



Crystal Engineering for Product & Process Design

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Special Thanks to Dan Green, DuPont Company

Acknowledgements

People

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Role of Engineer in Industry

To make, evaluate and justify technical decisions in support of business

Why Crystals?

- Crystalline organic solids ubiquitous in
 - chemicals & specialty chemicals
 - home & personal care
 - food and pharma
- Almost 100% of small MW drugs are isolated as crystalline materials
- Over 90% of ALL pharmaceutical products are *formulated* in particulate, generally crystalline form
- Pharma industry worldwide > \$300 billion/year sales

Why Modeling?

“If you can’t model your process, you don’t understand it. If you don’t understand it, you can’t improve it. And, if you can’t improve it, you won’t be competitive in the 21st century.”

Jim Trainham, DuPont

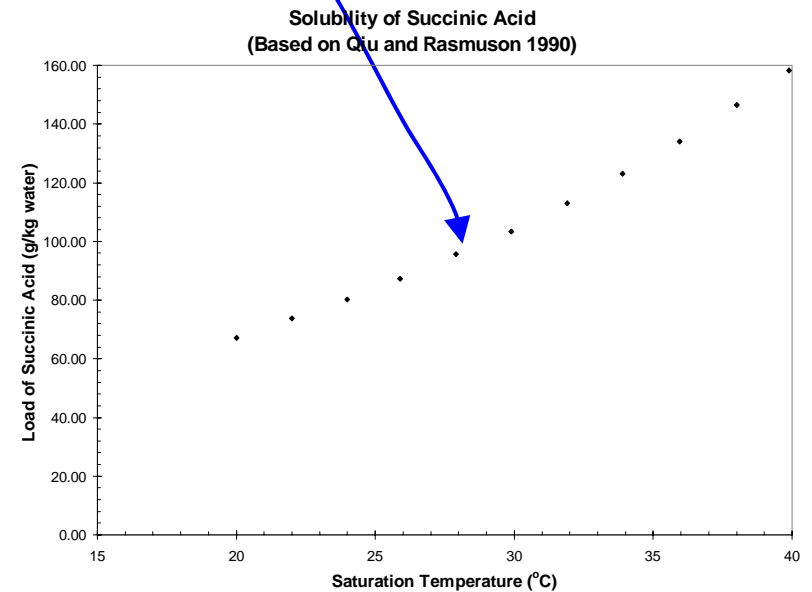
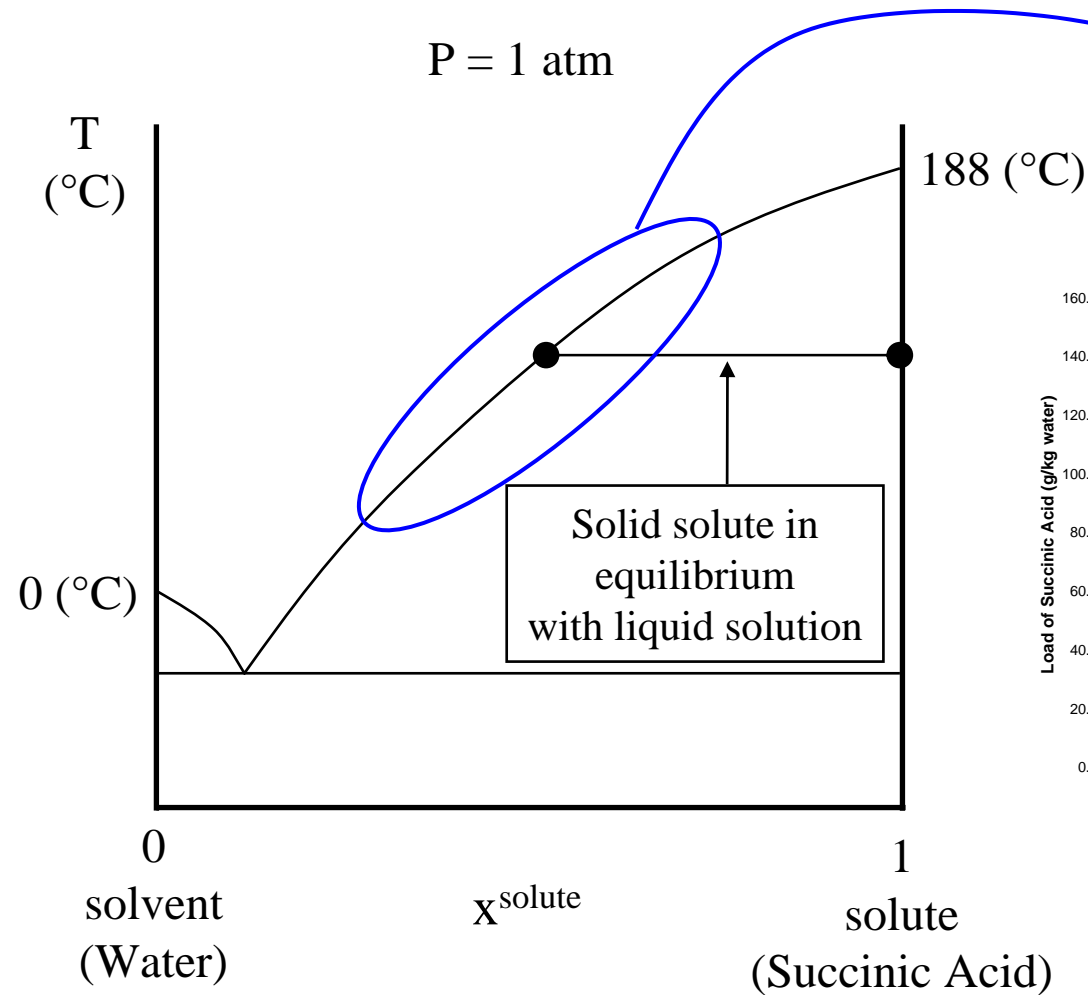
Perspectives

- Engineers believe that their models approximate nature
- Scientists believe that nature approximates their models
- Mathematicians don't give a damn either way

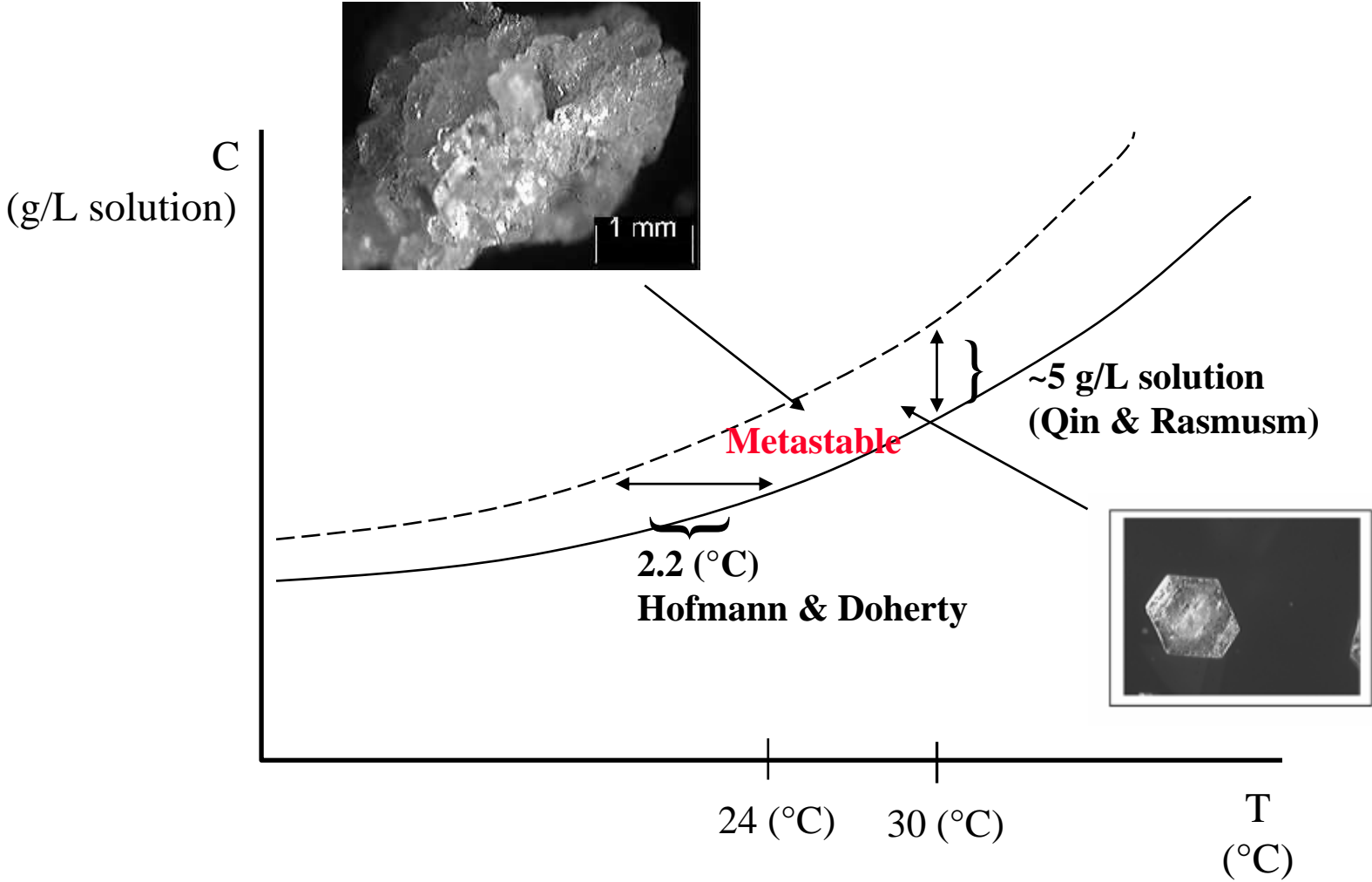
Outline

1. Phase diagrams & crystal quality
2. Material properties & product functionality
3. Design for desired material properties
 - crystal engineering for product design
4. Scale up & process synthesis

Solid – Liquid Equilibrium



Succinic Acid





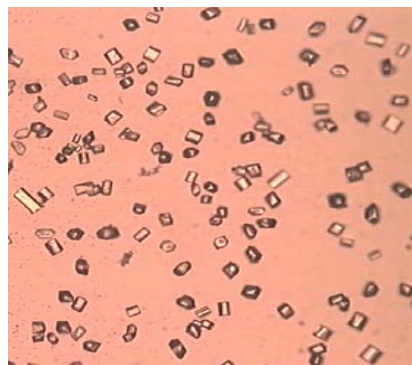
Apparatus after experiment of 30 min, 0.8K below the metastable zone width (succinic acid saturated at 24 C)



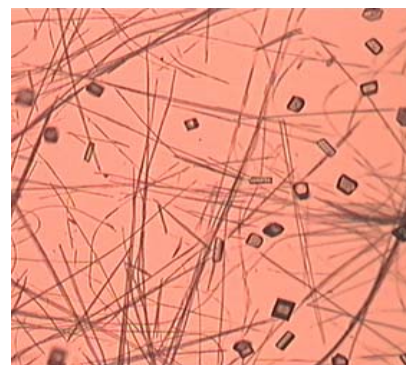
Polymorphism

- The polymorph that is selected can affect:
Solubility, Shape, Melting Point, Bioavailability,
Compressibility, Growth and Dissolution Rate,
Taste, Color, Stability, Flowability, ***Patentability***...
- The transition from one polymorph to another usually occurs more easily in a solution mediated mechanism, rather than a direct solid-solid transition.

Solution-Mediated Polymorphism

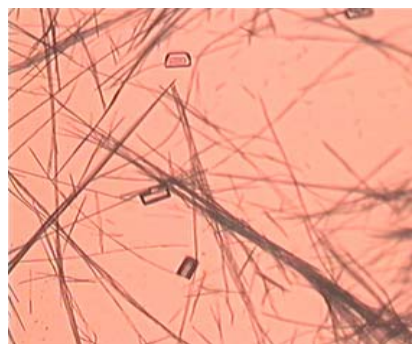


Time = 0 hrs.

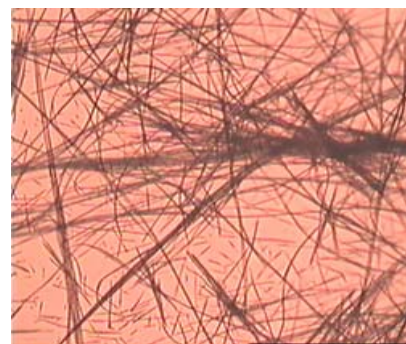


Time = 15 hrs.

0.2m
m



Time = 30 hrs.



Time = 45 hrs.

Time lapse photos of a transition between forms 1 and 2 of dihydroxybenzoic acid (Davey et al.)

Polymorphs of Ritonavir

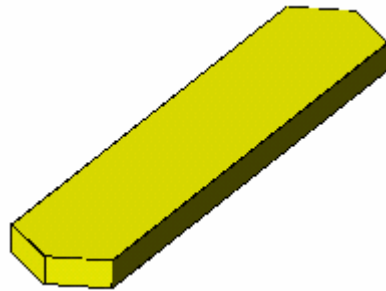
- Ritonavir – Main component in an Abbott Labs HIV drug
 - Commercial Startup – Jan. 1996
 - Early 1998 – Many final product lots began to fail a dissolution test
- A new, previously unknown, thermodynamically more stable and much less soluble crystalline form (polymorph) appeared after two years of production
 - They were no longer able to produce the marketed form.
 - US-FDA web site 1998, “Abbott Laboratories is experiencing manufacturing difficulties with the capsule formulation of our HIV protease inhibitor, Norvir (ritonavir), which will result in a shortage of capsules. We have encountered an undesired formation of a Norvir crystalline structure that affects how the capsule form of Norvir dissolves ...”
- It is *vital* to know about polymorphs as early as possible, and it is important to understand their interconversion for processing.

Chemburkar, et. al., “Dealing with the Impact of Ritonavir Polymorphs on the Late Stages of Bulk Drug Process Development,” *Organic Process Research and Development*, **4**, 413 (2000)

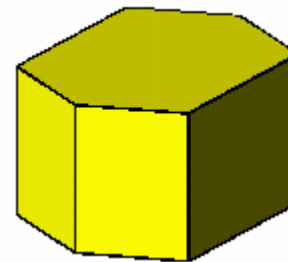
Crystal Shape - Ibuprofen

Gordon & Amin US Patent 4,476,248 issued to The Upjohn Company

- Objective of the invention: “an improved crystalline habit and crystal shape of ibuprofen”
- Method of crystallization from polar solvents, such as methanol, ethanol (instead of hexane or heptane).
- Faster dissolution rate, larger particle size, lower bulk volume, reduced sublimation rates and improved flow properties.



Ibuprofen grown out
of hexane



Ibuprofen grown out
of methanol

Crystal Size

- Beta-carotene – food colorant. Color shade is determined by the narrow size distribution in the submicron range
- New brilliant ink pigments in the nanoparticle size range
- Tungsten carbide particles – narrow size distribution in the 5-7 micron range

Key Issues for Process Development

- **How to design for the desired material properties?**
 - crystal purity
 - mean particle size and particle size distribution
 - polymorph
 - particle shape
 - enantiomer
- **How to scale up?**
 - vessel design
 - system design & process synthesis

Equilibrium Crystal Growth & Shape

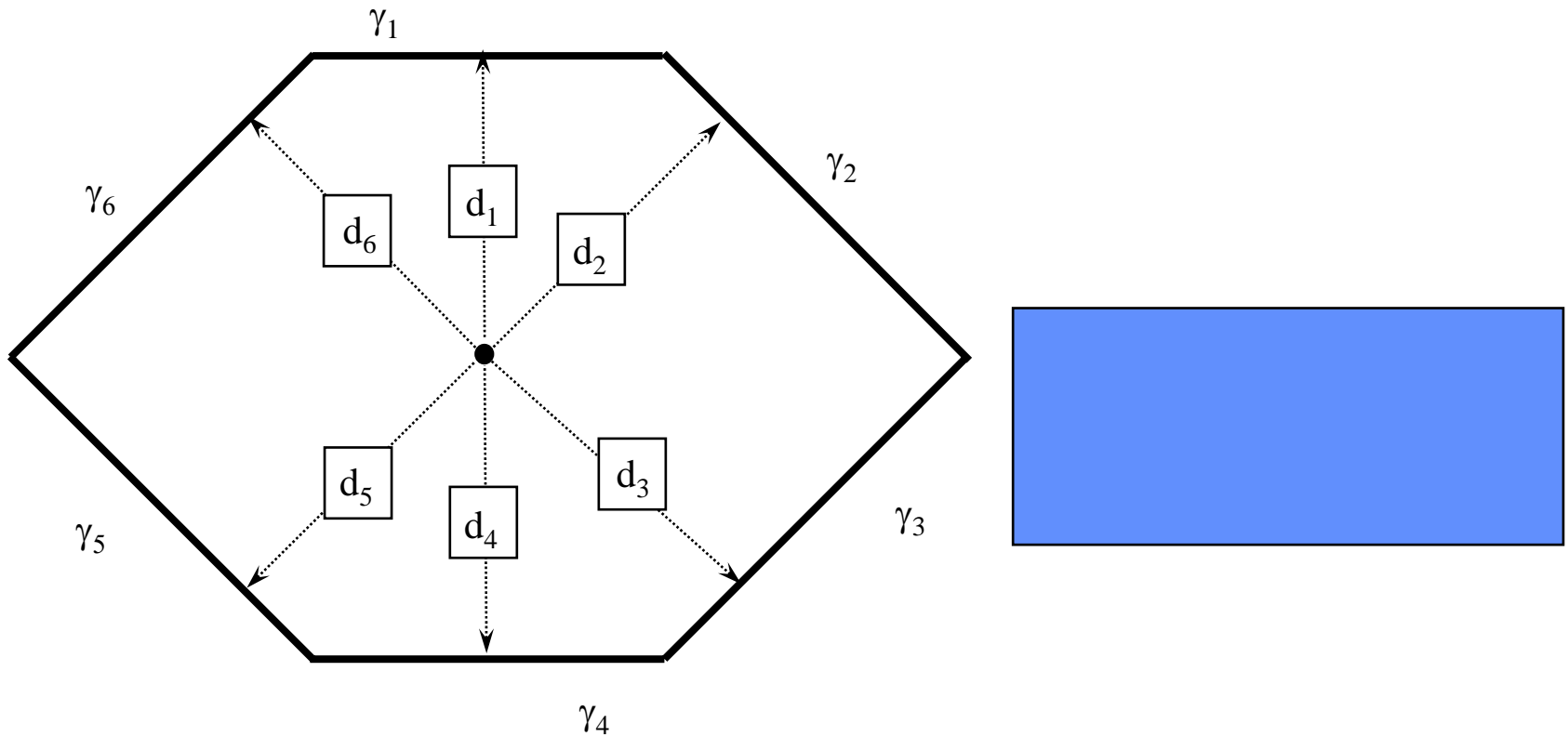
- Idealized shape at infinitesimal supersaturation and loooooooooooooong times
- Gibbs equilibrium condition for shape of faceted crystals (1877-78)

$$\min \sum_i \gamma_i A_i, \quad s.t. \text{ fixed } V$$

- Wulff (1901) construction - solves the Gibbs minimization problem

C. Herring, "Some Theorems on the Free Energies of Crystal Surfaces," *Phys. Rev.*, 82, 87-93 (1951)

Wulff Construction



Reservations About the Theory

Gibbs (Collected Works, pp. 325-326)

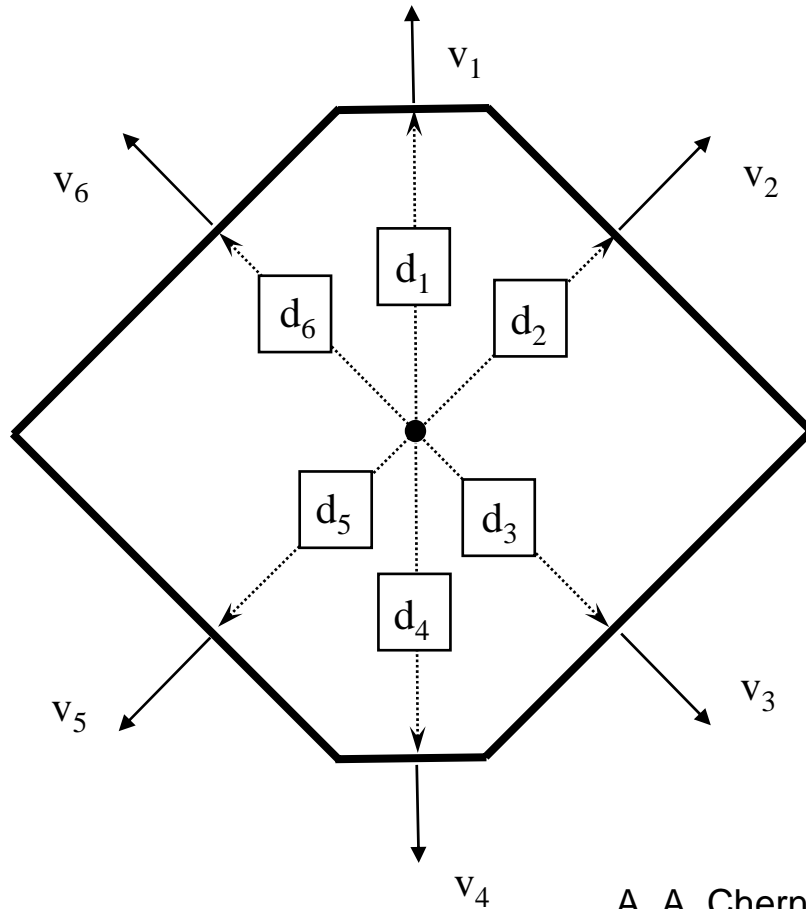
“On the whole it seems not improbable that the form of very minute crystals in equilibrium with solvents is principally determined by the condition that $(\sum \gamma_i A_i)$ shall be a minimum for the volume of the crystal, but as they grow larger (in a solvent no more supersaturated than is necessary to make them grow at all), the deposition of new matter on the different surfaces will be determined more by the orientation of the surfaces and less by their size and relations to the surrounding surfaces. As a final result, ***a large crystal, will generally be bounded by those surfaces alone on which the deposit of new matter takes place least readily. But the relative development of the different kinds of sides will not be such as to make $(\sum_i \gamma_i A_i)$ a minimum***”.

Reservations About the Theory

Landau & Lifshitz (Statistical Physics, p. 520)

“It must be emphasized that the crystal shape observed under ordinary conditions is determined by the condition of growth of the crystal and is not the equilibrium shape.”

Steady-State Growth Shapes



Real growth shapes at low supersaturation

Chernov Condition



A. A. Chernov, "The Kinetics of the Growth Forms of Crystals,"
Soviet Physics-Crystallography, 7, 728-730 (1963)

Facetted Growth

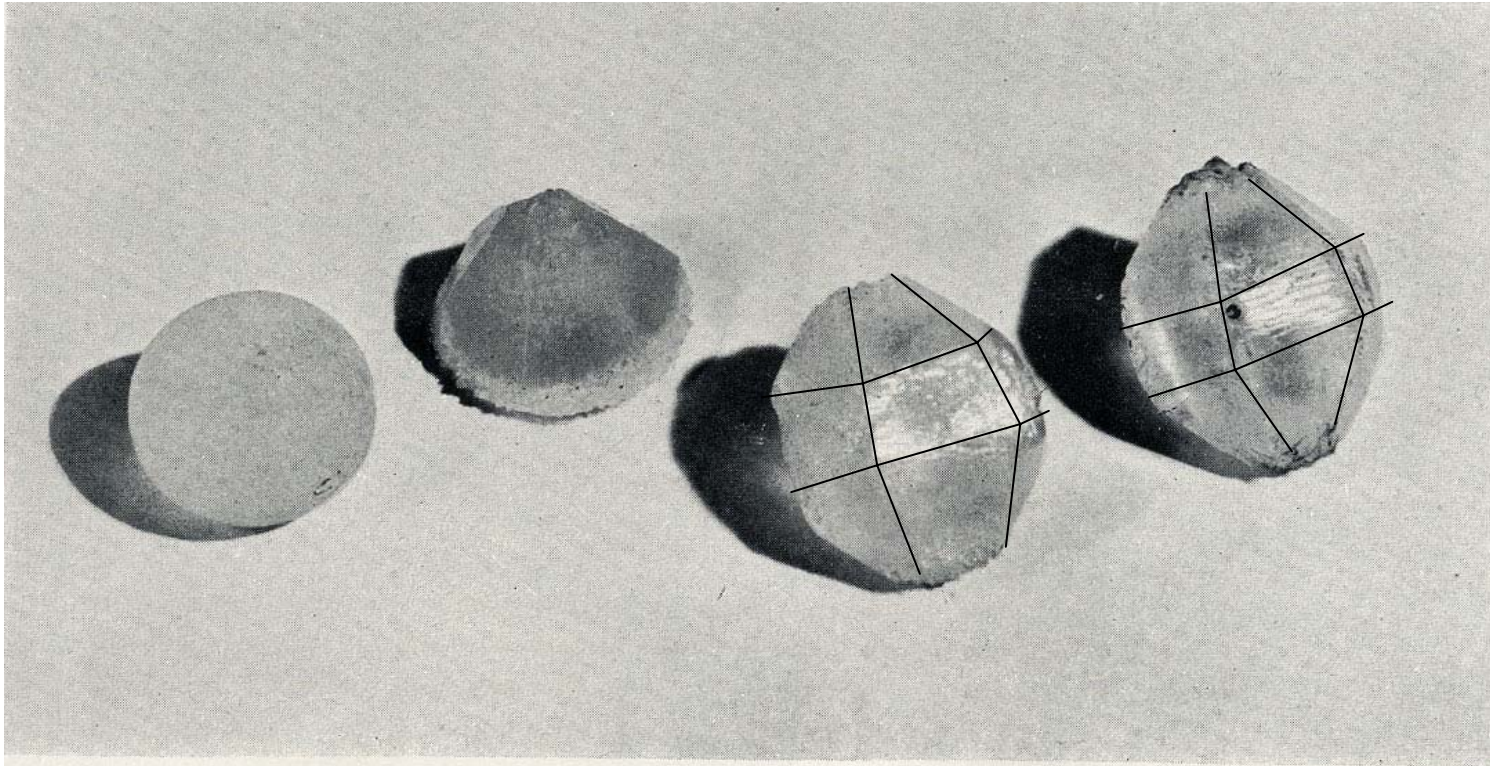


FIG. 2.—Growth of quartz on spherical seeds.

Thomas, L. A., N. Wooster, and W.A. Wooster,
Crystal Growth, *Discussions of the Faraday Society*, 343 (1949)

Crystal Shape and Growth Models

- Crystals grow by the flow of steps across the faces
- Sources of steps
 - 2-D nuclei - birth and spread model
 - spirals growing from screw dislocations
- Sources of edges – strong bond chains (PBC's)
- Sources of docking points for solute incorporation – kinks on edges (missing molecules along bond chains)

Spiral Growth of Organic Crystals

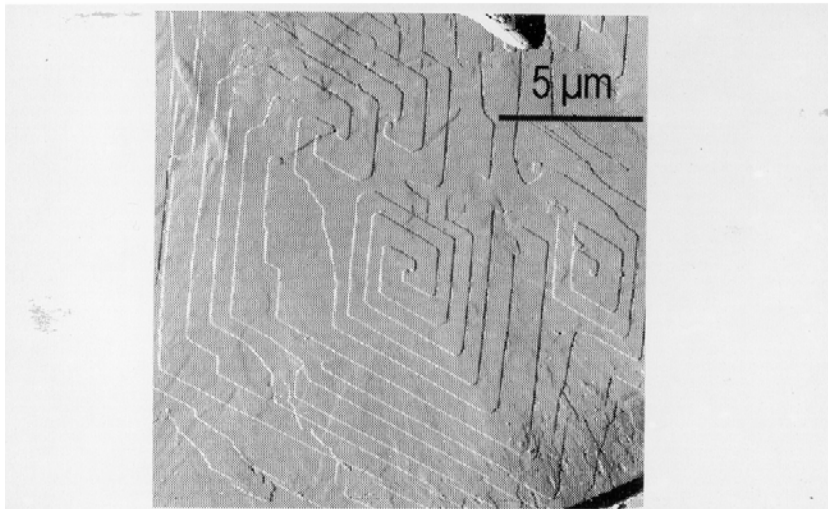
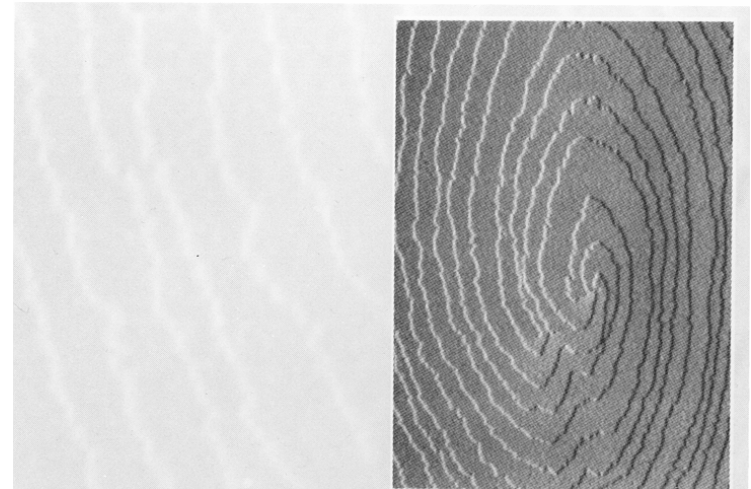


Figure 10.4: Part of the {001} surface of an n-C₄₀H₈₂ crystal with several polygonal spirals imaged by TM-AFM.



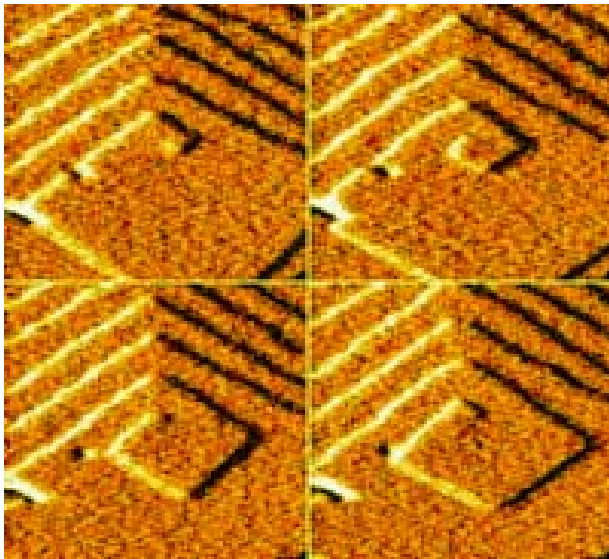
Acknowledgement

The cover design represents the {101} face of a tetragonal hen egg white lysozyme. R. Price, B. Donohoe, G. L. Taylor and P. J. Halfpenny (University of Strathclyde, UK).



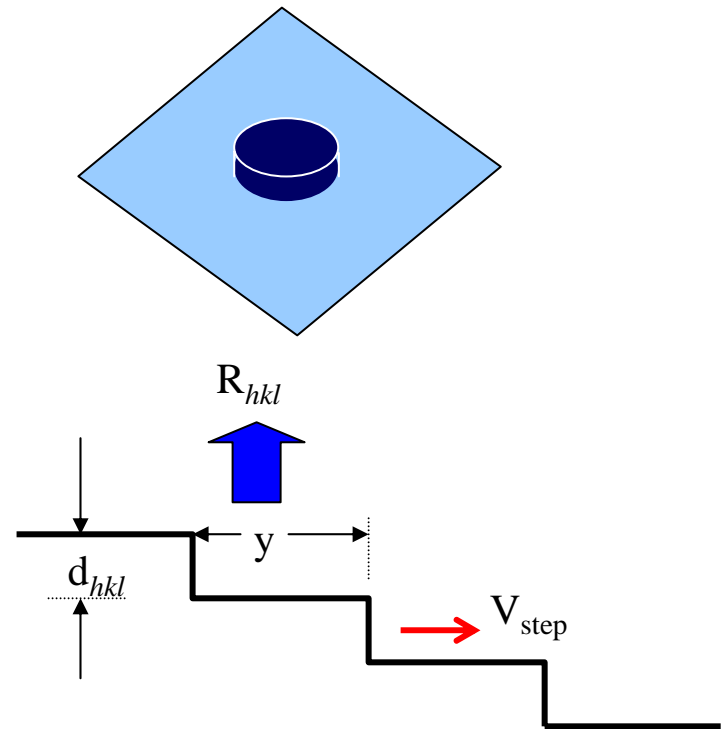
Step Formation

Spirals from a Screw Dislocation (BCF)



Paloczi, et. al., *Applied Physics Letters*, **73**,
1658 (1998)

2-D Nucleation / Birth & Spread

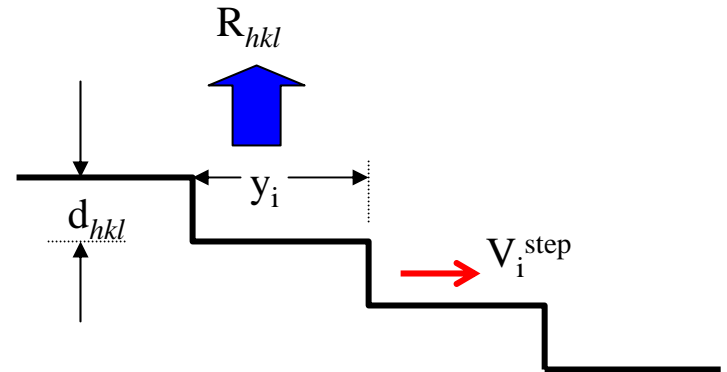


BCF Growth Model

Rate of growth normal to face hkl

$$R_{hkl} = (v_i d / y_i)_{hkl}$$

i = edge i on face hkl



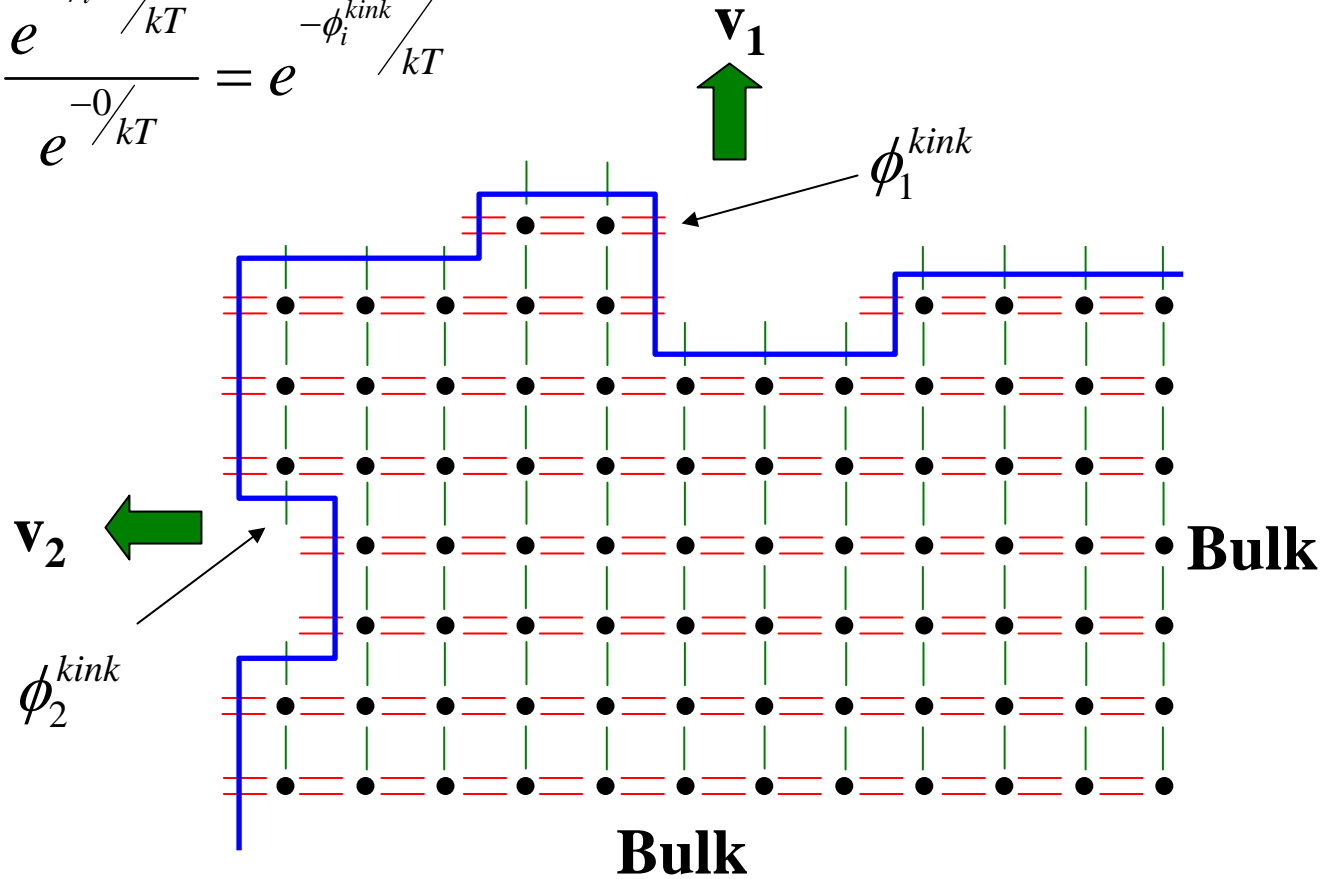
$(y_i)_{hkl}$ depends on shape of spiral and step velocities

$$(v_i)_{hkl} \propto a_p [1 + 0.5 \exp(\phi_{hkl}^{kink, i} / RT)]^{-1}$$

$$R_{hkl} \propto \frac{d_{hkl}}{(y_i)_{hkl}} a_p [1 + 0.5 \exp(\phi_{hkl}^{kink, i} / RT)]^{-1}$$

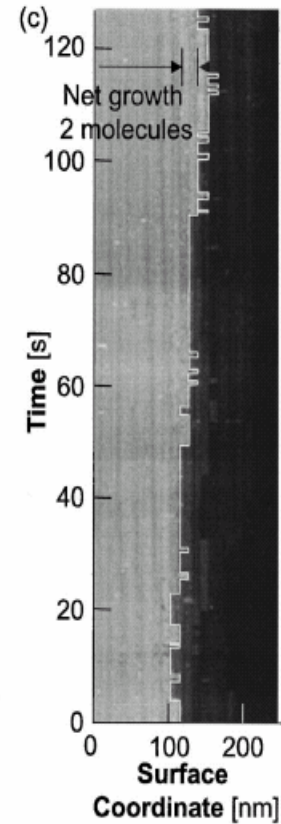
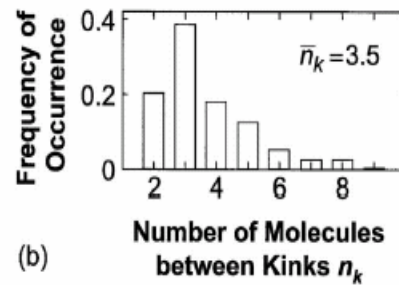
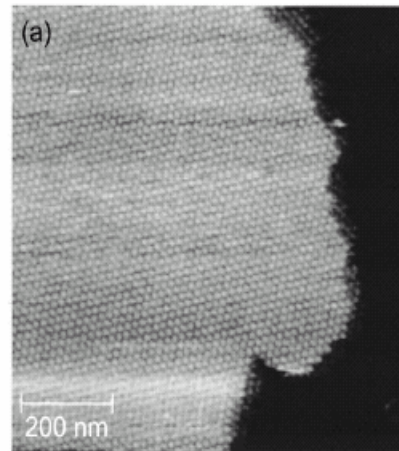
Boltzmann Distribution of Kinks

$$\frac{p(\text{kink}, i)}{p(\text{no kink})} = \frac{e^{-\phi_i^{\text{kink}}/kT}}{e^{-0/kT}} = e^{-\phi_i^{\text{kink}}/kT}$$



Kinks on Steps of Ferritin Crystal

KAI CHEN AND PETER G. VEKILOV



Solid State and Solvent Effects

Face velocities depend on:

- crystallography (unit cell, space group, etc)
- atom-atom pair potentials (including charge distribution)
- bond chains (we have a fast, automated new method for finding them) and kink energies
- growth unit
- solvent

$$\gamma_{ls} = \gamma_l + \gamma_s - W_A = \gamma_l + \gamma_s - 2 (\gamma_l^d \gamma_s)^{0.5}$$

General Principle

The **faster** the rate of growth of a face, the **smaller** its size on the crystal

Fast faces grow out and do not appear on the final steady growth shape

The Model

$$\frac{dH_i}{dt} = G_i$$

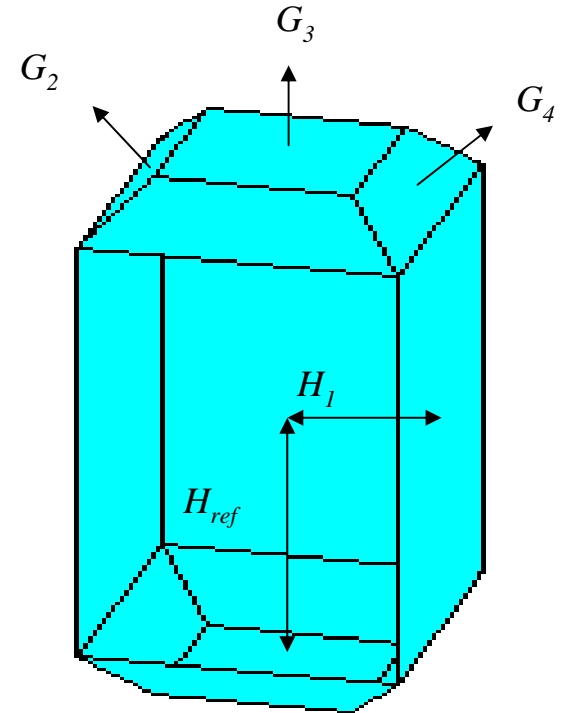
$$x_i = \frac{H_i}{H_{ref}} \quad R_i = \frac{G_i}{G_{ref}} \quad d\xi = \frac{G_{ref}}{H_{ref}} dt$$

$$\frac{dx_i}{dt} = \frac{G_{ref}}{H_{ref}} (R_i - x_i)$$

$$\frac{dx_i}{d\xi} = R_i - x_i, \quad i = 1, \dots, N-1$$

Eigenvalues = -1

Unique Stable Steady
State



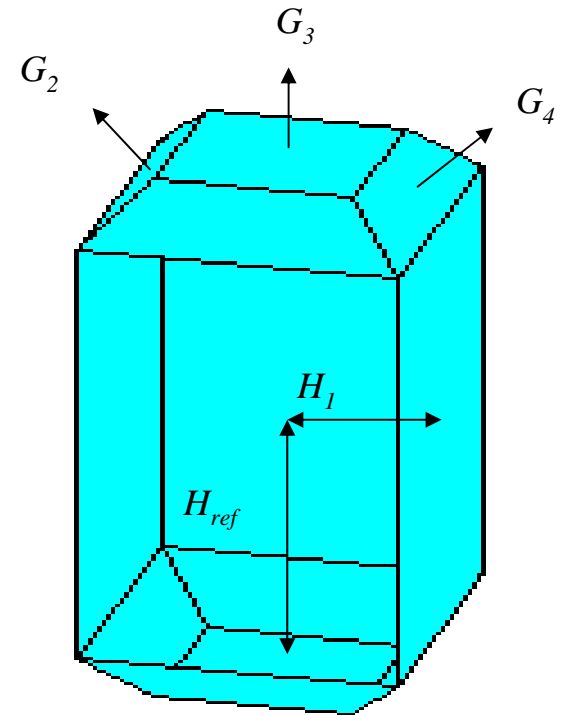
Steady States

$$\frac{dx_i}{d\xi} = R_i - x_i$$

$$R_i - x_i = 0$$

$$\frac{R_1}{x_1} = \frac{R_2}{x_2} = \dots = \frac{R_N}{x_N} = 1$$

$$\frac{G_1}{H_1} = \frac{G_2}{H_2} = \dots = \frac{G_N}{H_N} = \text{constant}$$



Chernov
Condition

Discrete Events at Vertices

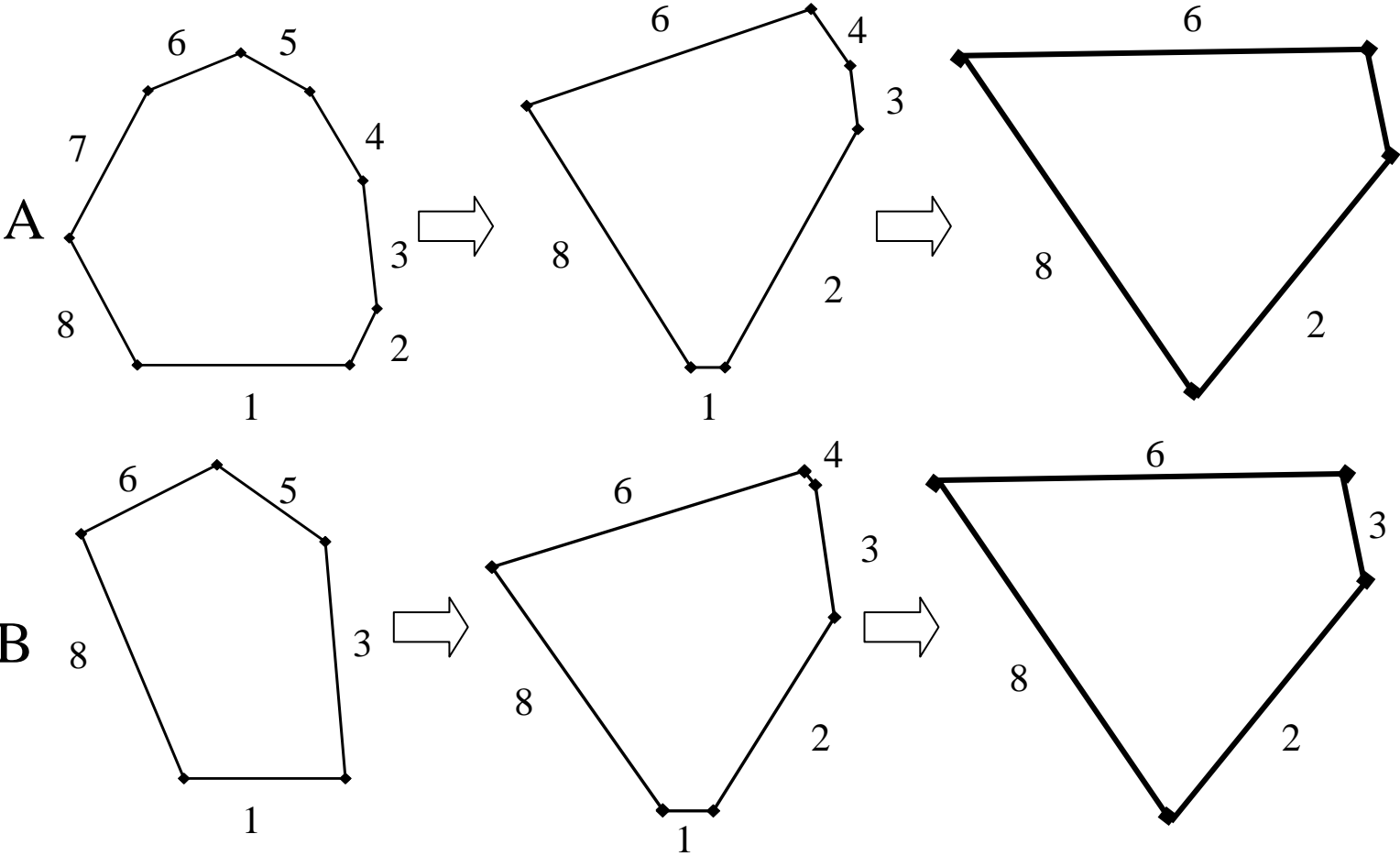
- Geometric Elements
 - Crystal: 3-D polyhedron bounded by flat faces
 - Edges: intersection of 2 faces
 - Vertices: intersection of 3 or more faces
- Euler's Polyhedral Rule
 - Convex polyhedron $F + V - E = 2$
 - Under shape changes $\Delta F + \Delta V - \Delta E = 0$
 - Number of virtual faces, edges

$$\Delta V_{\max} = {}^N C_3 - 1, \quad \Delta E_{\max} = {}^N C_2 - E^V$$

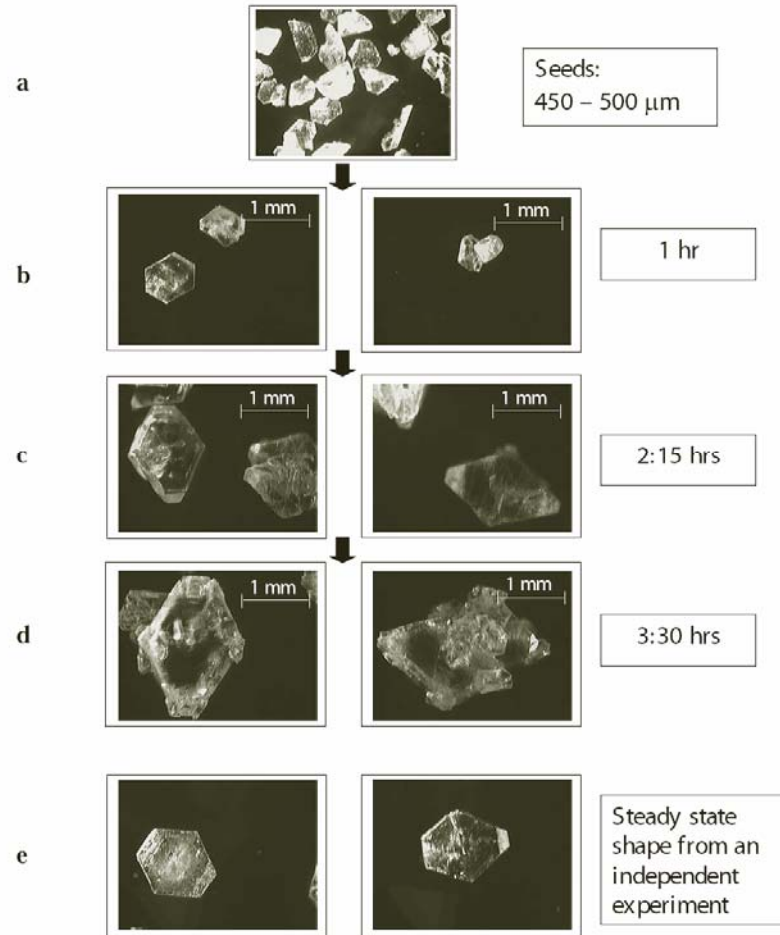
N = number of faces that meet at the vertex under consideration

E^V = number of edges that meet at the vertex under consideration = N

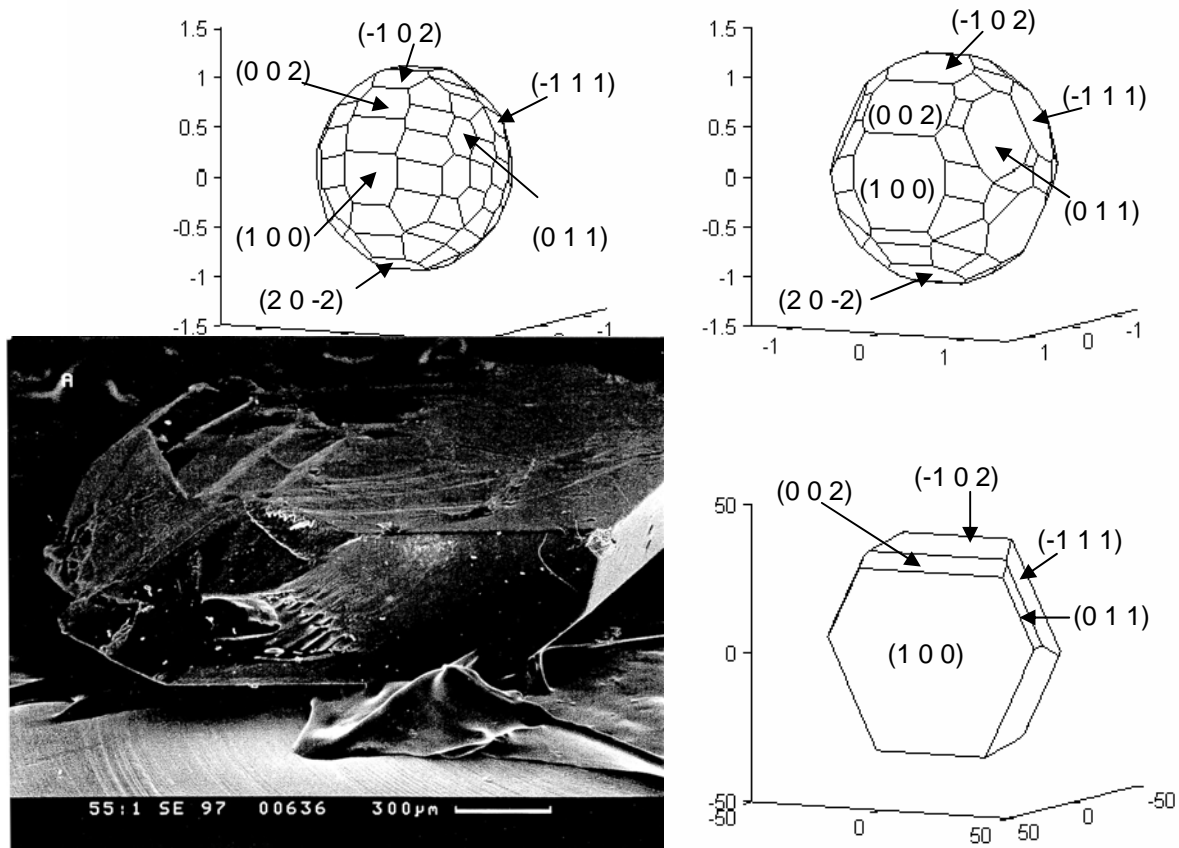
Effect of Random Seed Shape



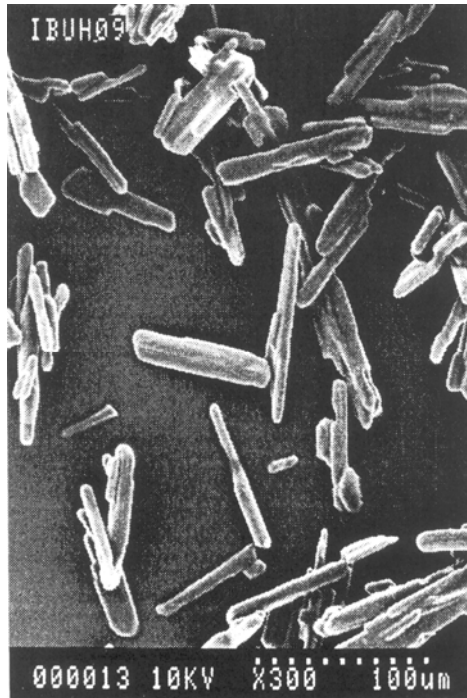
Succinic Acid Grown from Water



3-D Shape Evolution: Adipic Acid

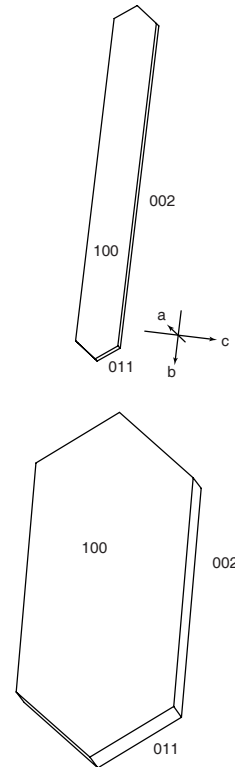
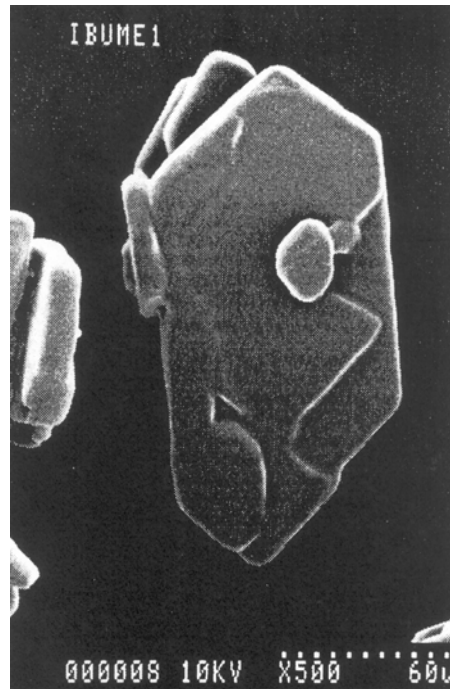


Application - Ibuprofen



Storey & York (1997)
Ibuprofen grown from hexane

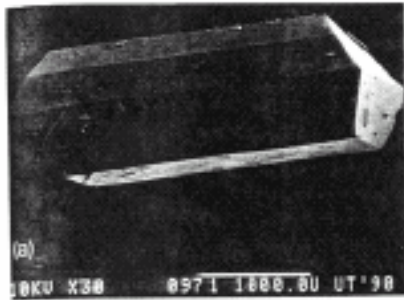
Storey & York (1997)
Ibuprofen grown from methanol



Predicted – ibuprofen grown
from hexane (top) and methanol (bottom)

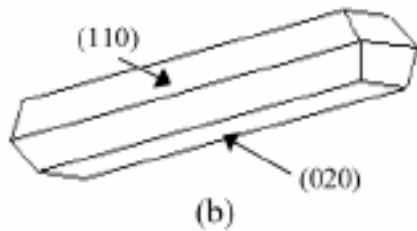
Application – alpha glycine

alpha-glycine grown from aqueous solution



(a)

Experiment – Boek, Feil, Briels & Bennema,
J. Cryst. Growth, (1991)

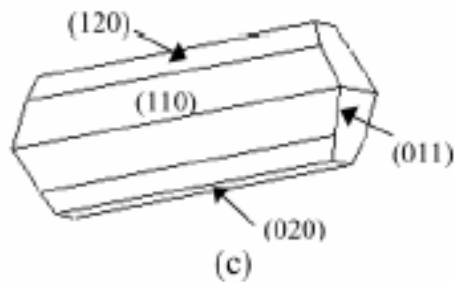


(b)

Prediction – Bisker-Leib & Doherty,
Crystal Growth Des., (2003)

(b) dimer growth unit

(c) monomer growth unit



(c)

Population Balance Modeling

- Shape Factor: $k_v(h_{hkl}) = \frac{V_{\text{cryst}}}{h_{hkl}^3} = f(h_{hkl}, h_{hkl}^0)$

- **Link:** Shape Evolution Model $\xrightarrow{k_v(h_{hkl}), G_{hkl}}$ PBM

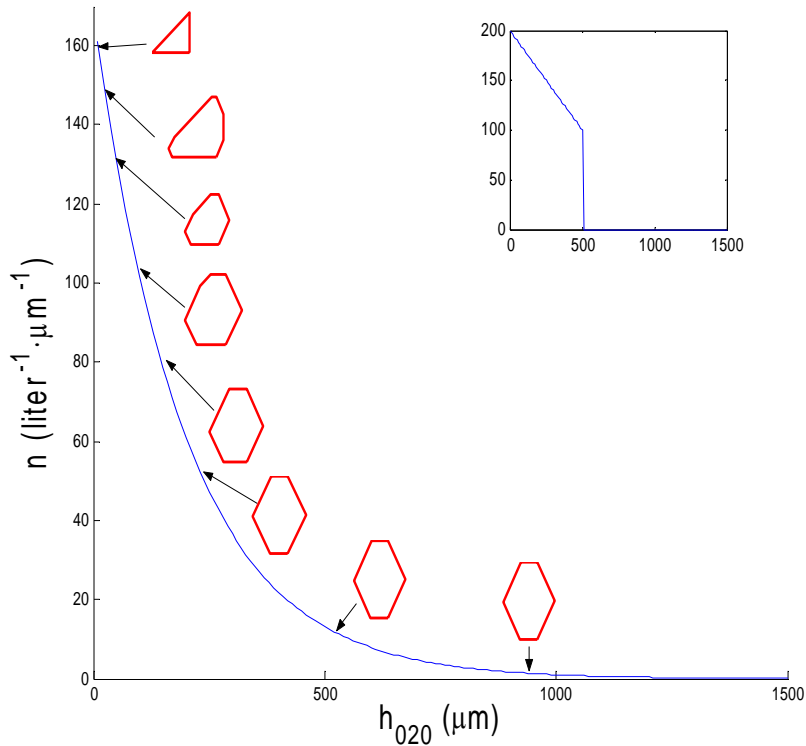
- One Dimensional MSMPR Crystallizer

Population Balance: $\frac{\partial n}{\partial t} = -G_{hkl} \frac{\partial n}{\partial h_{hkl}} - \frac{n}{\tau}$

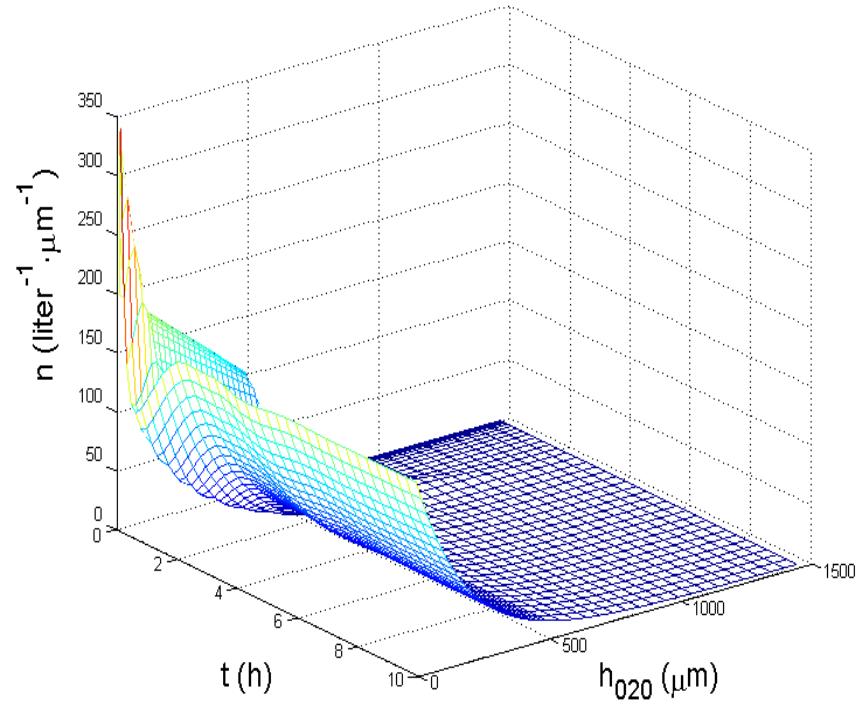
Solute Mass Balance: $\frac{dc}{dt} = \frac{(\rho - c)}{\tau} + \frac{(c_{in} - \rho)}{\epsilon \tau} + \frac{(\rho - c)}{\epsilon} \frac{d\epsilon}{dt}$

$$\epsilon = 1 - \int_0^{\infty} \frac{n k_v(h_{hkl}) h_{hkl}^3}{dh_{hkl}}$$

Size & Shape Evolution – Succinic Acid



Initial and steady-state distribution



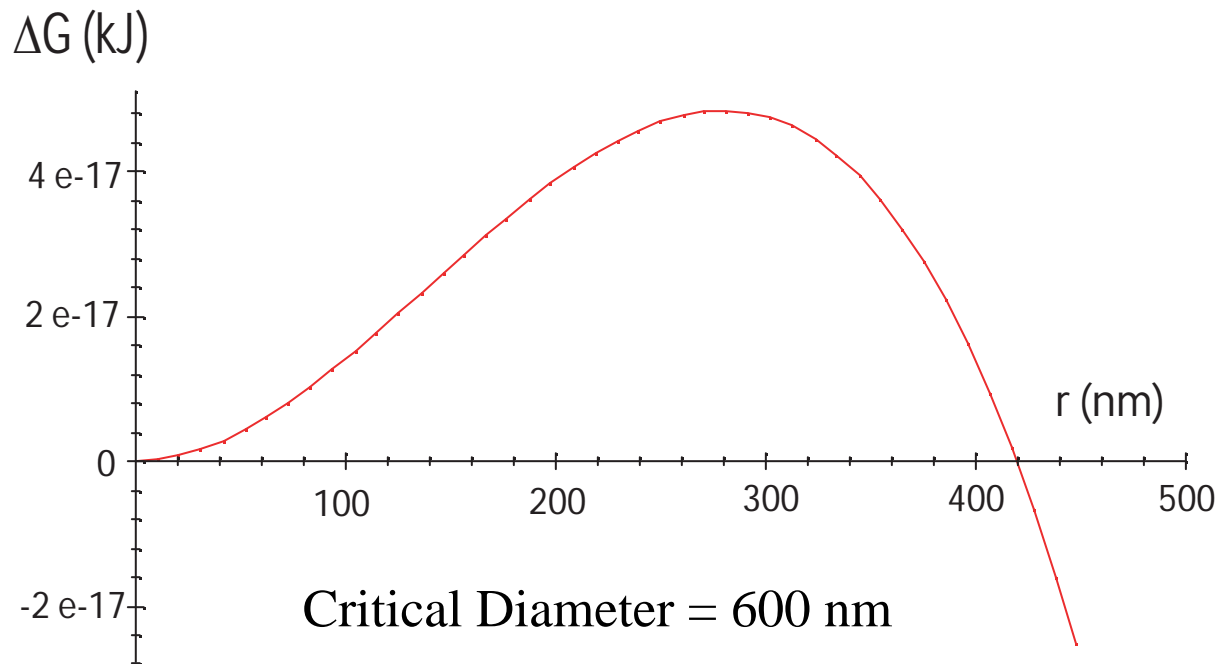
Size distribution transient dynamics

Initializing the Model: Nucleation & Polymorph Selection

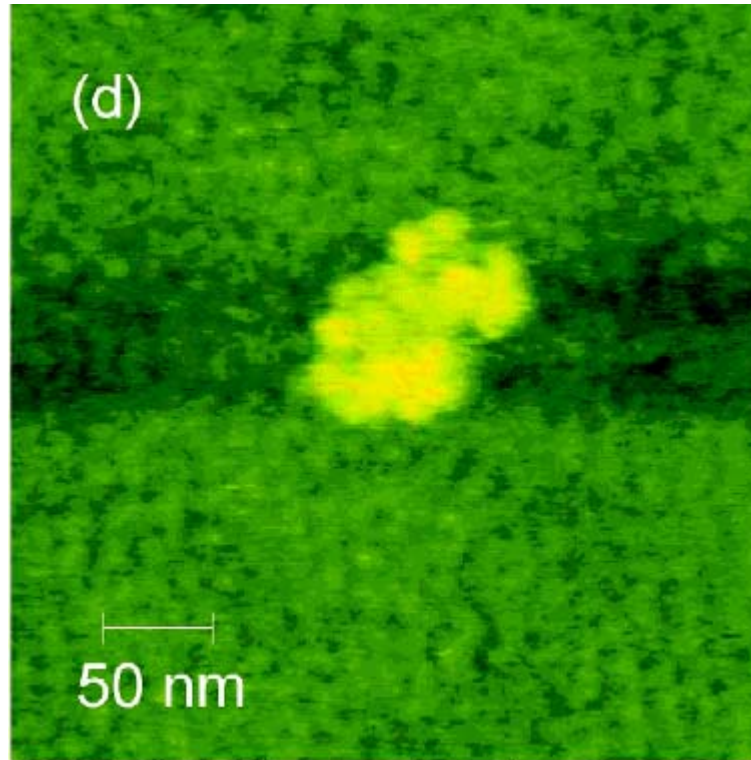
Gibbs-Thomson Theory

$$\Delta G = -\frac{4}{3} \pi r^3 \frac{\Delta\mu_{solute}}{v_{solute}} + 4\pi r^2 \gamma \quad (1)$$

3D Nucleation of α -glycine



Recent Experiments



A flat near-critical sized cluster consisting of approx. 20 apoferritin molecules (Yau and Vekilov, *Nature* 2000).

Observations

- Critical nucleus sizes are in the range of 10's of nm, e.g., 40 nm for apoferritin
- Molecular arrangement within the nucleus is similar to that in the bulk crystal
- “Contrary to the general belief, the observed nuclei are not compact molecular clusters, but planar arrays of several rods of 4-7 molecules set in 1 or 2 monomolecular layers. Similar unexpected nuclei structures might be common, especially for anisotropic molecules. Hence, the ***nucleus structure should be considered as a variable*** by advanced theoretical treatments.” (Yau & Vekilov)

Additional Important Issues

- Scale-up
 - CFD – spatially non-uniform conditions
- Optimization & control
 - Compartmental models (Bermingham et al., Delft)
 - Exchange rates between cells?
- Process synthesis
 - Douglas, Ng, et al.
 - Crystallization paths are useful
 - Process alternatives selected on the basis of economics
- Material properties (product design) not yet considered (other than size)

Opportunities

- Polymorphic phase transformations
- Additives & impurities
- Nucleation and polymorph selection
- Solvents/co-solvents/anti-solvents
- Complex bond chains, H-bonds, growth units
- Racemic mixtures, enantiomeric resolution
- From single particles to suspensions
- Process models & process systems engineering
- Process intensification by *division* of tasks
- Experiments
 - on surfaces for model validation
 - for polymorph selection
 - growth units & precursors

Molecules to Products

