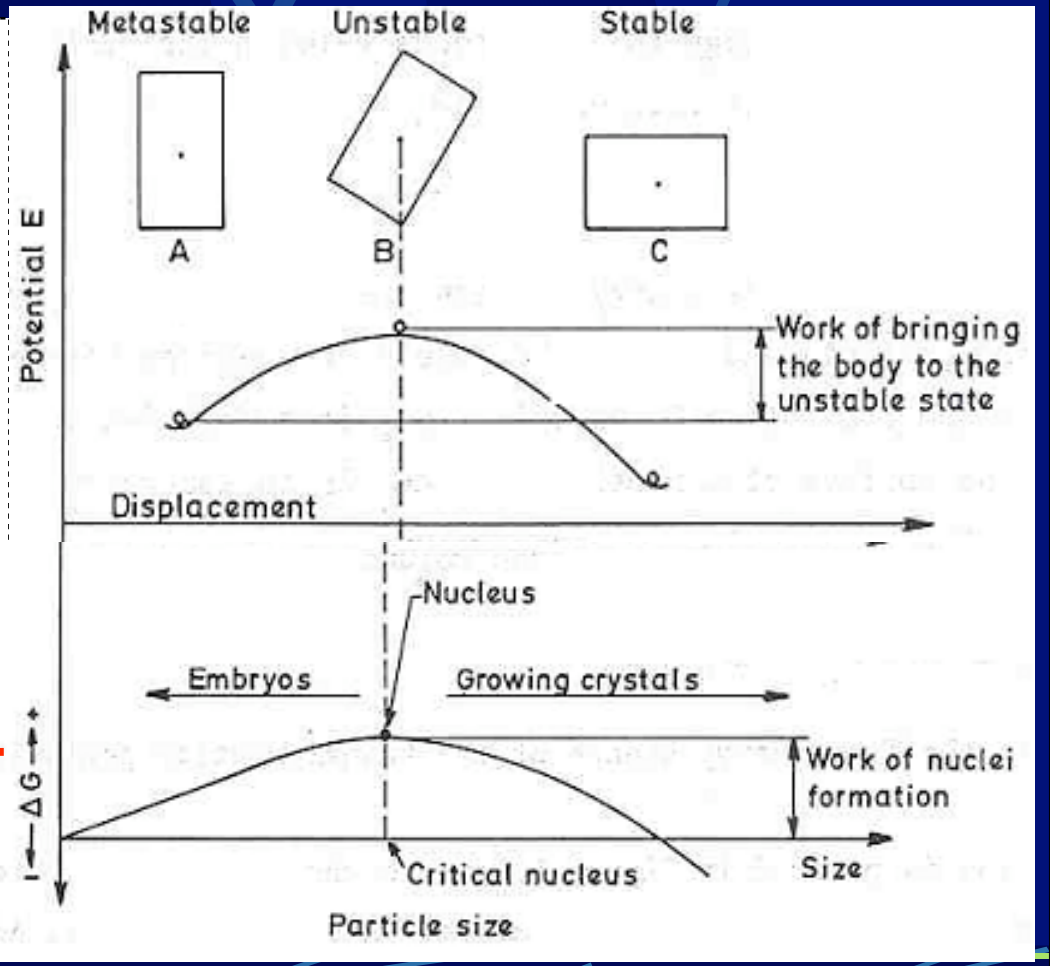
v_m: specific volume of solute molecules

S_B: supersaturation of the solution

γ: solid-liquid interfacial tension

Free Energy Diagram





Heterogeneous Nucleation

Ø Heterogeneous nucleation: caused by dust, dirt, rough spots on walls, etc
Ø In industrial processes, homogeneous nucleation is rare
Ø Nucleation is usually heterogeneous and/or secondary

Heterogeneous Nucleation

Ø Lower energy barrier

$$\Delta G_{het} = \phi \, \Delta G_{\text{hom}}$$

Energy Ratio

$$\phi = \frac{(2 + \cos\theta)(1 - \cos\theta)^2}{4}$$

Contact angle

$$0 < \phi < 1$$

Empirical Nucleation Model

$$J = k_n \Delta c_{\max}^{m}$$

$$\Delta c_{\max} = c - c^{*}$$

J :Nucleation rate

k_n:Nucleation rate constant

m:Nucleation order

C*:equilibrium concentration at nucleation temperature

C:solution concentration

Secondary Nucleation

Ø Nucleation caused by interaction of existing crystals with vessel, impeller or by collisions

Ø The main source of nuclei in many industrial applications

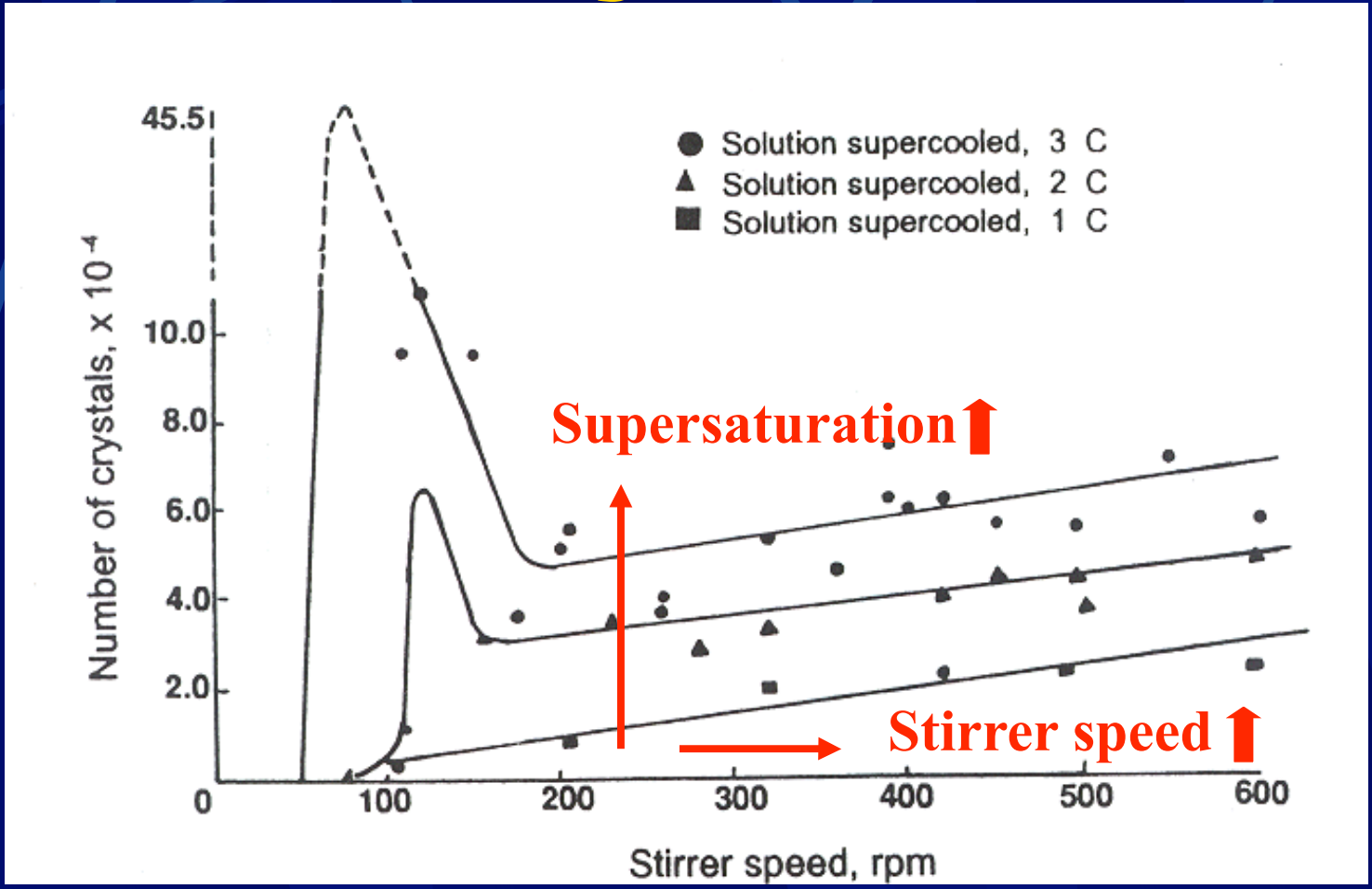
Ø Empirical model: B secondary nucleation rate

Stirring rate

Suspension density

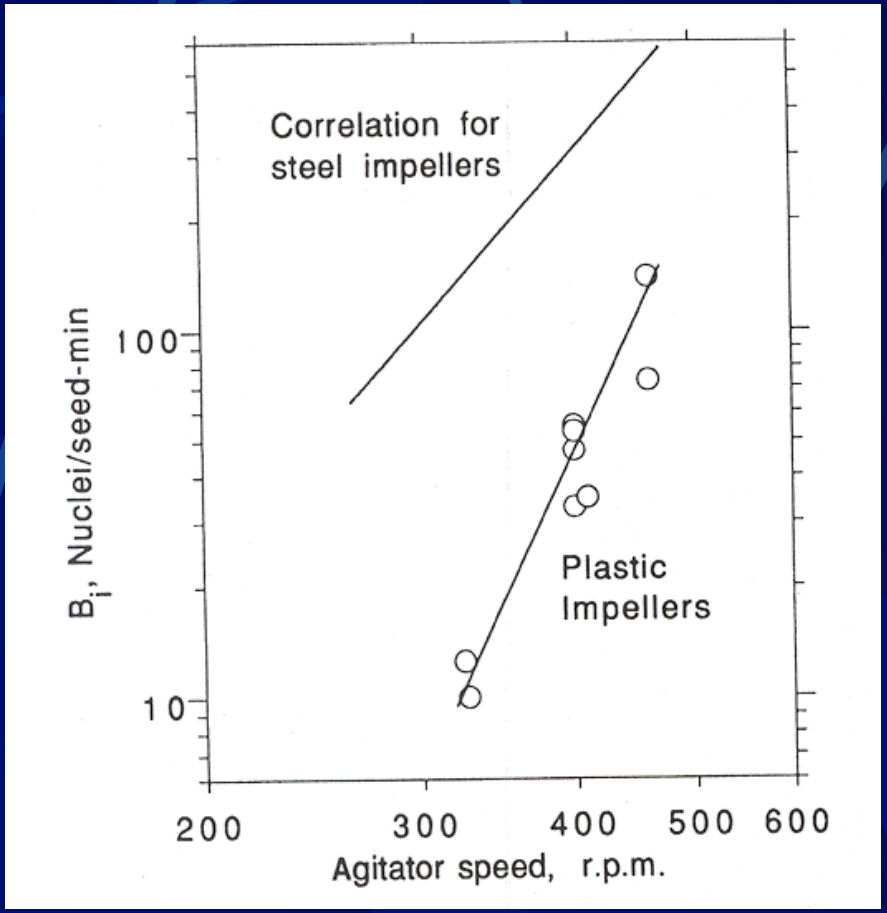
$$B = k_n N^i M_T^j \Delta C^m$$

Secondary Nucleation



Secondary Nucleation of Potassium Chloride

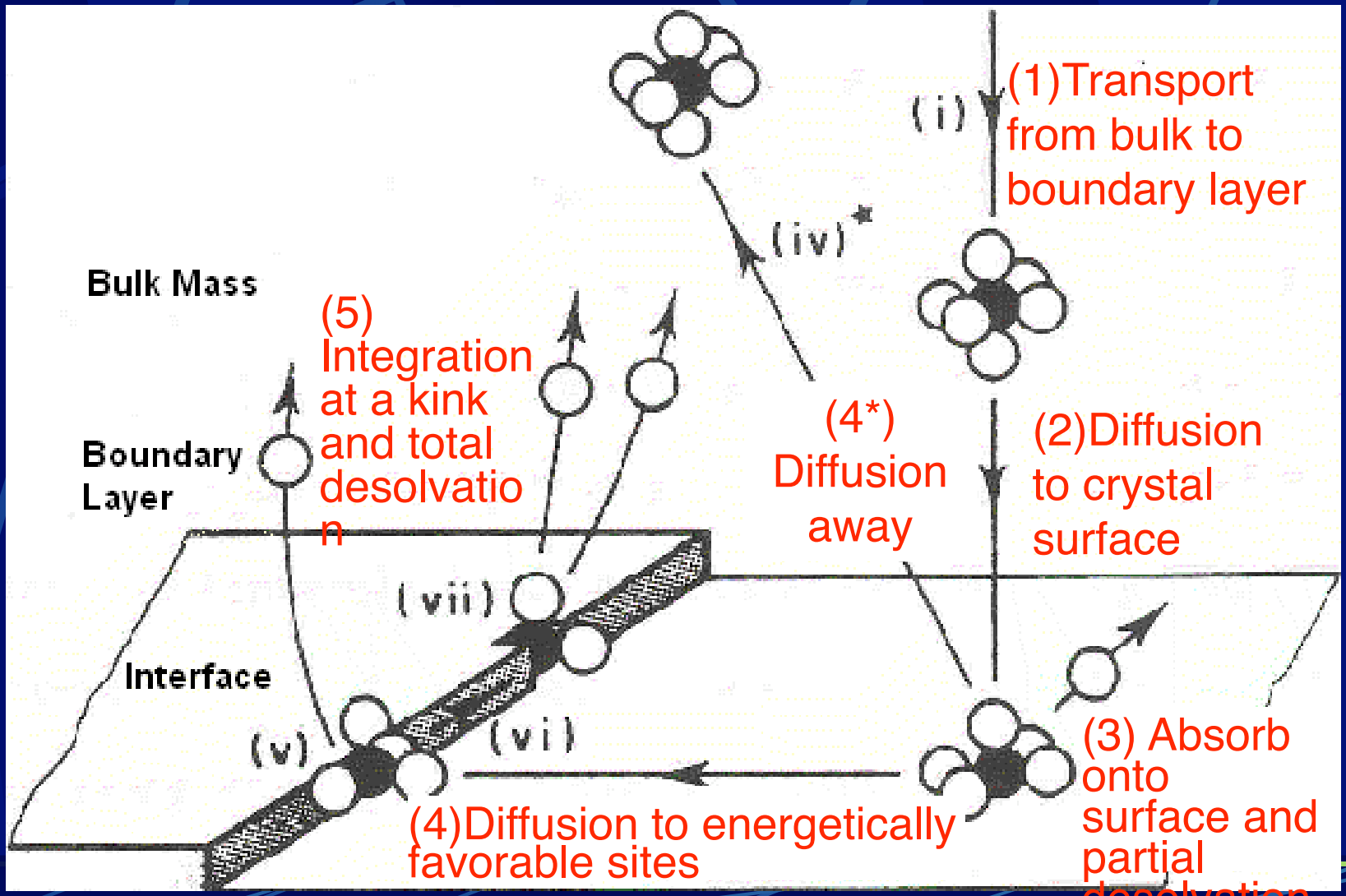
Secondary Nucleation



Ø Higher secondary nucleation rate using steel impeller

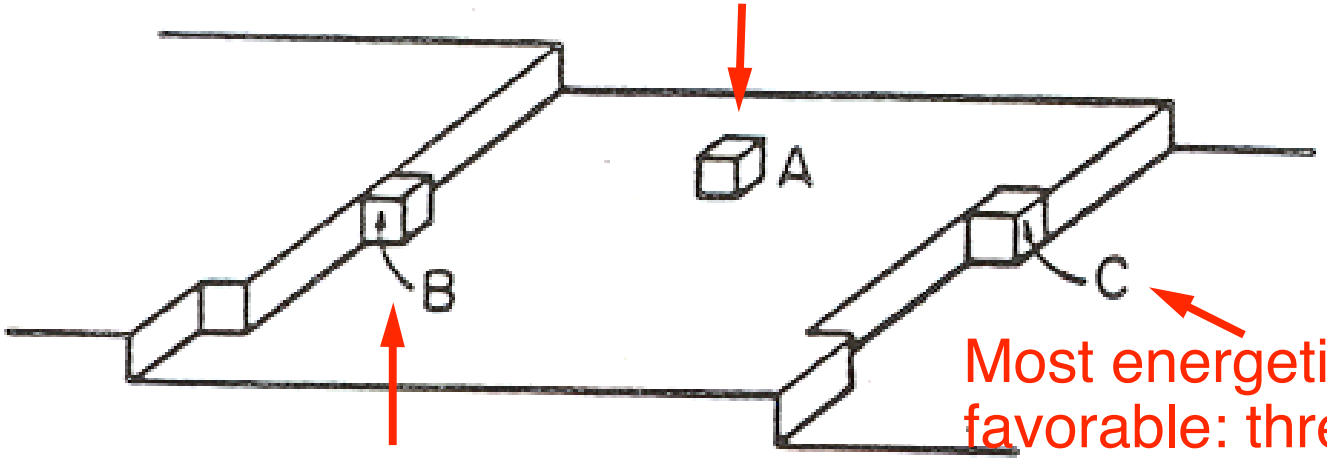
Ø Secondary nucleation rate increases as agitator speed rises

Crystal Growth



Molecule Incorporation

Single molecule incorporation on flat areas of a crystal face is not energetically favorable

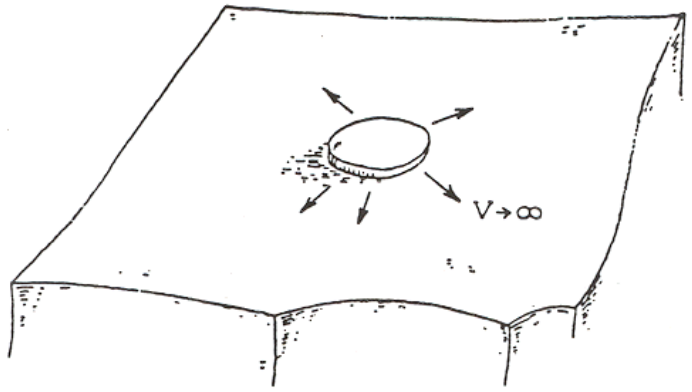


Molecule is bonded both to a step face as well as to the surface

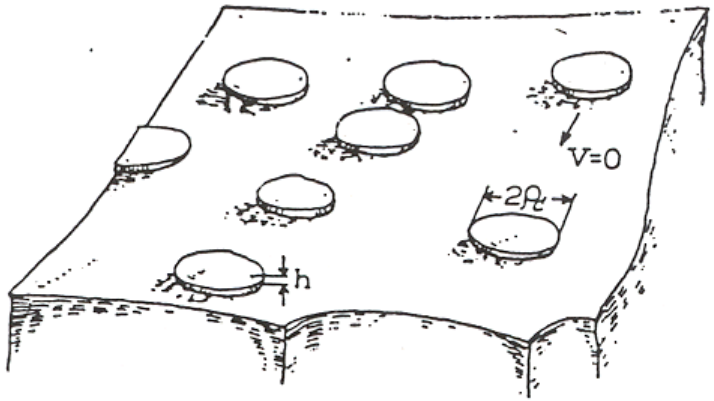
Most energetically favorable: three sides of molecular cube are bonded (kink site)

Surface Structure of a Growing Crystal

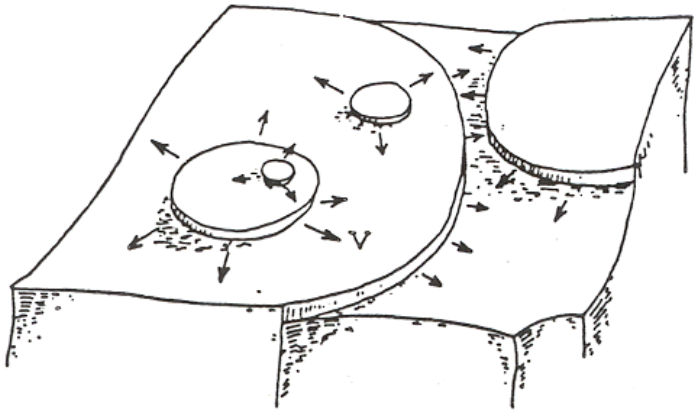
Crystal Growth Theories



Mononuclear Model



Polynuclear Model

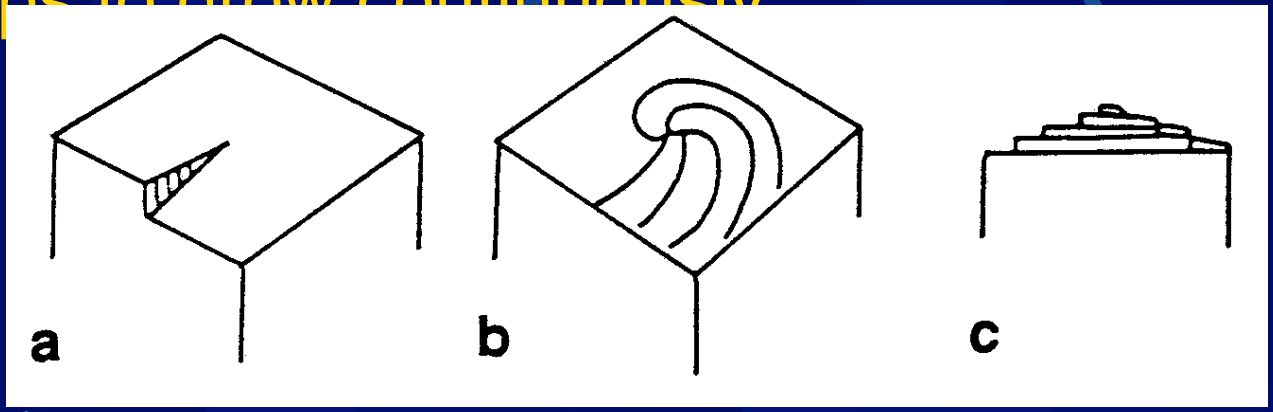


Birth and Spread Model

BCF (Burton Cabrera Frank) Theory

Ø Dislocations in the crystal are the source of new steps (dislocations are a certain type of irregularity in the structure of the crystal lattice)

Ø Screw dislocation provides a way for the steps to grow continuously



Spiral Growth from a Screw

Empirical Growth Model

Mass Deposition Rate

$$R_G = \frac{1}{A_T}\frac{dm}{dt} = k_G \Delta c^g$$

Overall Linear Growth Rate

$$G = \frac{dL}{dt}$$

$$R_G = 3\frac{\alpha}{\beta}\rho G$$

g: Growth order is generally between 0 and 2.5, most commonly equal to 1;

k_G: Overall rate constant,depends on temperature, crystal size, hydrodynamics and presence of impurities;

A_T: Total surface area of the crystals

m: Mass of the crystals; L : Mean crystal size;

α, β : volume and area shape factors; ρ : Crystal density

Particle Engineering

Physicochemical

Chemical purity
Crystal Habit
Crystal Structure (Polymorphism/ hydrate/imperfe-ction)
Thermodynamic properties

Physicotechnical

Mechanical properties (compressibility) packing & flowability

Particulate Properties

Crystal size, shape & surface

Bioavailability (solubility)
Chemical and physical stability

Seeding Technology

Objectives:

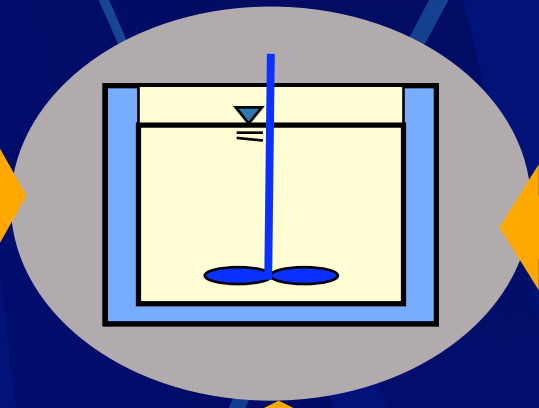
Ø Design the crystallization process to achieve a certain final product size using seeds

Ø By seeding the preferable polymorph form, obtain desired crystal morphology and polymorph or pseudo-polymorph

Approach

MultiMax reactor system

4x50ml scale
Temperature
Stirring rate
Dosing rate



BET
Particle surface area

Lasentec FBRM In-situ particle sizing

PXRD
Polymorphic form

Model

Population balance equation

$$\frac{dn(L,t)}{dt} + G\frac{\partial n(L,t)}{\partial L} = B_{nuc}\delta(L_i - L_0)$$

Crystal growth

$$G(T) = k_g(T)\Delta c^g(T) = \frac{dL}{dt}$$

Nucleation

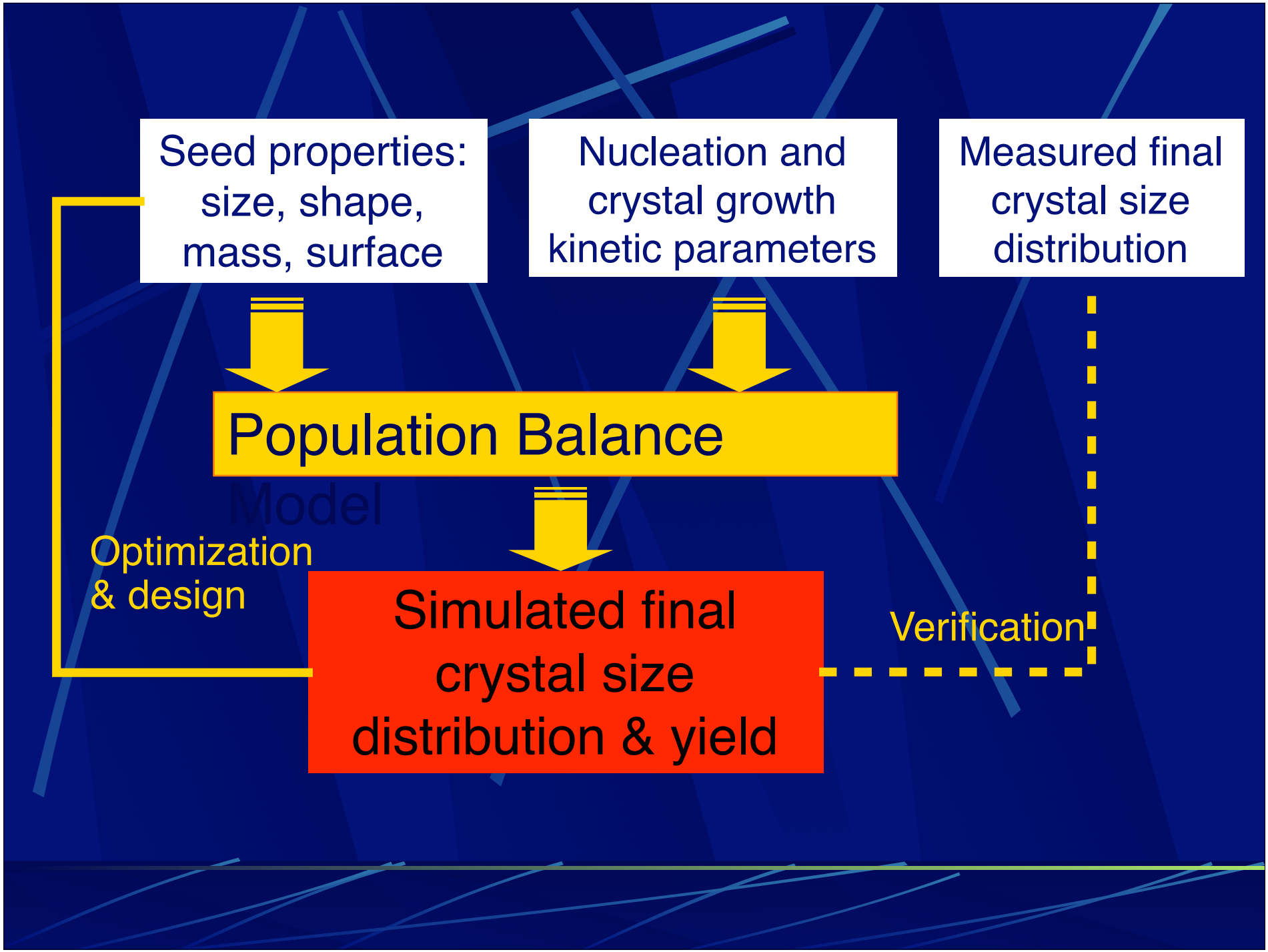
$$B_{nuc} = k_N N^a M_{tol}^b \Delta c^c$$

Super-saturation balance

$$\frac{d\Delta c}{dt} = -\frac{dc^*}{dT}\cdot\frac{dT}{dt} - N_G - N_{nuc}$$

Solubility

$$c^*(T) = a_1 T^2 + a_2 T + a_3$$


Seed properties: size, shape, mass, surface
Nucleation and crystal growth kinetic parameters
Measured final crystal size distribution
Population Balance
Model
Optimization & design
Simulated final crystal size distribution & yield
Verification

What do we do?

Ø Crystallization process development and optimization

Ø Nonphotochemical laser-induced nucleation of small molecules and proteins

Ø Template-directed nucleation and growth of molecular crystals

Ø Electrodynamic levitation of single solution droplet to study the activity of supersaturated small molecule and protein solutions

Questions?