Crystal Engineering for Process and Product Design

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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 > $500 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/PPG

Conceptual Design

You can’t understand the process if you don’t understand the chemistry

Role of Engineer in Industry

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

Why Crystal Shape?

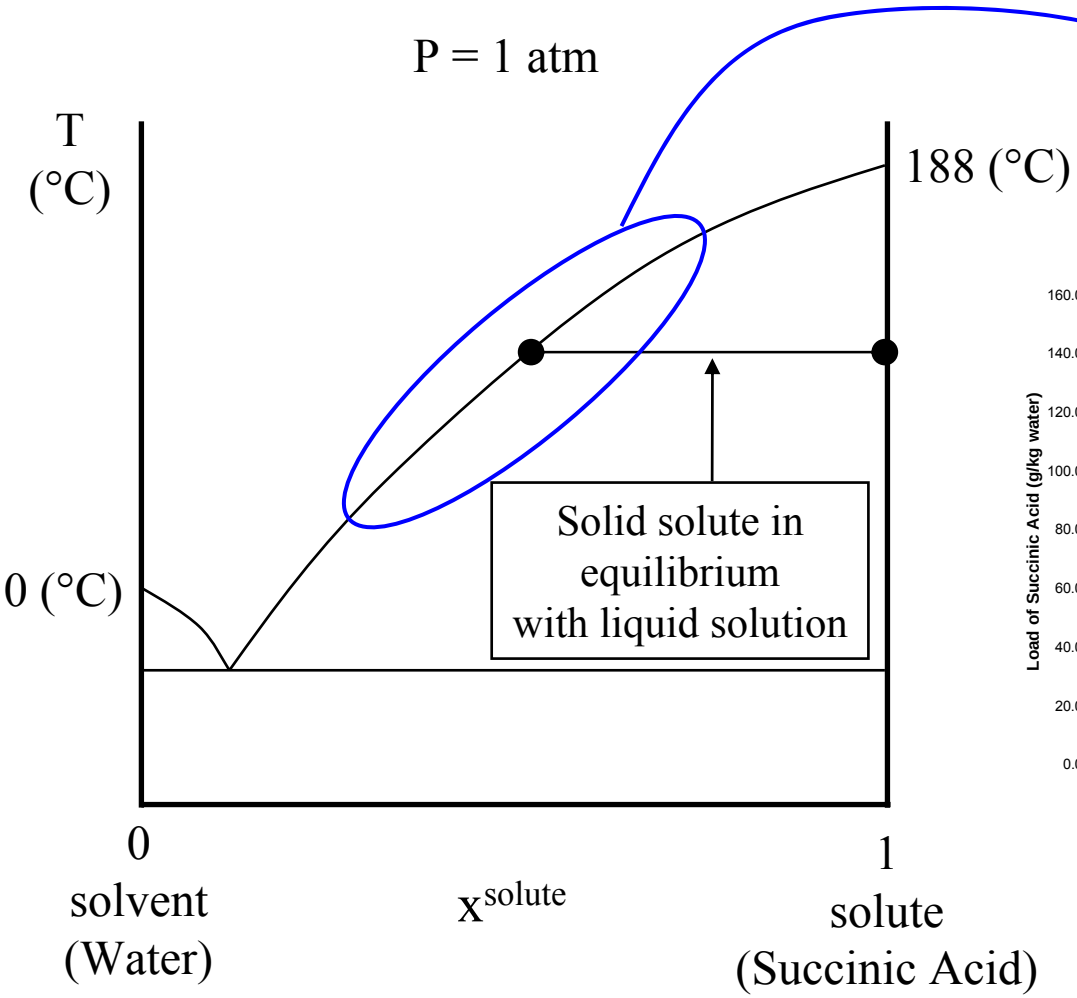
- Crystal shape impacts:
  - Downstream processing – filtering, washing, drying, etc (avoid needles and flakes)
  - End use properties – bulk density, mechanical strength, flowability, dispersibility and stability of crystals in suspension, dissolution rate, bioavailability, catalytic properties
  - Nano switches, …..

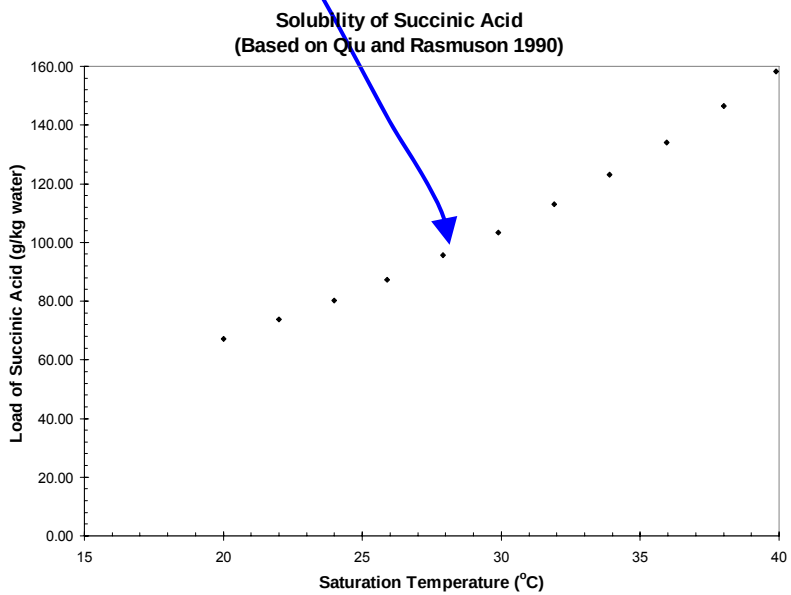
- The ability to predict and manipulate crystal shape enables optimized product & process design

Crystallization – Multiple Tasks

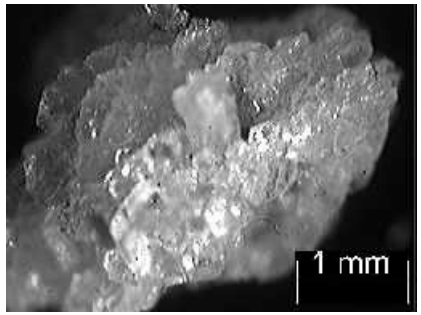
- **Separation and purification task**
  - crude separation followed by recrystallization
  - crystal purity
  - enantiomer
  - hydrate, solvate, co-crystal
- **Particle formation task**
  - mean particle size and particle size distribution
  - particle shape
- **Structure formation task**
  - internal crystal structure or polymorph

Solid – Liquid Equilibrium





Low Supersaturation: Succinic Acid

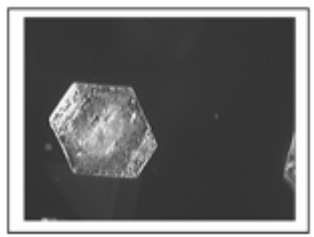


C
(g/L solution)

~5 g/L solution
(Qin & Rasmusm)

Metastable

2.2 (°C)
Hofmann & Doherty



24 (°C)

30 (°C)

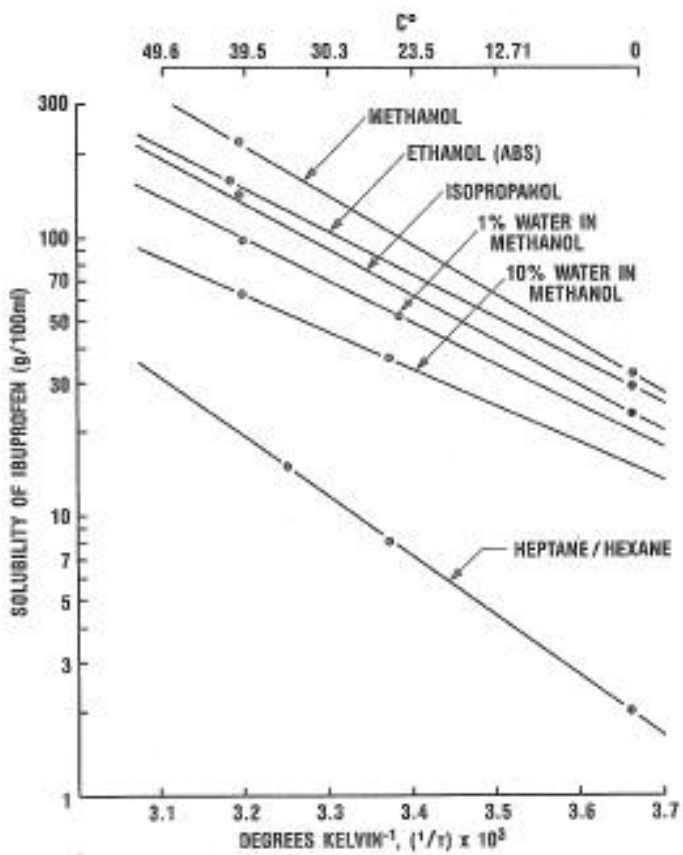
T
(°C)

Slow growth for higher purity and well-formed morphology

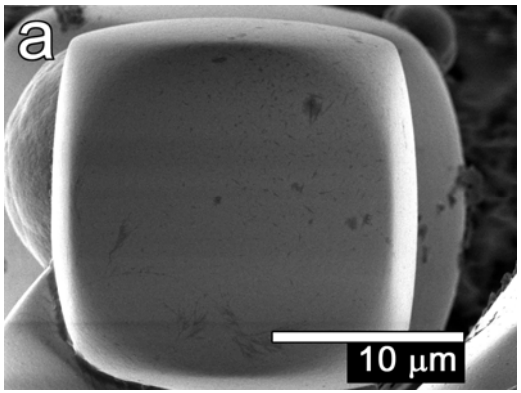
Solubility of Ibuprofen in Various Solvents

FIGURE 1

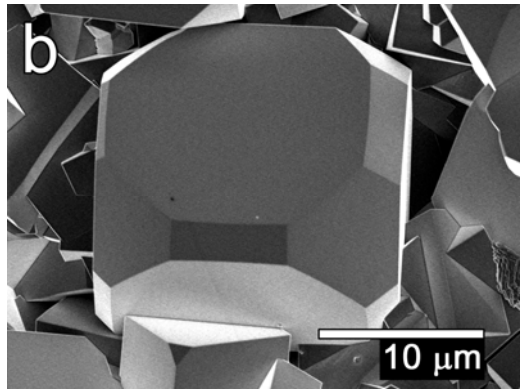
SOLUBILITY OF IBUPROFEN IN VARIOUS SOLVENTS



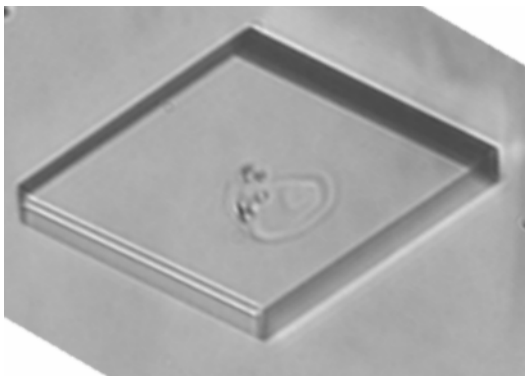
Crystals Form in Various Shapes



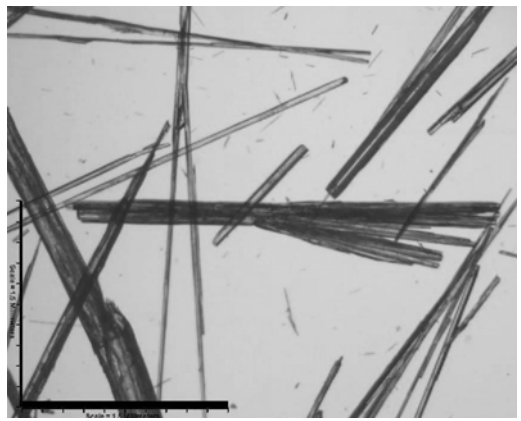
Zeolite



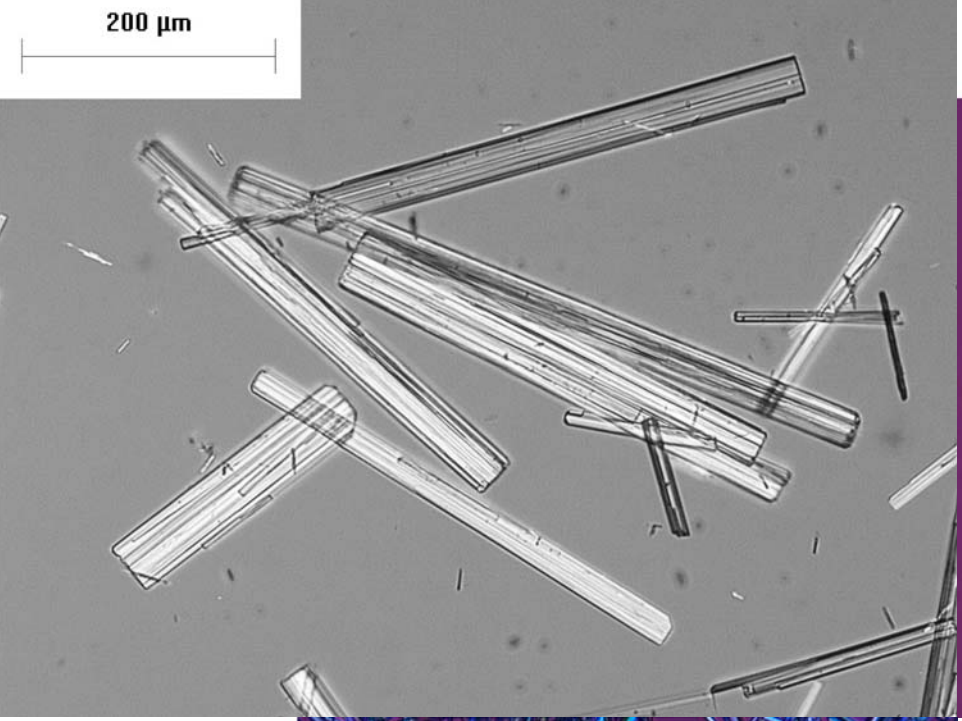
Zeolite

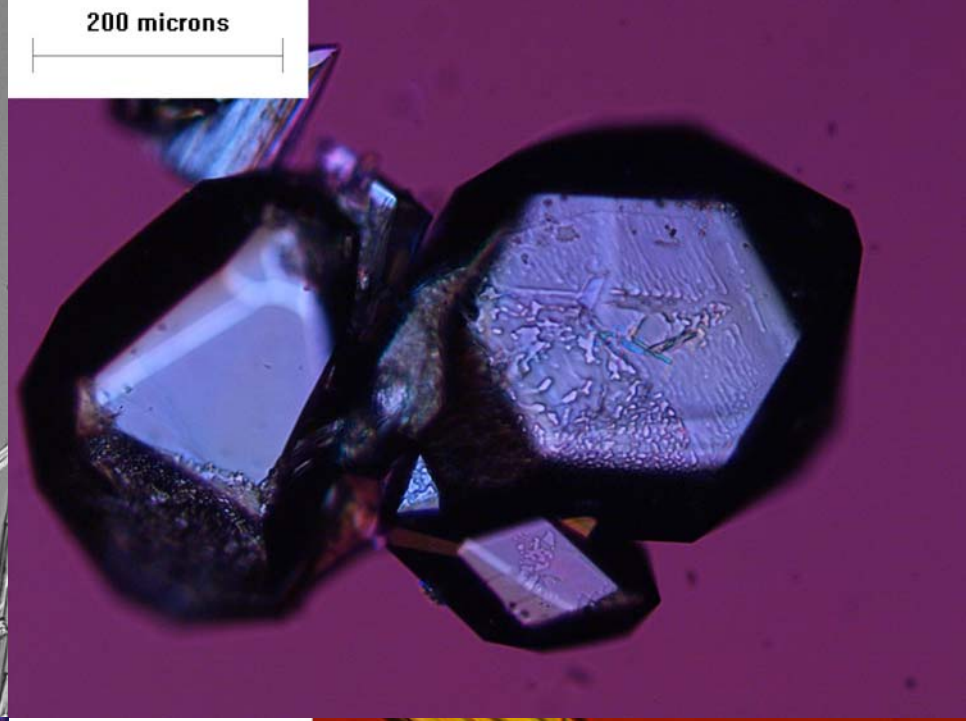


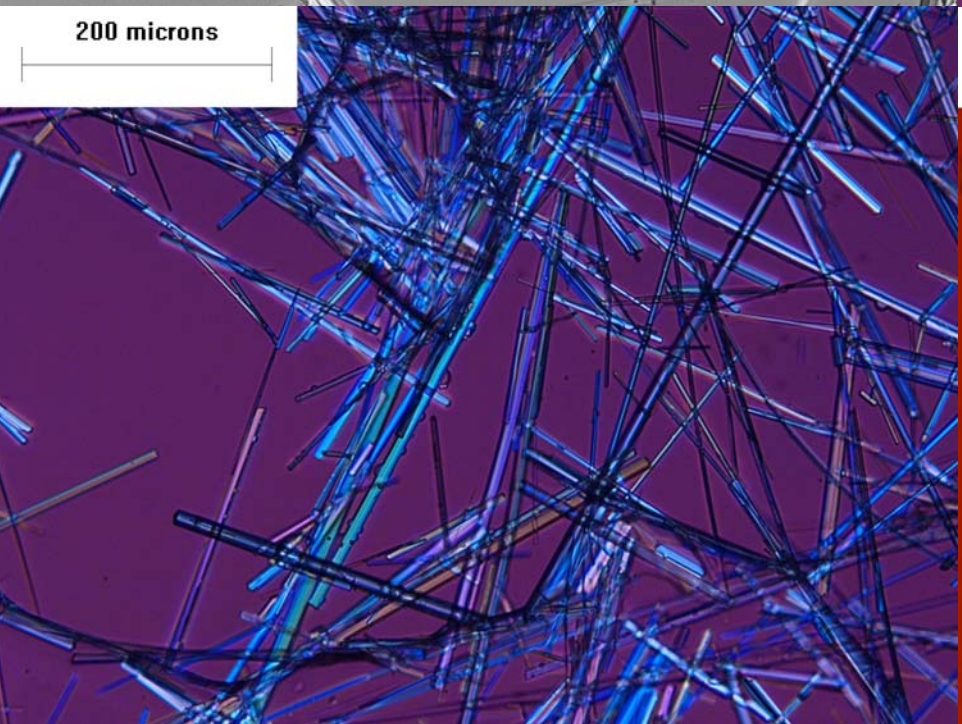
Succinic acid

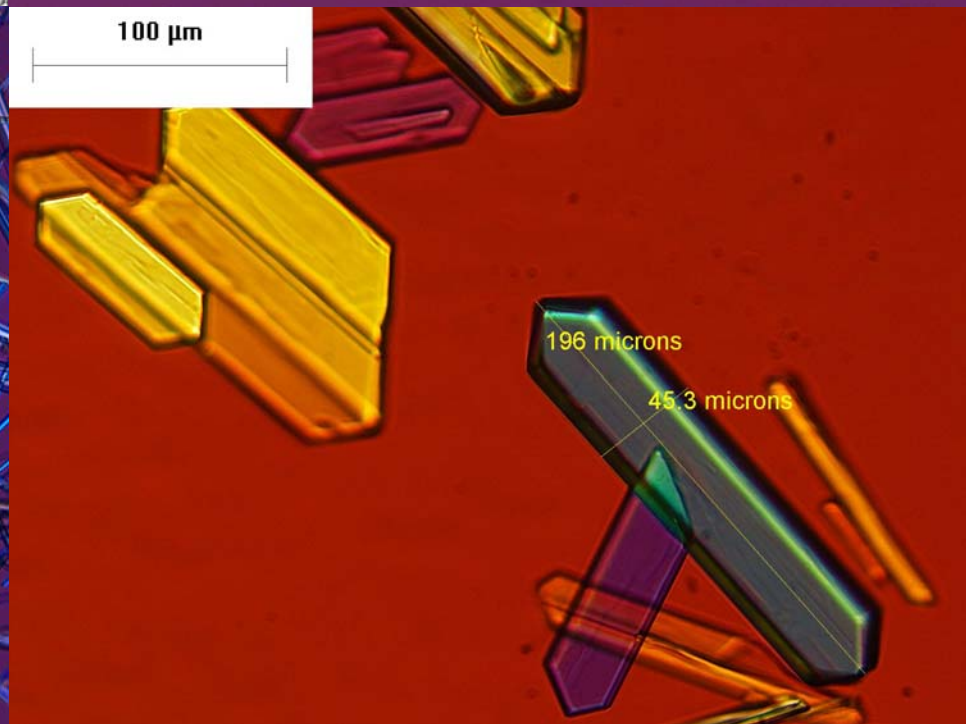


PABA

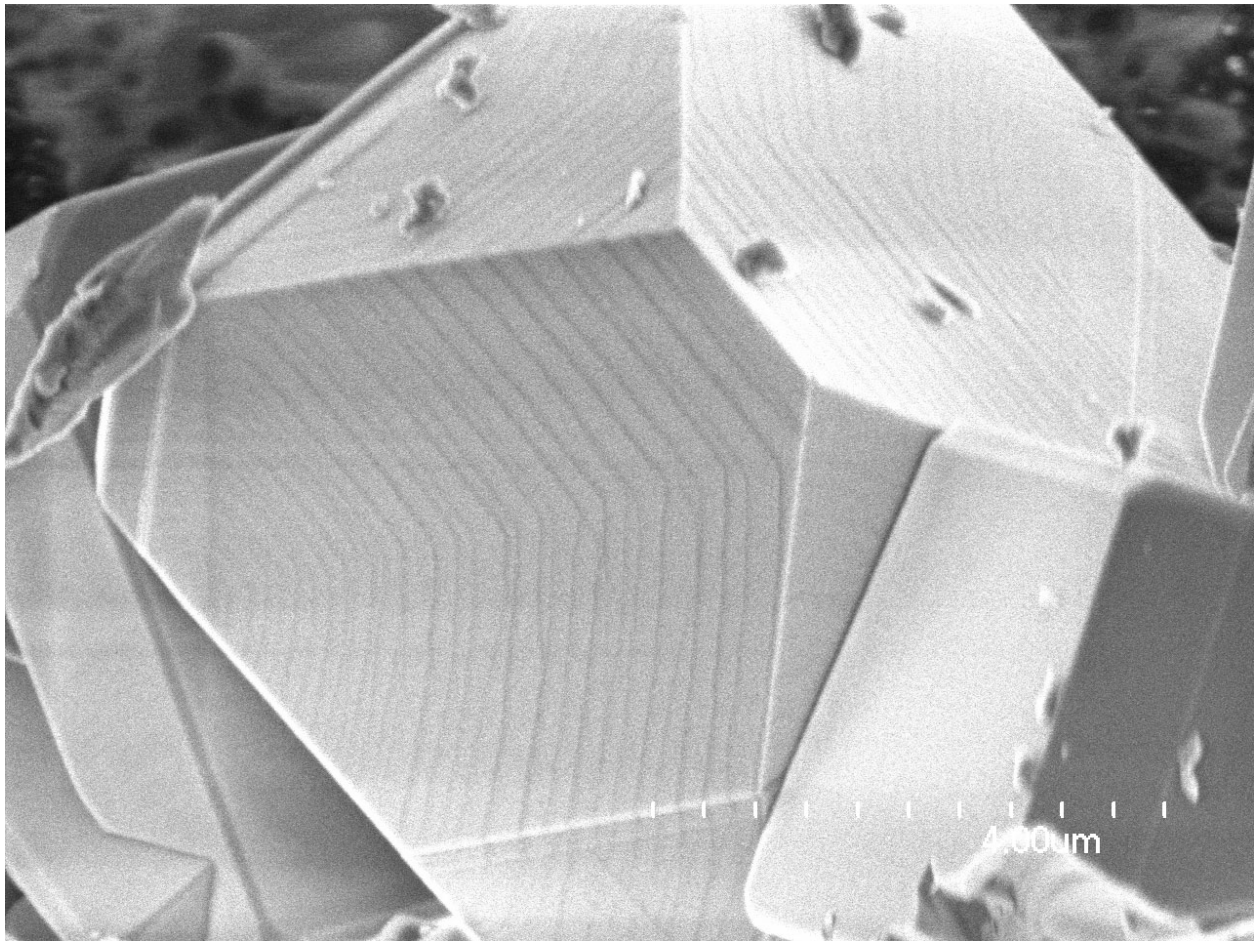

200 µm


200 microns


200 microns


100 µm
196 microns
45.3 microns

Faujasite FCC Catalyst

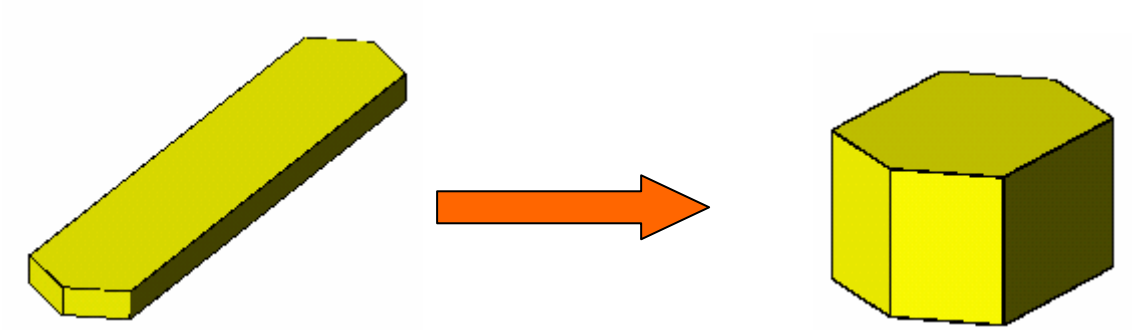


Thanks to Michael Lovette – Albert Sacco group

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 solvents with $\delta H>8$, 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

Klug & Van Mil Patent: DuPont Adipic Acid Shape Modification

US005296639A

United States Patent [19]

Klug et al.

[11] **Patent Number: 5,296,639**

[45] **Date of Patent: Mar. 22, 1994**

[54] **ADIPIC ACID PURIFICATION**

[75] Inventors: **Diana L. Klug**, Wilmington, Del.; **Johannus H. Van Mil**, Ramat Gan, Israel

[73] Assignee: **E. I. Du Pont de Nemours and Company**, Wilmington, Del.

[21] Appl. No.: **993,276**

[22] Filed: **Dec. 18, 1992**

[51] **Int. Cl.**[5] **C07C 51/42**

[52] **U.S. Cl.** **562/593**; 562/530; 203/15; 203/48

[58] **Field of Search** 562/593, 530; 203/15, 203/48

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5,034,105	7/1991	Berglund et al.	562/593 X
5,104,492	4/1992	King et al.	562/593 X

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1216844	3/1991	United Kingdom .

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Addadi et al., Angew. Chem. Int. Ed. Engl., vol. 24, pp. 466–485 (1985).

Shimon et al., Nouveau J. de Chemie, vol. 10, No. 12, pp. 723–737 (1986).

Addadi et al., Top. Stereochem., 16, 1 (1986).

Primary Examiner—Arthur C. Prescott

[57] **ABSTRACT**

A process for purification of adipic acid during crystallization by modifying the crystal morphology to decrease incorporation of impurities through the introduction of an effective amount of an additive to the crystallizing solution.

7 Claims, 11 Drawing Sheets

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 CSD 5-7 microns
- Formulated drugs – CSD 30-70 microns
- Inhalable drugs – CSD 1-5 microns (<10 microns)
- Injectable drugs – CSD 200-500 nm

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

Crystal Shape Evolution

- Crystals do not grow into their equilibrium shapes
- What Gibbs thought
- Crystals spontaneously form facets
- The evolution model for faceted crystals
- Steady-state shapes

Equilibrium Crystal Growth & Shape

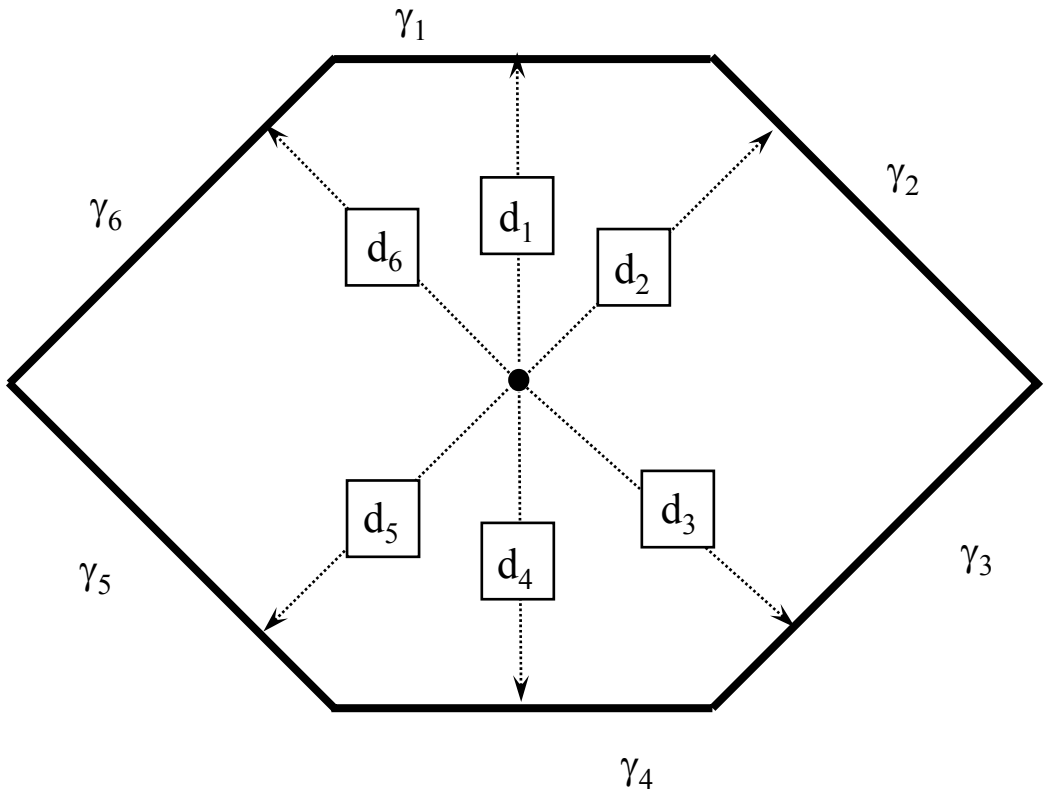
- Idealized shape at infinitesimal supersaturation and looooooooooong times
- Gibbs equilibrium condition for shape of facetted crystals (1877-78)

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

- 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



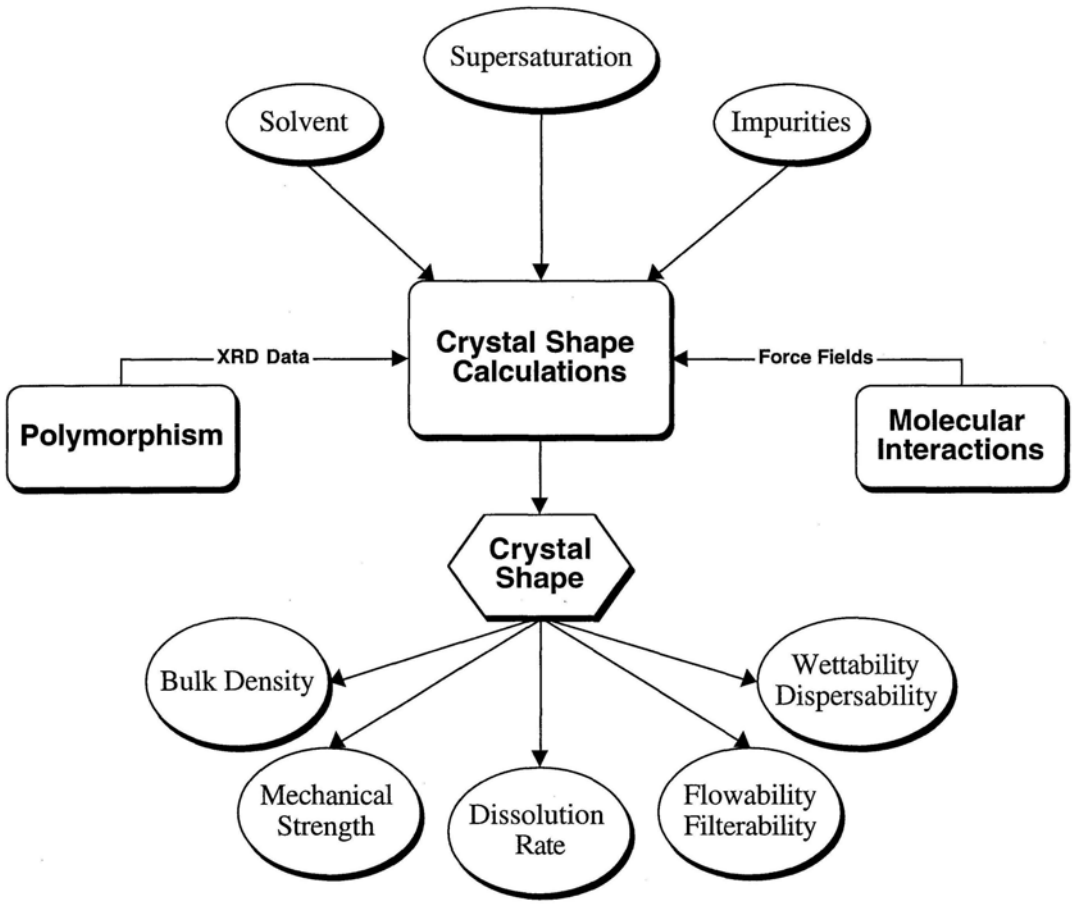
$$\frac{\gamma_1}{d_1} = \frac{\gamma_2}{d_2} = \cdots = \frac{\gamma_i}{d_i}$$

What Gibbs Thought

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 ($\sum_i \gamma_i A_i$) 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".***

Methodology for Calculating Shape



Perspectives

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

Faceted Growth

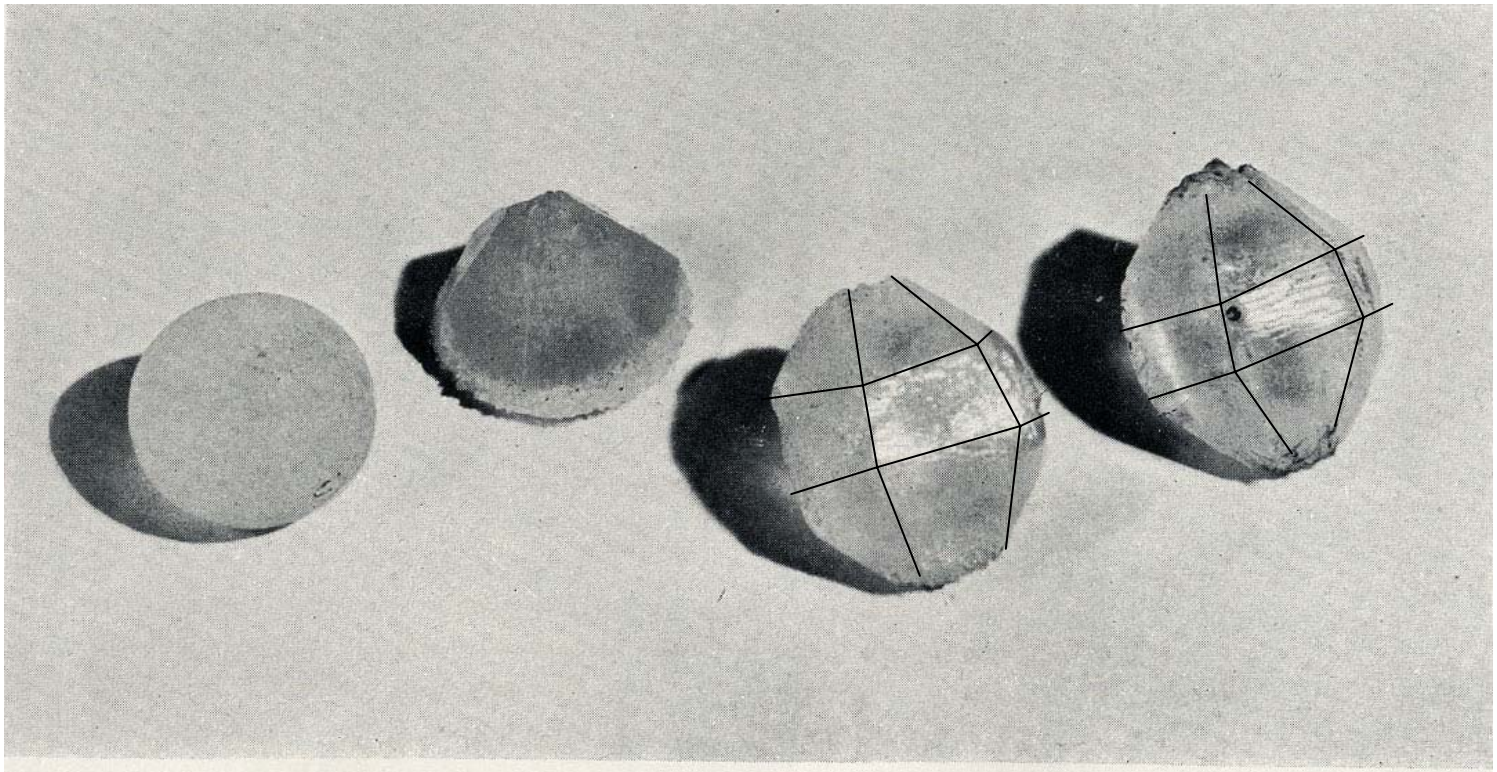
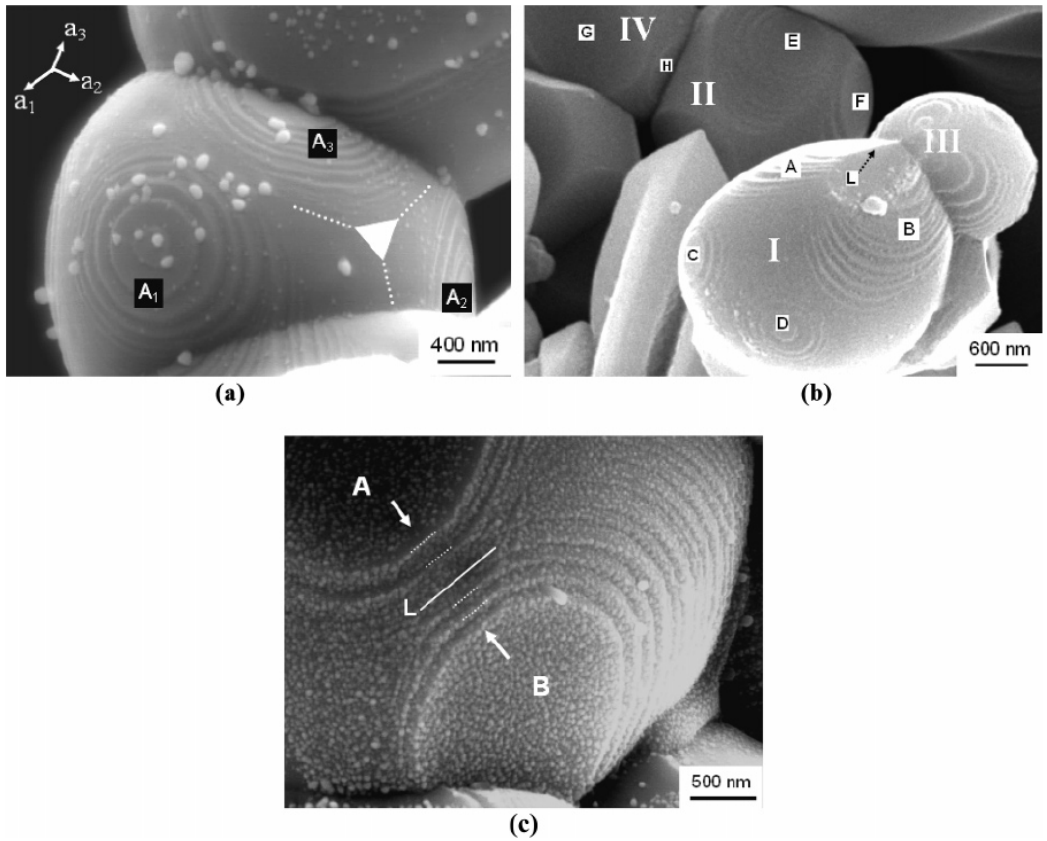


FIG. 2.—Growth of quartz on spherical seeds.

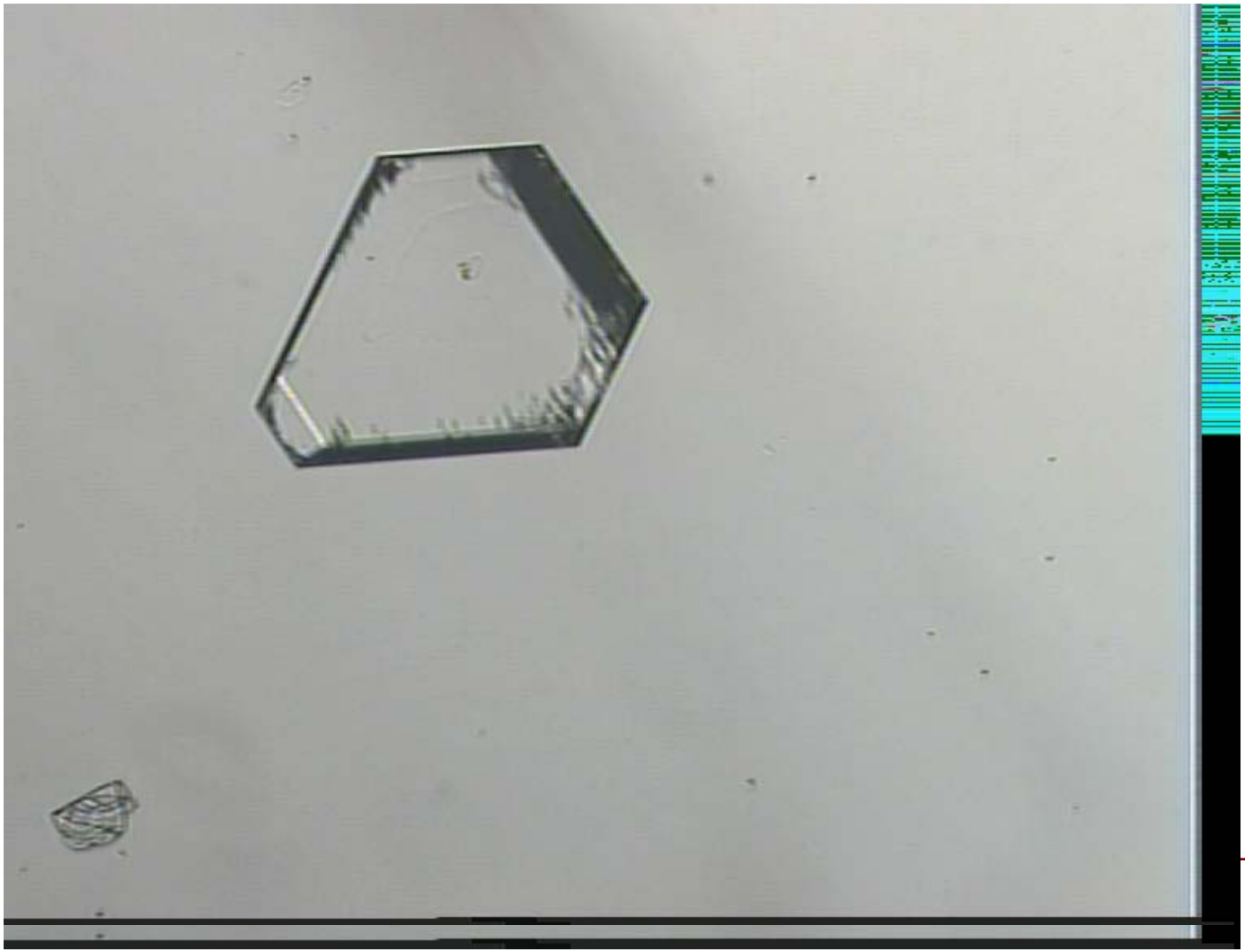
Thomas, L. A., N. Wooster, and W.A. Wooster,
Crystal Growth, *Discussions of the Faraday Society*, 343 (1949)

Spontaneous Faceting of TiN



SEM micrographs showing faceting process of spherical TiN seeds
Liu et al., *Crystal Growth & Design, 6*, 2404 (2006)

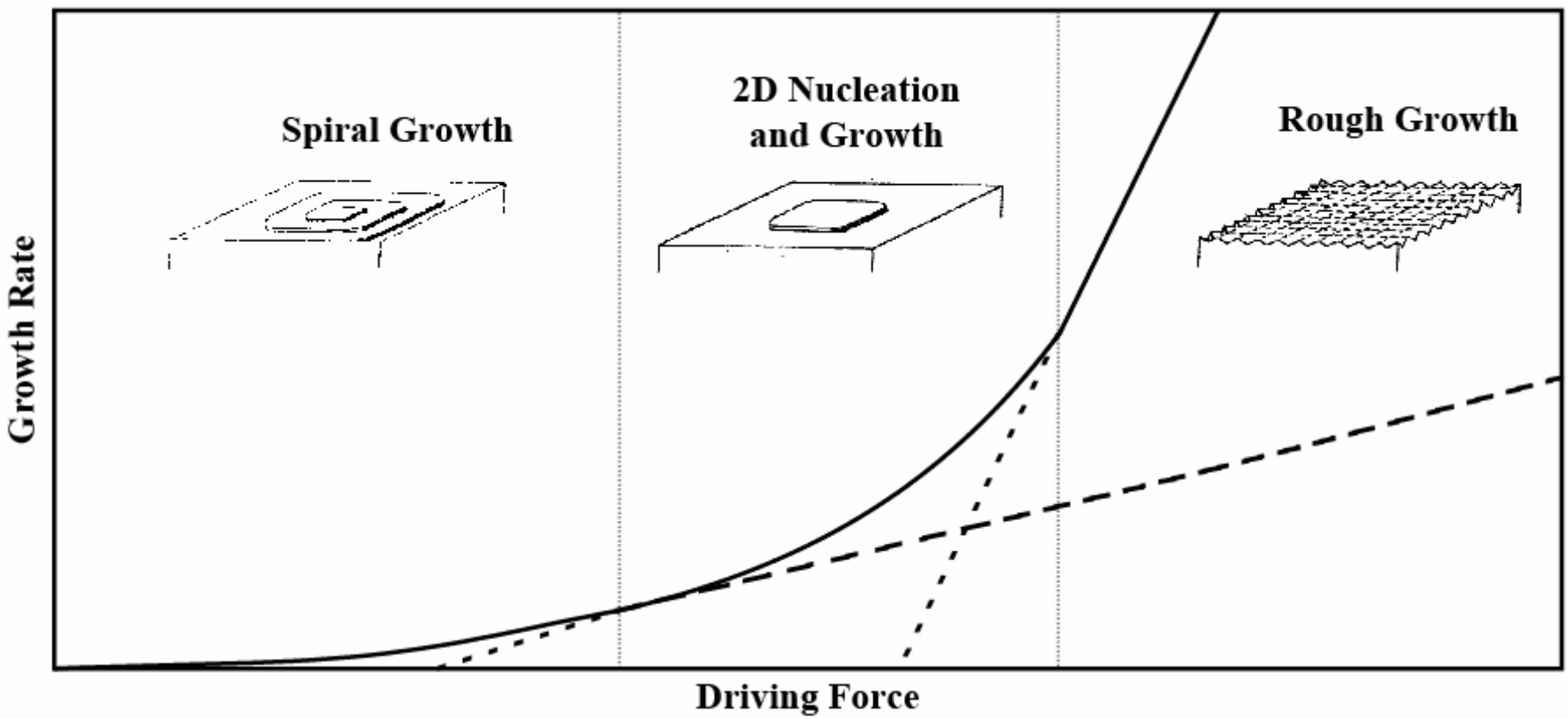
Faceted Growth of Succinic Acid



100 µm

1 picture =
1 min. exp.

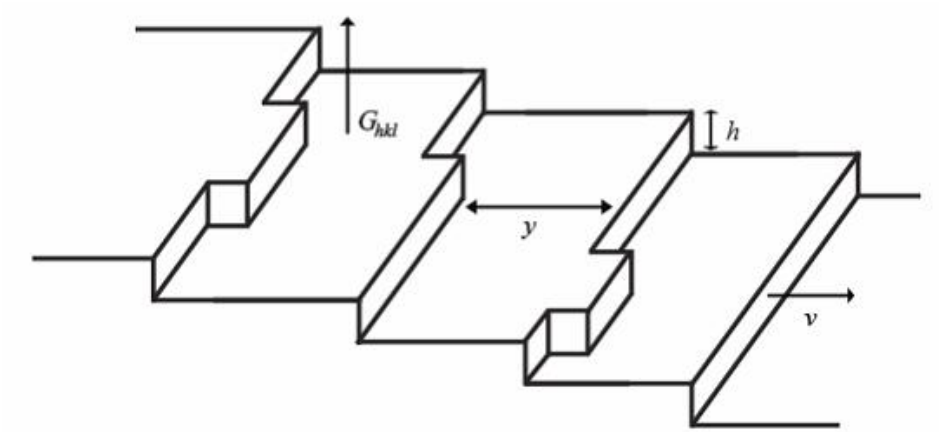
Growth Mechanisms



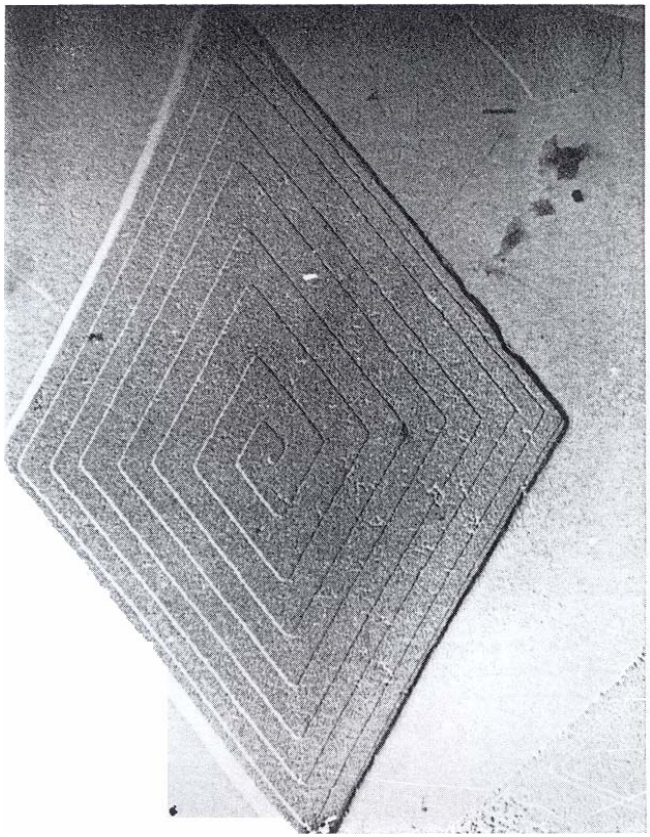
Growth modes for a crystal face as a function of supersaturation. The solid line is the growth rate. The short dashed lines are the growth rates if 2D nucleation or rough growth continued to be dominant below their applicable driving force ranges. The long dashed line is the rate if spiral growth was the persistent mechanism above its applicable range of driving force.

Crystal Shape and Growth Models

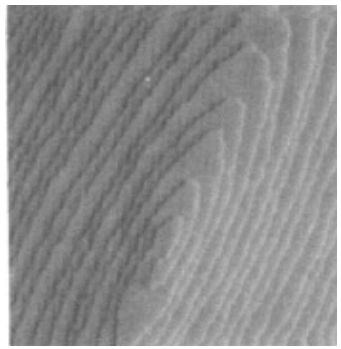
- Crystals grow by the flow of steps across the faces
- Sources of steps
  - 2-D nuclei - birth and spread model
  - spirals growing from screw dislocations
- Sources of edges – strong bond chains (PBC's)
- Sources of docking points for solute incorporation – kinks on edges (missing molecules along bond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

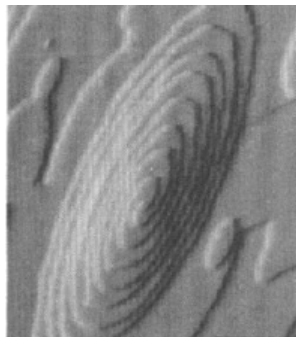


Spiral Growth of Organic Crystals

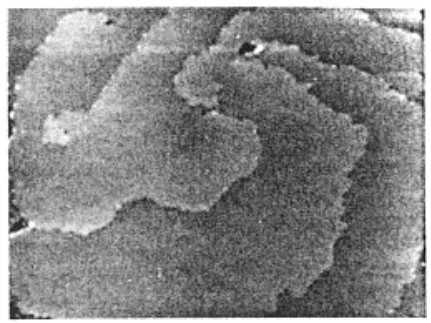


First electron micrographs of spirals: long chain paraffin n-hexatriacontane, $C_{36}H_{74}$ x 16000 (Dawson and Vand, *Proc. Roy. Soc*., 1951)





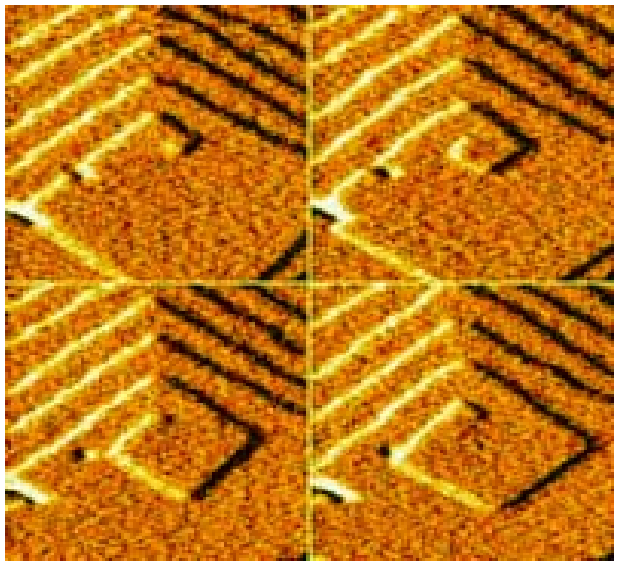
AFM images of spiral growth on hen egg white lysozyme surface (Durban, Carlson and Saros, *J. Phys. D: Appl. Phys*., 1993)



AFM image of spiral growth on a 50μm canavalin protein surface (Land et al., *Phys. Rev. Lett*., 1996)

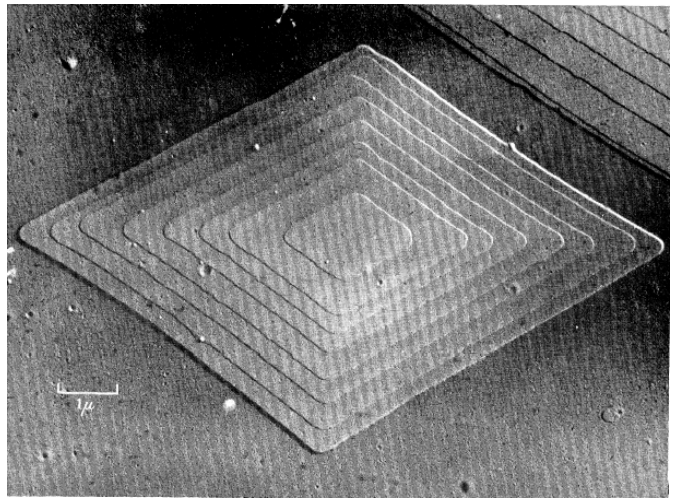
Step Formation

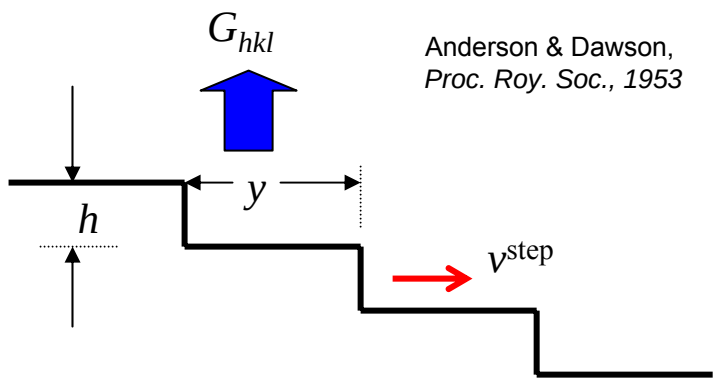
Spirals from a Screw Dislocation (BCF) on Calcite



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

2-D Nucleation / Birth & Spread on a Parrafin Crystal



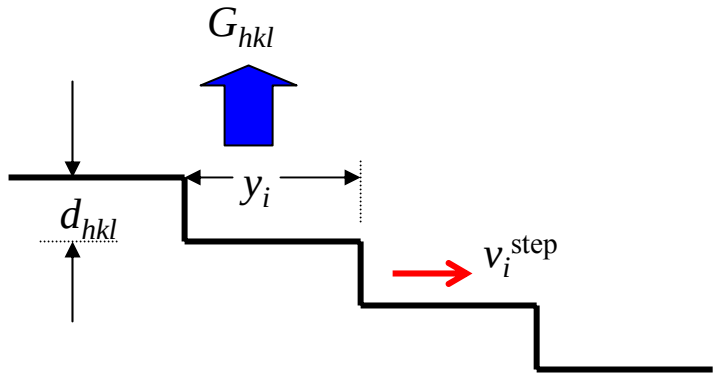


Anderson & Dawson, *Proc. Roy. Soc., 1953*

BCF Growth Model

Rate of growth normal to face *hkl*

$$G_{hkl} = (v_i \; d / y_i)_{hkl}$$



i = edge i on face *hkl*

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

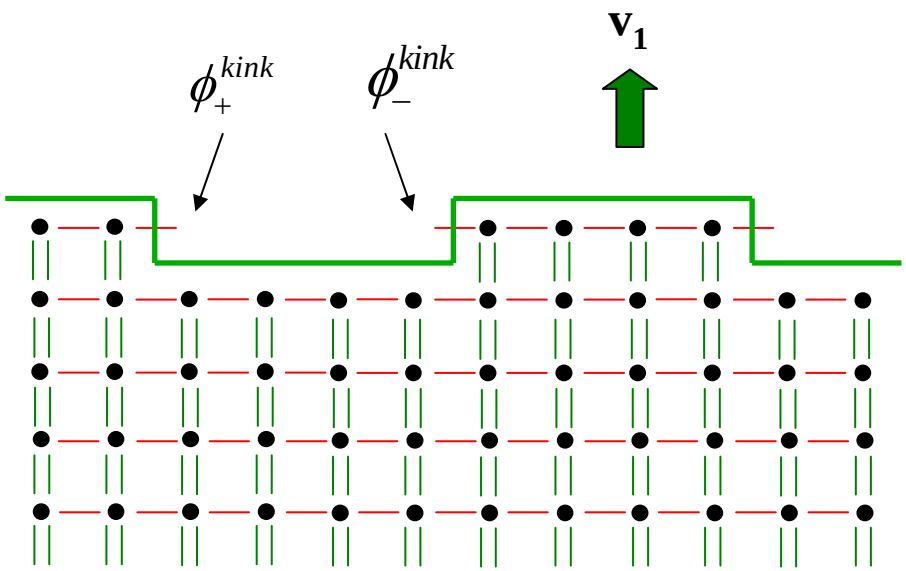
$$(v_i)_{hkl} \propto a_p [1 + 0.5 \exp(\phi_{hkl}^{kink,\,i} / RT)]^{-1}$$

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

Distribution of Kinks

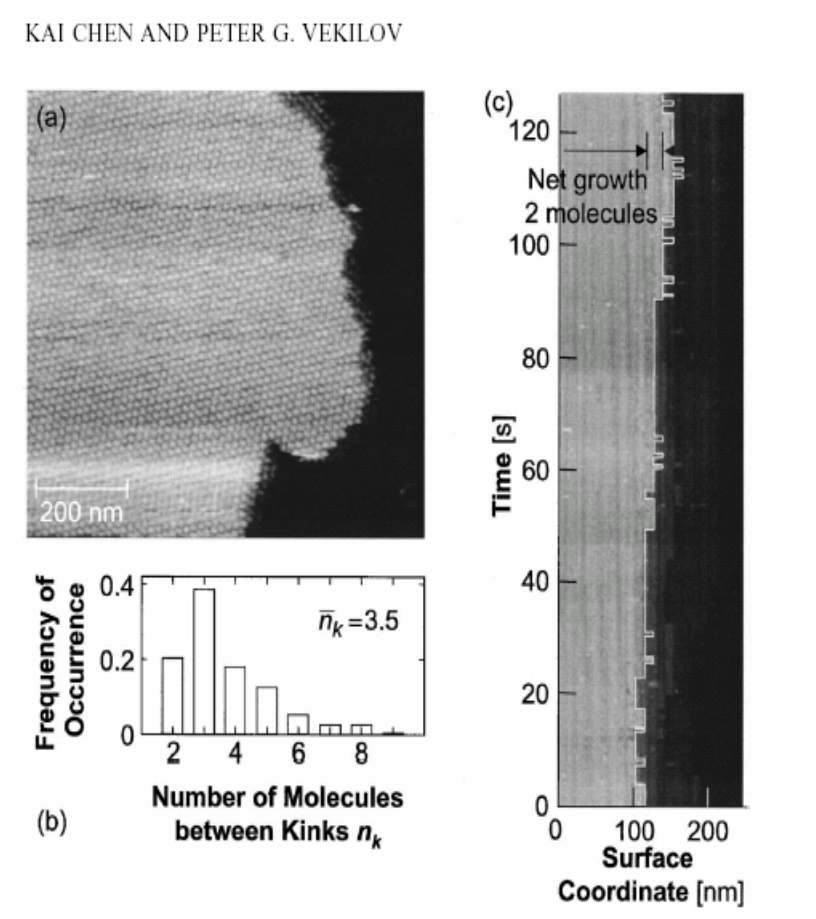
$$p_+ = \frac{e^{-\phi_+^{kink}/kT}}{Q} \qquad p_- = \frac{e^{-\phi_-^{kink}/kT}}{Q} \qquad p_{overall} = p_+ + p_-$$

$$Q = e^{-0/kT} + e^{-\phi_+^{kink}/kT} + e^{-\phi_-^{kink}/kT}$$



- Three microstates
- Boltzmann factors
- Partition function (Q)
- What is the probability of finding a kink at a site on the bond chain?

Kinks on Steps of Ferritin Crystal



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

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

Spiral Growth Model

$$G_{hkl} = \left(\frac{v_\infty h}{y} \right)_{hkl} = \left(\frac{h}{\tau} \right)_{hkl}$$

$$\tau = \sum_{i=1}^{N} \frac{l_{c,i-1}}{v_i} \sin(\alpha_{i,i-1})$$

$$v_{step} = \begin{cases} 0 \; if \; l_{step} < l_c \\ v_\infty \; if \; l_{step} \geq l_c \end{cases}$$

- Each spiral side on each face can have different energetics. (Different velocities and critical lengths)

- Unknown: l_c, v, N, h
- Characteristic Spiral Time – τ
  - Time required for the formation of the first spiral turn.
  - The time that occurs between consecutive step passes by the same location.
- N = number of spiral relevant sides

Critical Length: Gibbs-Thomson

$$\Delta G = -N\Delta\mu_{solute} + A\gamma$$

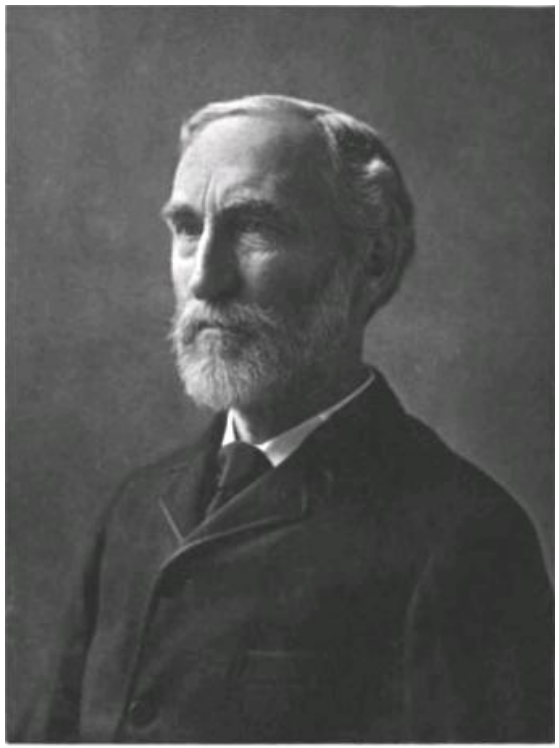
moles of solute transferred to nucleus

$$\Delta\mu_{solute} = \mu_{solute}^{solution} - \mu_{solute}^{nucleus} > 0$$

First Term: Free energy decrease due to formation of the bulk solid phase

Second Term: Free energy increase due to formation of surface

One Gibbs But Which Thomson?

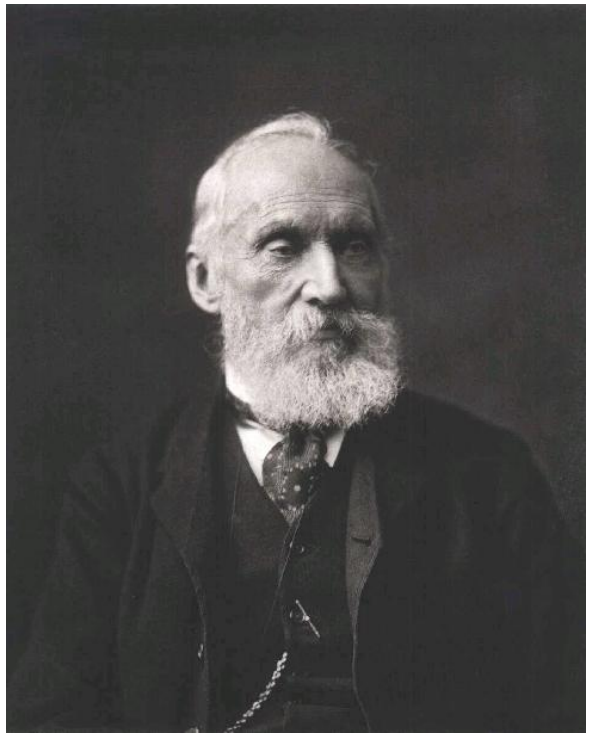


J. Willard Gibbs

1839-1903

$$W = \sigma s - (p' - p'')v', \qquad 2\sigma = (p' - p'')r,$$

1877-78



William Thomson (Lord Kelvin)
1824-1907

Mid 1870's

J. J. Thomson
1856-1940

$$\delta p = \frac{2\rho}{\sigma - \rho}\frac{T}{a}\cdots\cdots$$

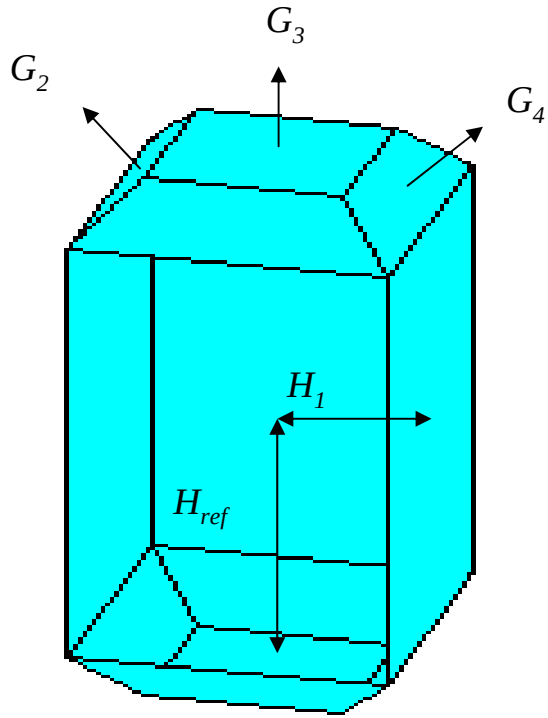
1888

Shape Evolution Models

- **Curved surfaces – Hamilton-Jacobi equation**
  - Most general case (PDE's)
  - Complete mathematical treatment by Lighthill & Whitham, "On Kinematic Waves I & 2," *Proc. Roy. Soc., 229*, 281 & 317 (1955)
  - Sir Charles Frank, Alexander Chernov, circa 1960

- **Faceted surfaces – new model (ODE's)**
  - Zhang, Sizemore and Doherty, "Shape Evolution of 3-Dimensional Faceted Crystals," *AIChEJ, 52*, 1906 (2006)
  - Snyder and Doherty, "Faceted Crystal Shape Evolution During Dissolution or Growth," *AIChEJ, 53*, 1377 (2007)

Shape Evolution Model



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

$$x_i = \frac{H_i}{H_{ref}} \qquad R_i = \frac{G_i}{G_{ref}}$$

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

$G_i > 0$ Growth

$G_i < 0$ Dissolution

Shape Evolution Model

Growth:

$$\frac{dx_i}{d\xi} = R_i^G - x_i, \qquad d\xi = \frac{G_{ref}}{H_{ref}} dt$$

eigenvalues = -1
Stable Steady State
(Chernov Condition)

Dissolution:

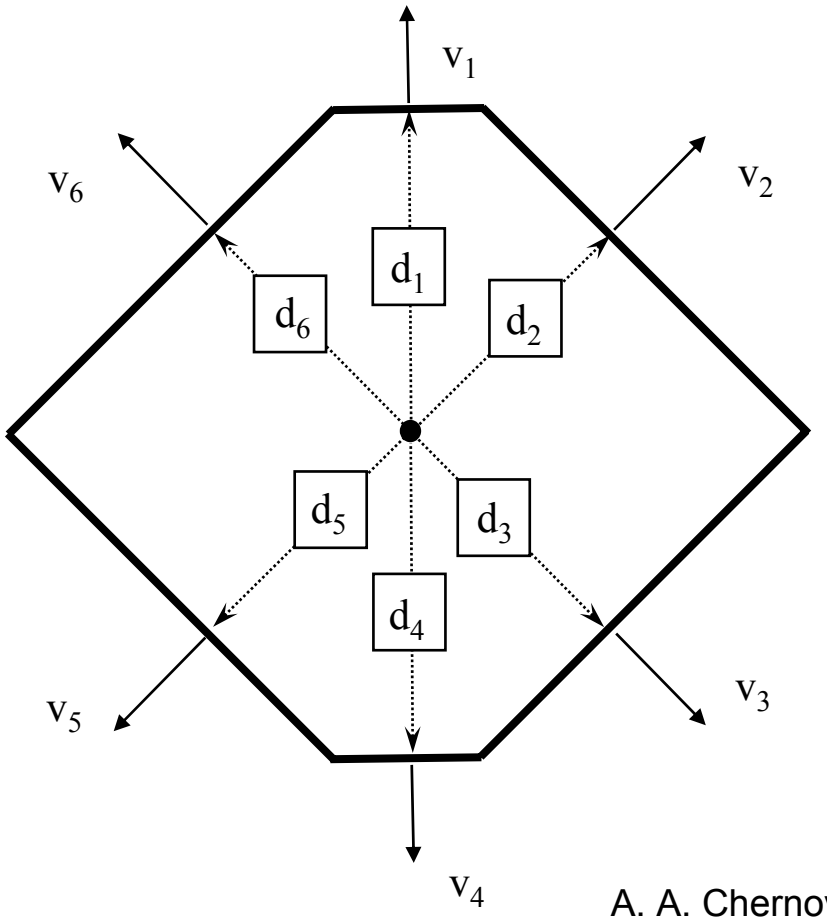
$$\frac{dx_i}{d\xi} = x_i - R_i^D, \qquad d\xi = -\frac{G_{ref}}{H_{ref}} dt$$

eigenvalues = +1
Unstable Steady State
(Unrealizable)

$$R_i - x_i = 0$$

Unique Steady State
(different for growth & dissolution)

Steady-State Growth Shapes



Real growth shapes at low supersaturation

Frank-Chernov Condition

$$\frac{v_1}{d_1} = \frac{v_2}{d_2} = \cdots = \frac{v_i}{d_i}$$

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

General Principle

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

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

Relative Growth & Dissolution Rates

- Experime
  - e.g., th cetamol crystal
    Shekun ic Studies of the Growth a ophen). I. Growth Kinetics,
- Semi-Me
  - BFDH
  - AE mo
- Mechanis
  - Spiral g

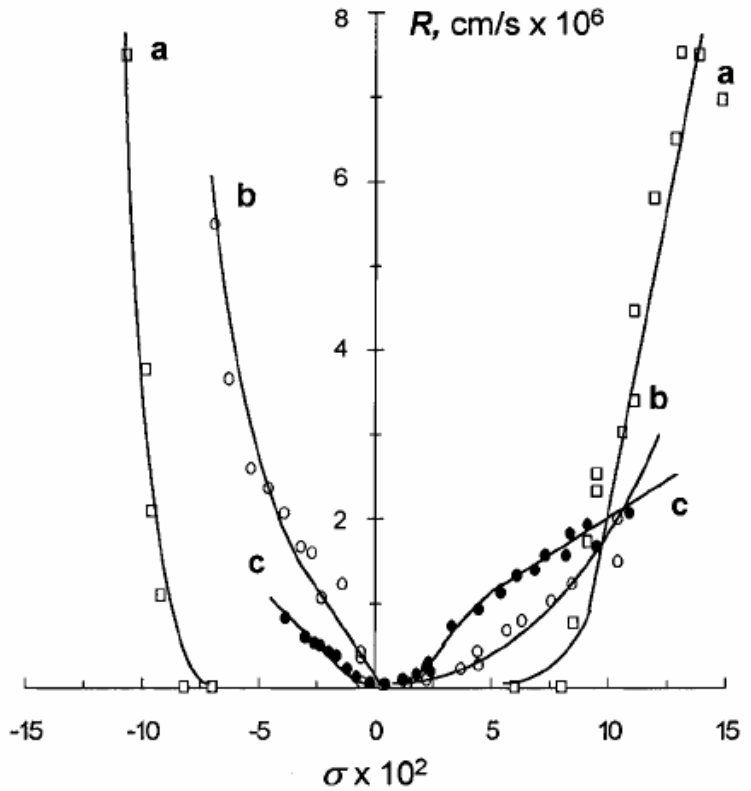


Figure 6. Dependence of normal growth rate R on supersaturation σ for the following faces: (a, □) {110}; (b, ○) {20$\bar{1}$}; (c, ●) {001}.

3-Dimensional Crystal Shape Evolution

- Shape Evolution Scenarios
  - Continuous evolution: change in relative sizes of faces → *ODE*
  - Discrete events: face, edges and vertices appearance/disappearance → *Major Task*
- Face Appearance/Disappearance
  - Always associated with edge and vertex changes
    - On a simple vertex
    - On a compound vertex
  - Euler's rule must be obeyed $F + V - E = 2$

Identify List of Candidate Planes

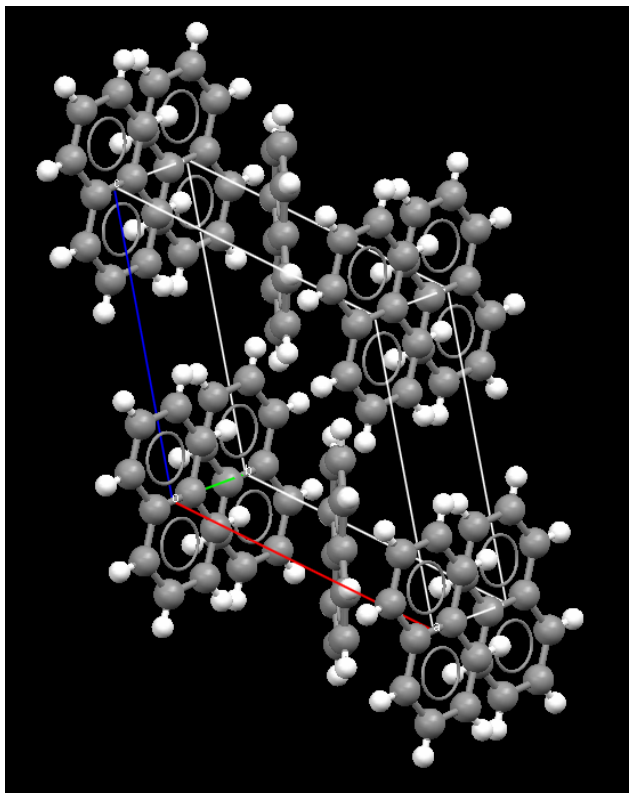
- Growth shape is dominated by SLOW moving faces
  - Include all low index planes in list
- Dissolution shape is dominated by FAST moving faces
  - Higher index planes move faster – how to identify the correct planes and cut off the list?
- Selecting the candidate faces is different for growth and dissolution

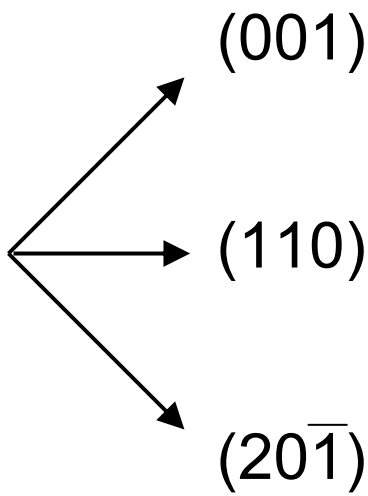
The Model

- Crystallography defines the set of candidate faces
- Relative normal growth velocities known from first principles
- Known initial shape (links to nucleation)

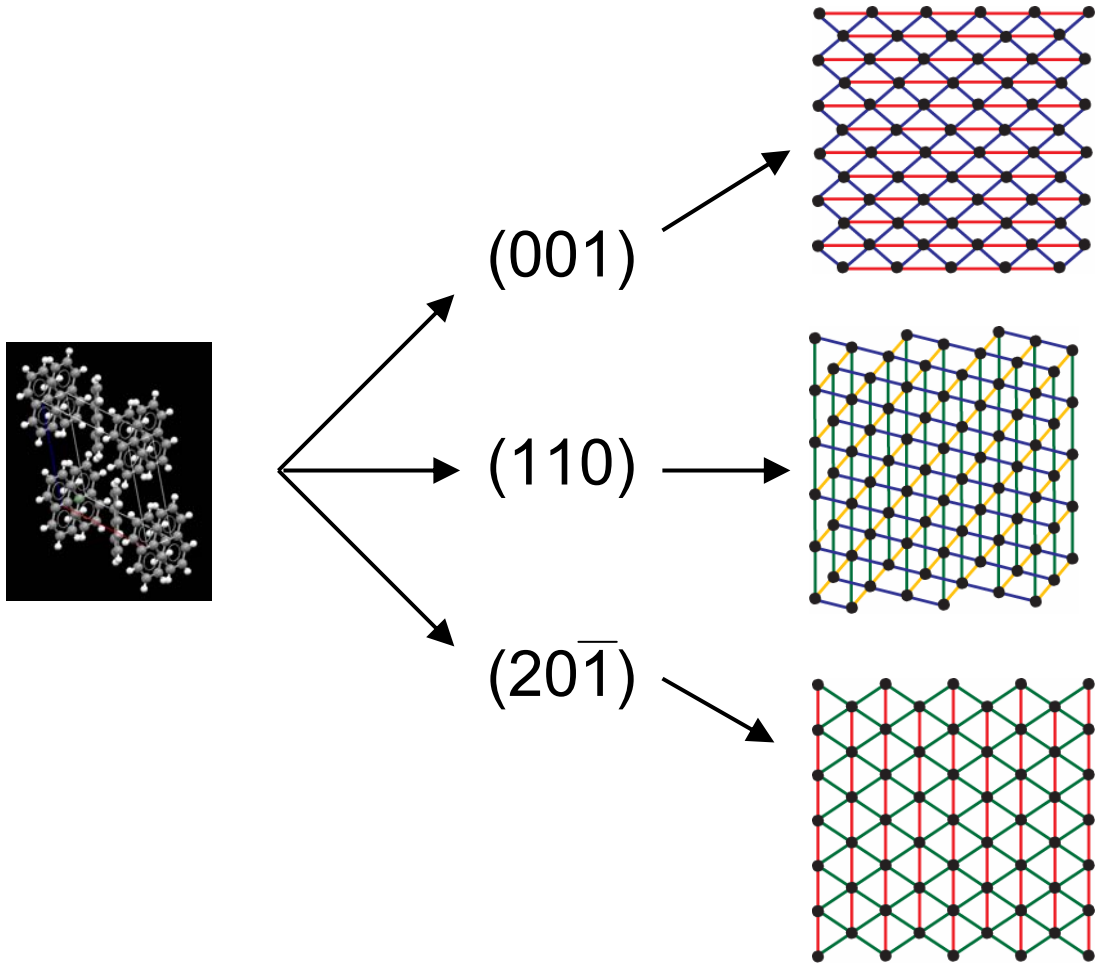
Naphthalene

Calculate molecular interactions and slow growing planes

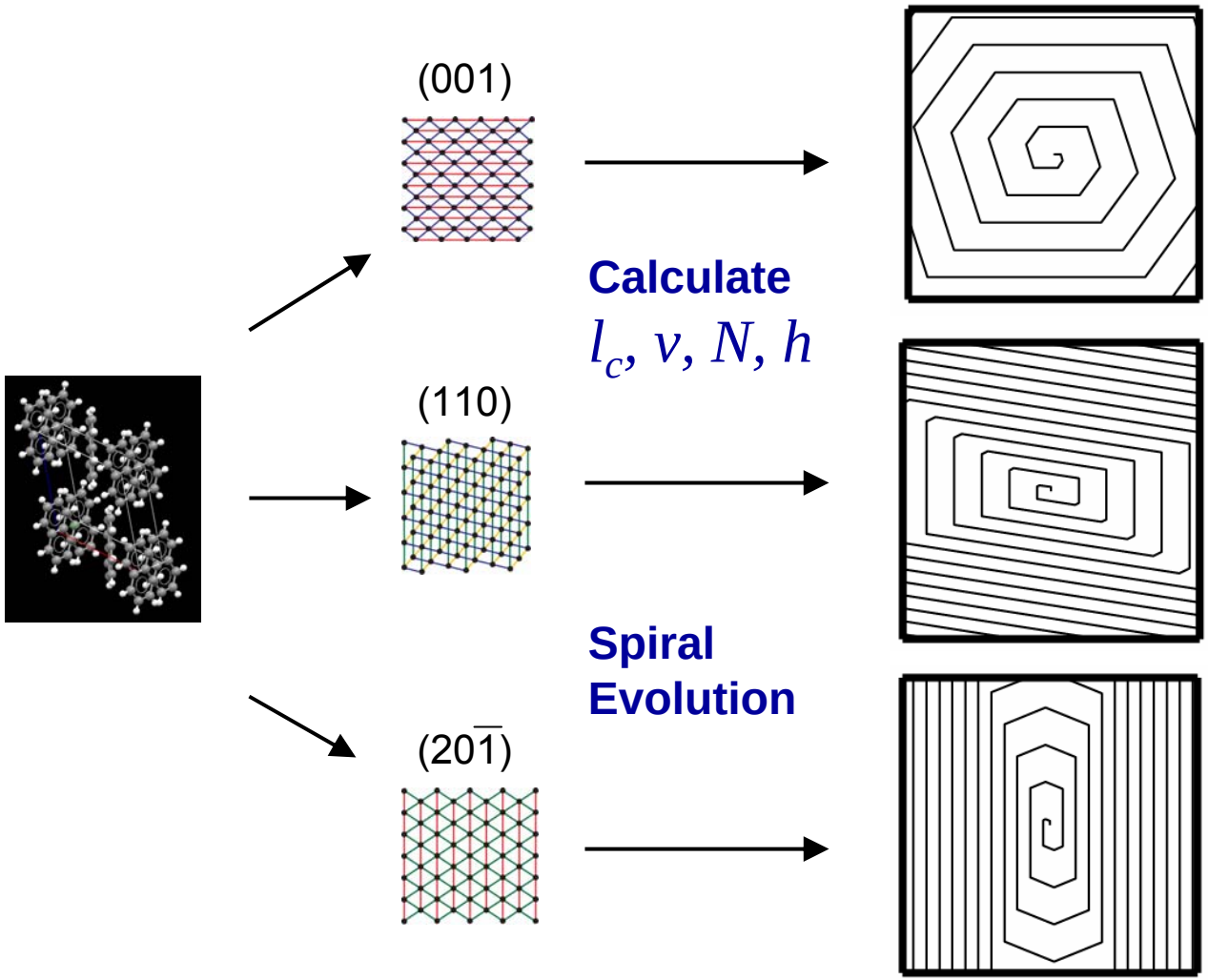




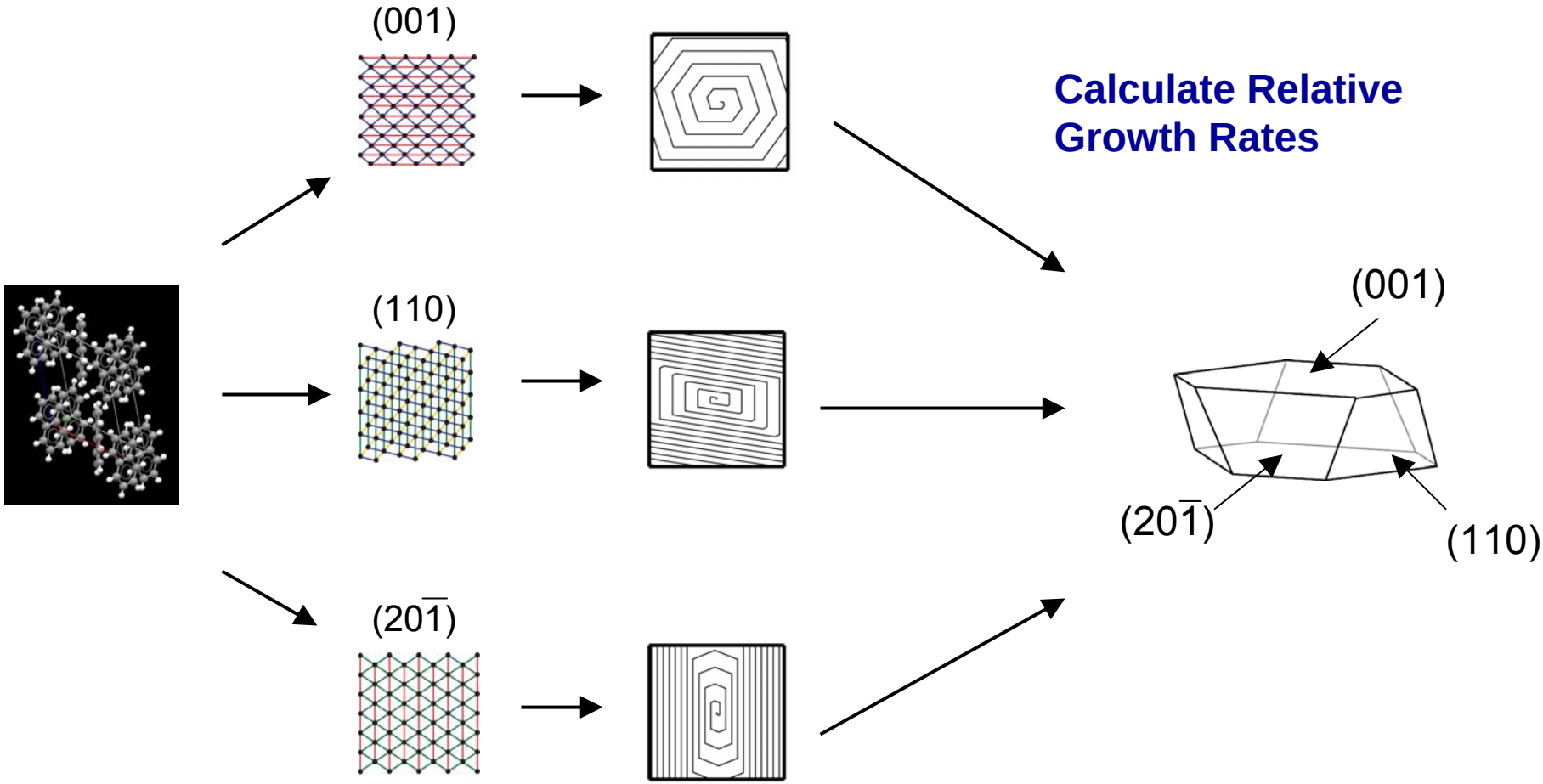
Naphthalene



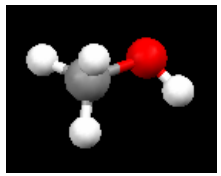
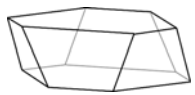
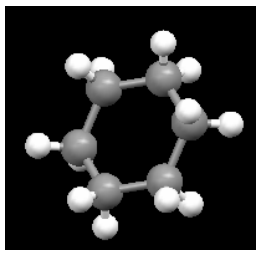
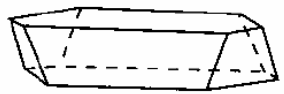
Naphthalene

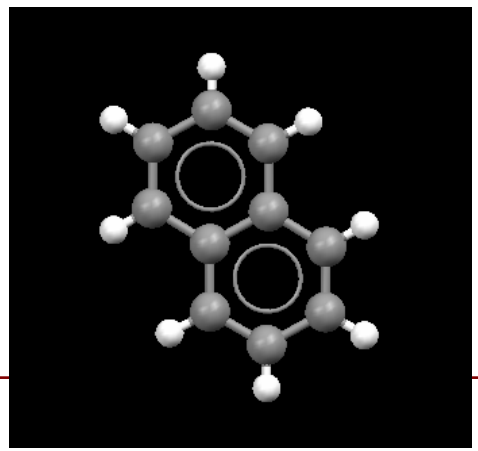


Naphthalene



Naphthalene

Solvent		Prediction	Experiment*
	Ethanol:		
	Cyclohexane:		



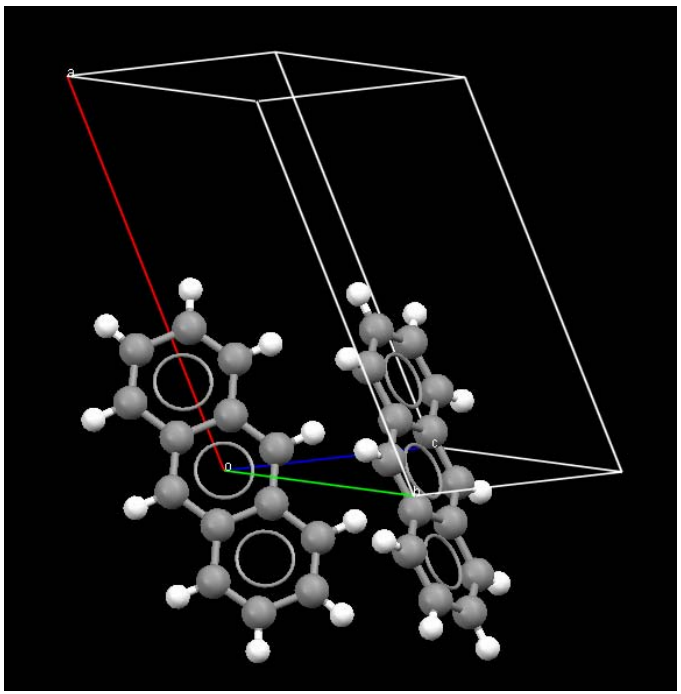
Solvent Effect

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

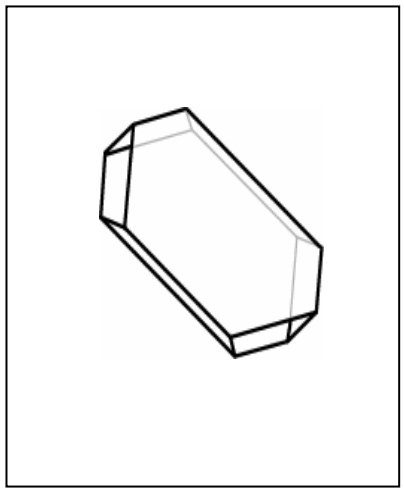
$$\gamma_{cyclo} = 25.3\ erg/cm^2 \qquad \gamma_{ethanol} = 22.8\ erg/cm^2$$

*Grimbergen, et. al. *J. Phys. Chem B*, **1998**, 102, 2646-2653.

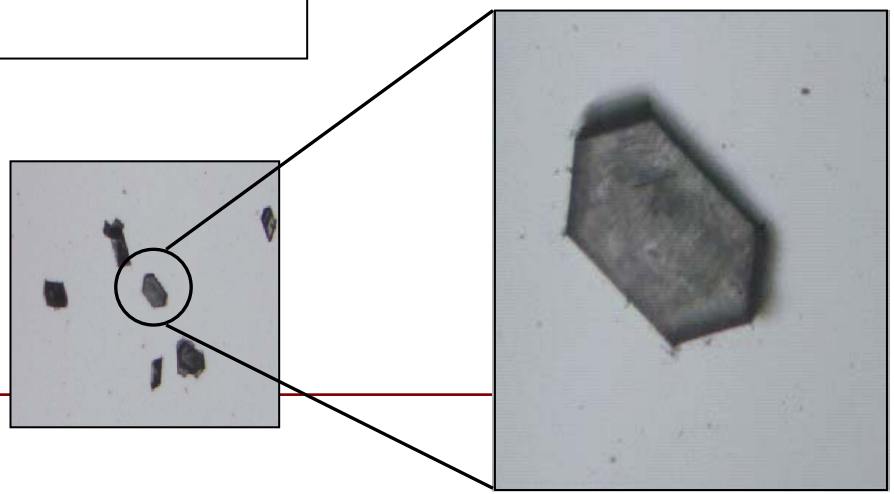
Anthracene in 2-propanol



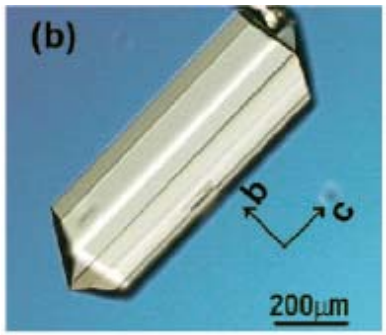
Prediction



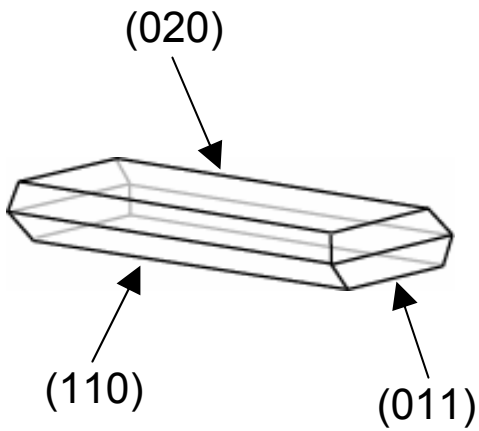
Experiment



α-Glycine in Water

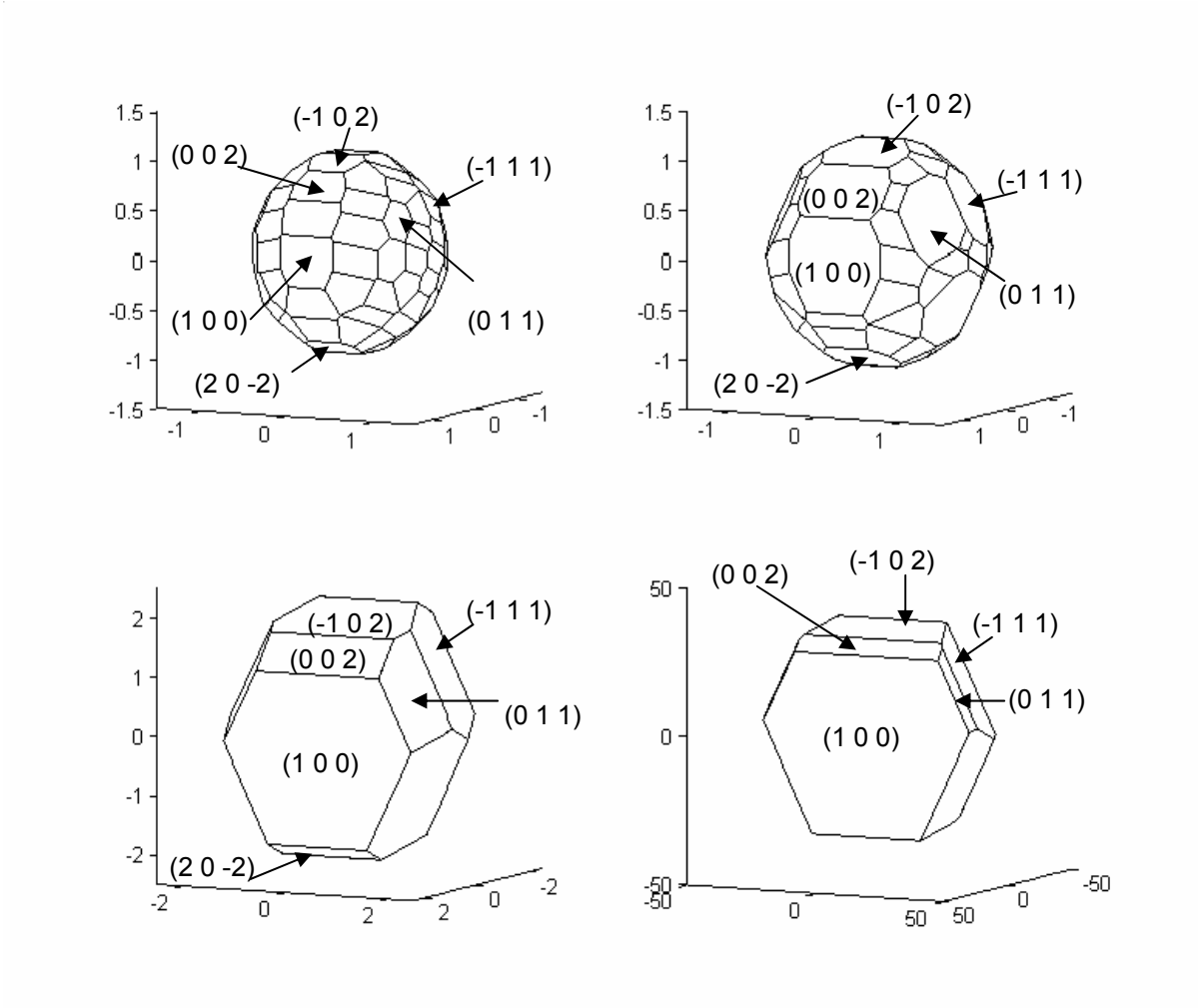


Experiment – Poornachary, Chow and Tan *Cryst. Growth & Des.*, (2007)

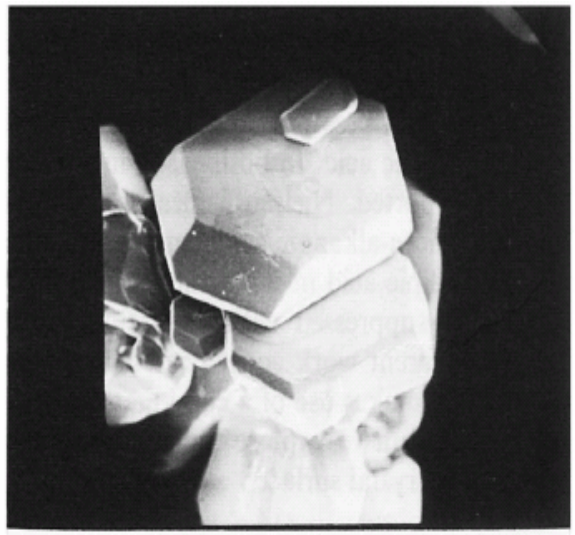


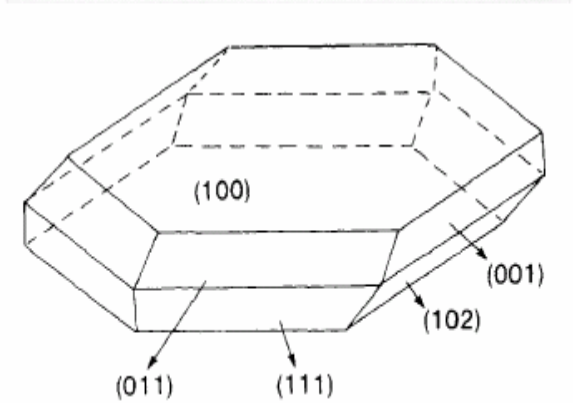
Prediction based on a hydrogen bonded dimer growth unit

3-D Shape Evolution: Adipic Acid



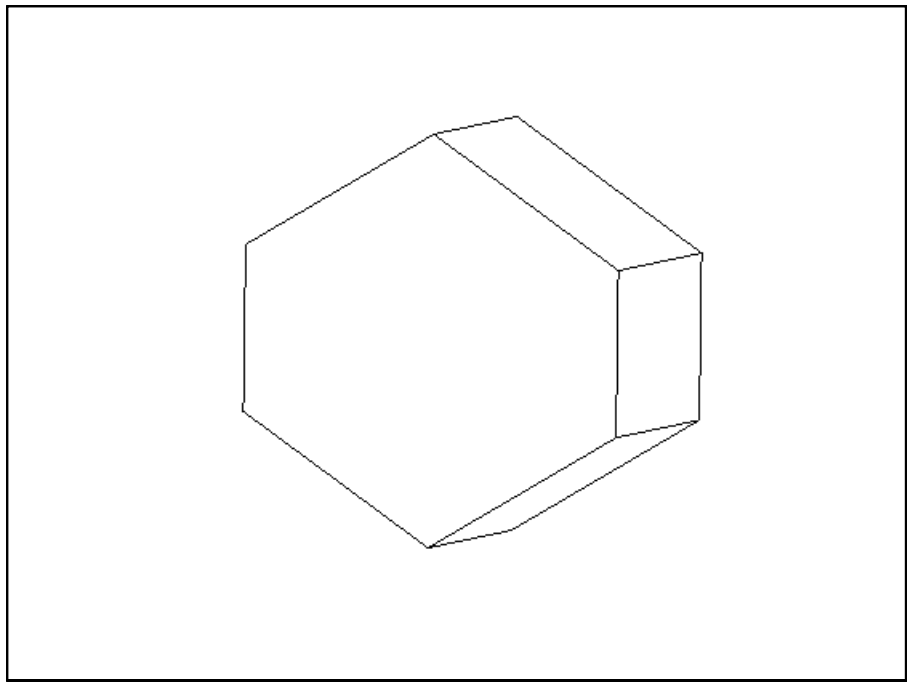
Experimental Shape



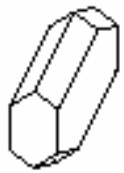


Davey et al., *J. Chem. Soc. Faraday Trans., 88*, 3461 (1992)

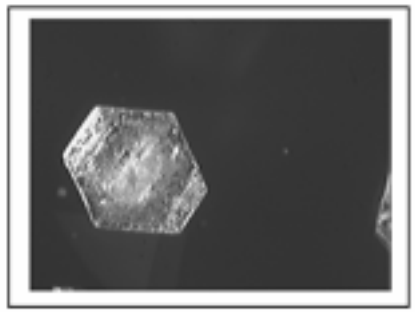
Shape Evolution from Equilibrium-Shaped Seed



Seed Shape:

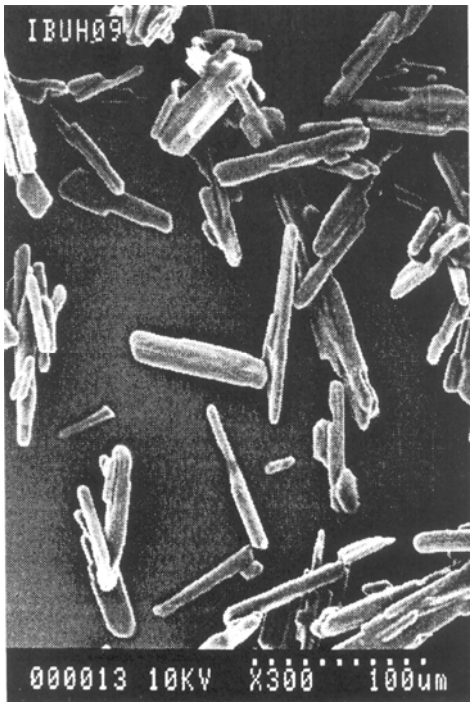


Experiment:



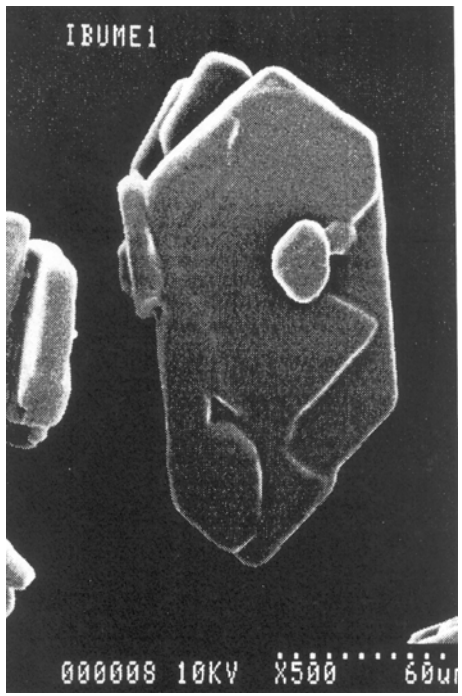
- Evolution of a succinic acid crystal grown out of water from a seed (here chosen as the equilibrium shape) to its steady state shape.

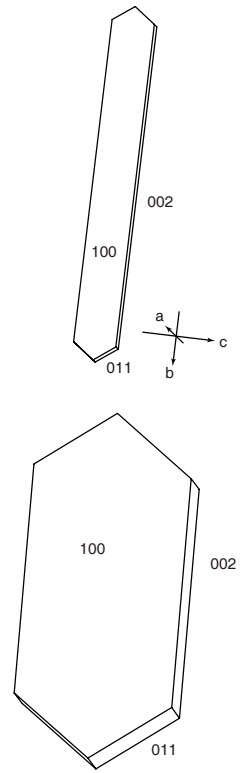
Application - Ibuprofen



Storey & York (1997)
Ibuprofen grown from hexane

Storey & York (1997)
Ibuprofen grown from methanol





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

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:

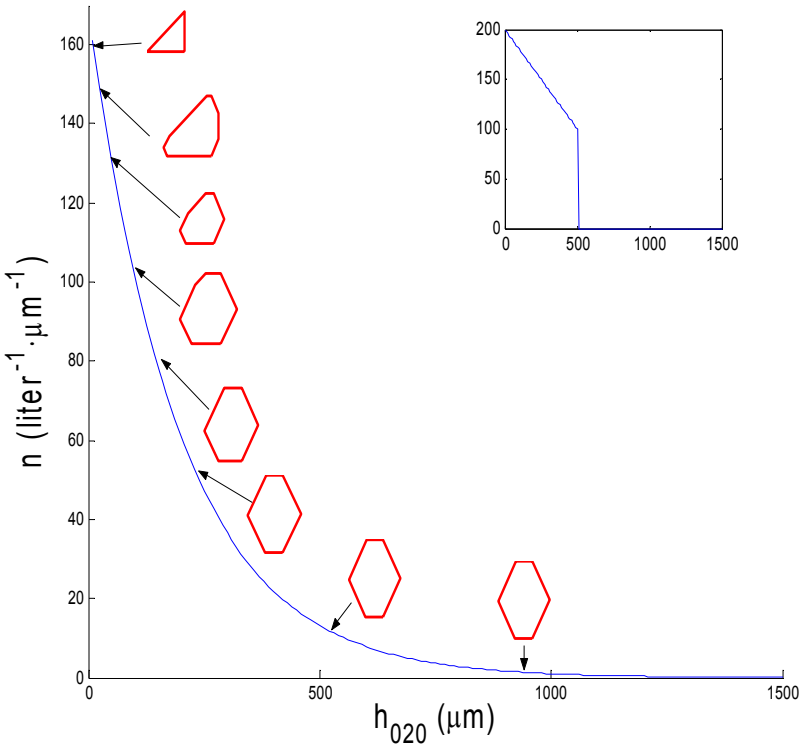
$$\frac{\partial n}{\partial t} = -G_{hkl}\frac{\partial n}{\partial h_{hkl}} - \frac{n}{\tau}$$

Solute Mass Balance:

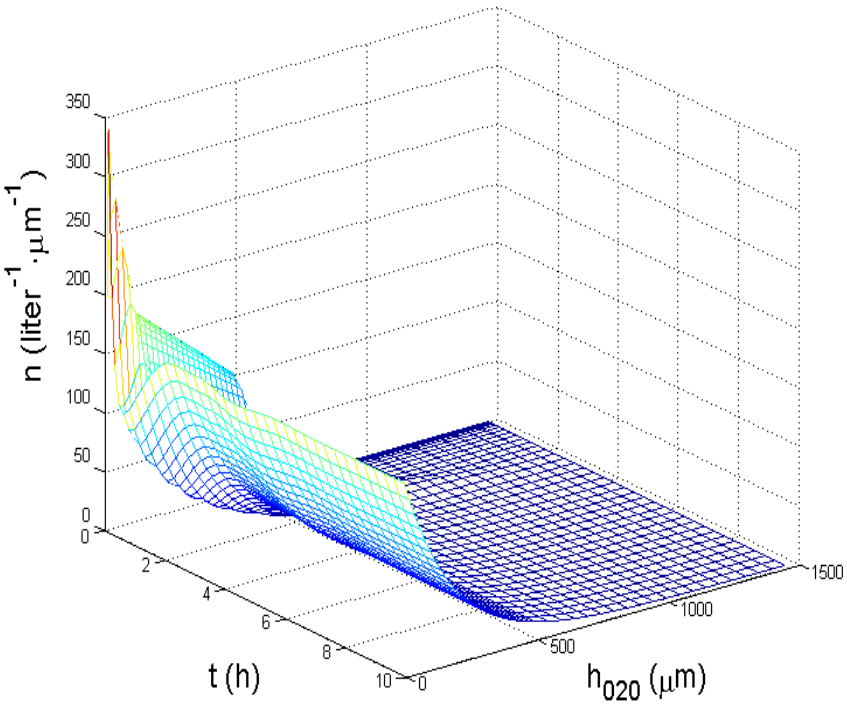
$$\frac{dc}{dt} = \frac{(\rho - c)}{\tau} + \frac{(c_{in} - \rho)}{\epsilon\tau} + \frac{(\rho - c)}{\epsilon}\frac{d\epsilon}{dt}$$

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

Size & Shape Evolution – Succinic Acid



Initial and steady-state distribution



Size distribution transient dynamics

General Guidelines for Pharma

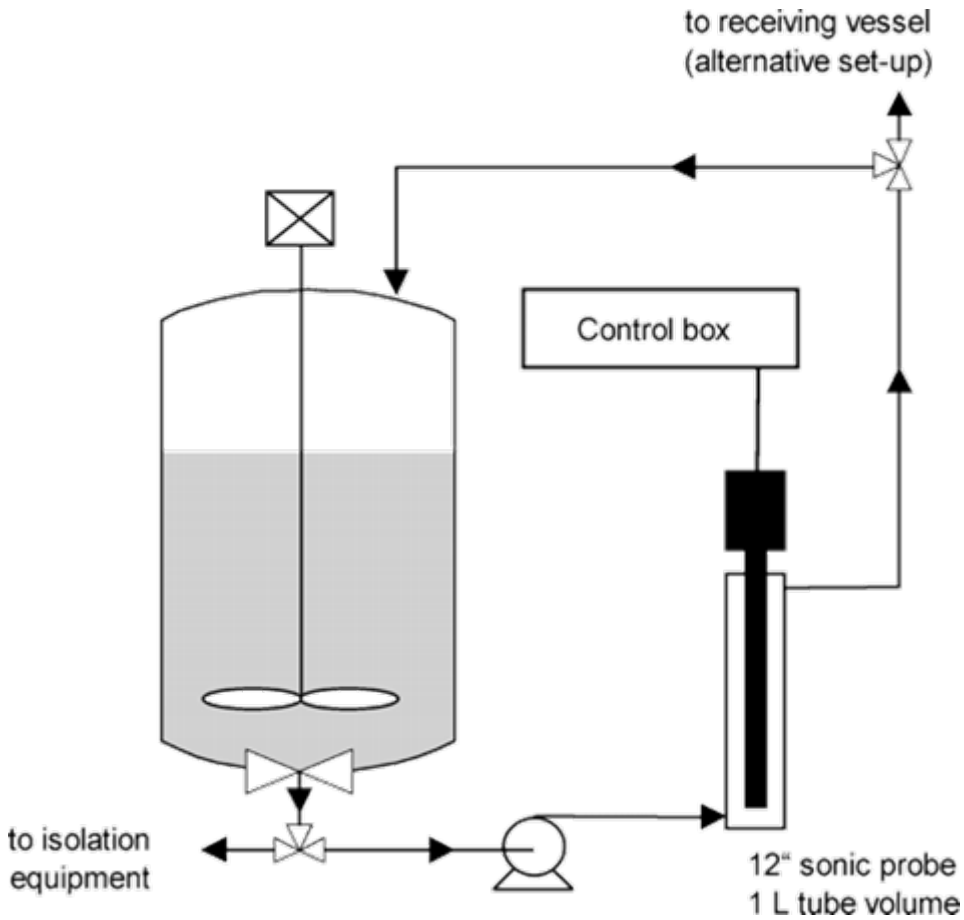
"From Form to Function: Crystallization of Active Pharmaceutical Ingredients,"
N. Variankaval, A. S. Cote and M. F. Doherty (Merck & UCSB), *AIChEJ, 54*, 1682 (2008)

- Drive down production costs
- Internal survey at Merck revealed that dry milling (pin or jet milling) costs more than the entire drug product formulation process. Additional, problems
  - serious industrial hygiene concerns due to dust
  - crystal form/crystallinity difficult (or impossible) to preserve across the dry milling step
  - product from dry milling is often rich in fines and/or highly electrostatic – downstream processing very difficult
- Quality by Design – adopt a strategy that incorporates particle size and shape control into the final crystallization directly so that dry milling is eliminated from manufacturing processes

Adopt a New Approach

- Develop growth-dominated processes in which nucleation, agglomeration, and particle breakage are minimized
  - provide ample seed surface area
  - provide rapid micro-mixing in order to avoid locally high supersaturation at the feed point where antisolvent or reagent is introduced
  - charge reagents to the system via a recycle loop set up to circulate locally around the crystallizer. Use mixing tees, static mixers, or other devices to achieve rapid micro-mixing in the loop, which removes this burden from the vessel agitator
  - design and operate vessel agitator to provide low shear blending and solids suspension

Wet Milling by Sonication



Kim et al., Crystallization Process Development …, *Org. Process R&D, 7*, 997 (2003)

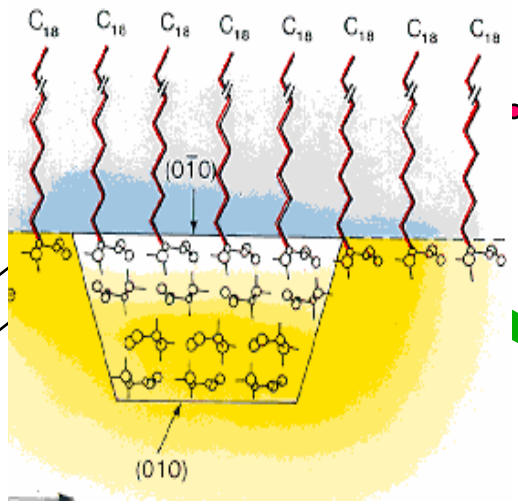
Opportunities: Other Materials

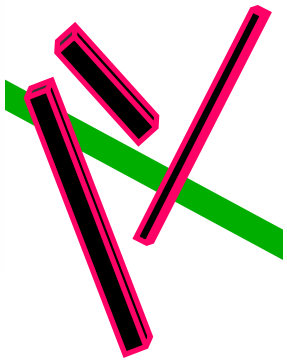
- Inorganic crystals
  - zeolites, tungston carbide for lighting, ZnO nanocrystals, photovoltaics ….
- Proteins and colloids
- Metals and metal oxide catalysts

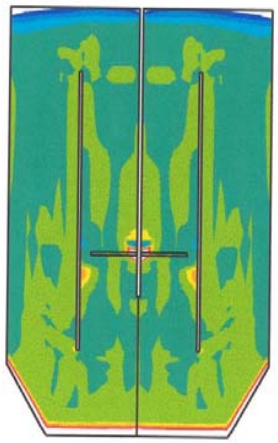
Opportunities

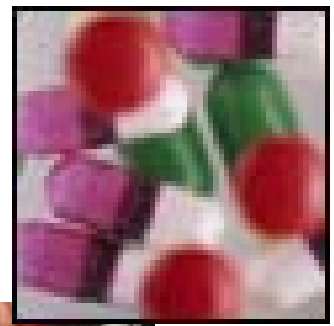
- Process models & process systems engineering
- Improving the model
  - Complex bond chains, growth units, kinks – **pharma molecules**
  - Critical edge length – thermodynamic or kinetic?
  - Supersaturation-dependent **relative velocities**
  - Absolute growth rates – can this be done?
- Co-solvents & anti-solvents
- Co-crystals – hydrates, solvates, and genuine co-solids (inclusion compounds)
- Polymorphic phase transformations
- Additives & impurities
- Nucleation and polymorph selection
- Racemic mixtures, enantiomeric resolution
- From single particles to suspensions
- Experiments
  - on surfaces for growth model validation
  - for polymorph selection
  - growth units & precursors
  - nucleation of API molecules – size, structure and shape of nuclei?

Molecules to Products



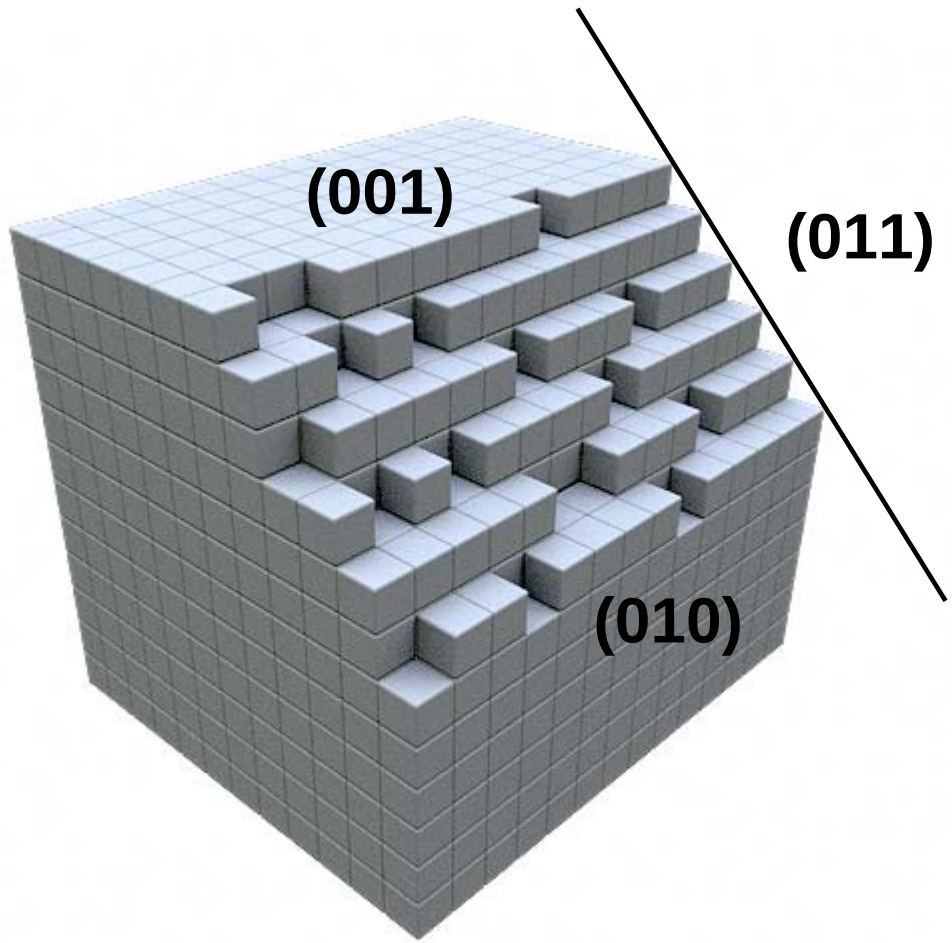






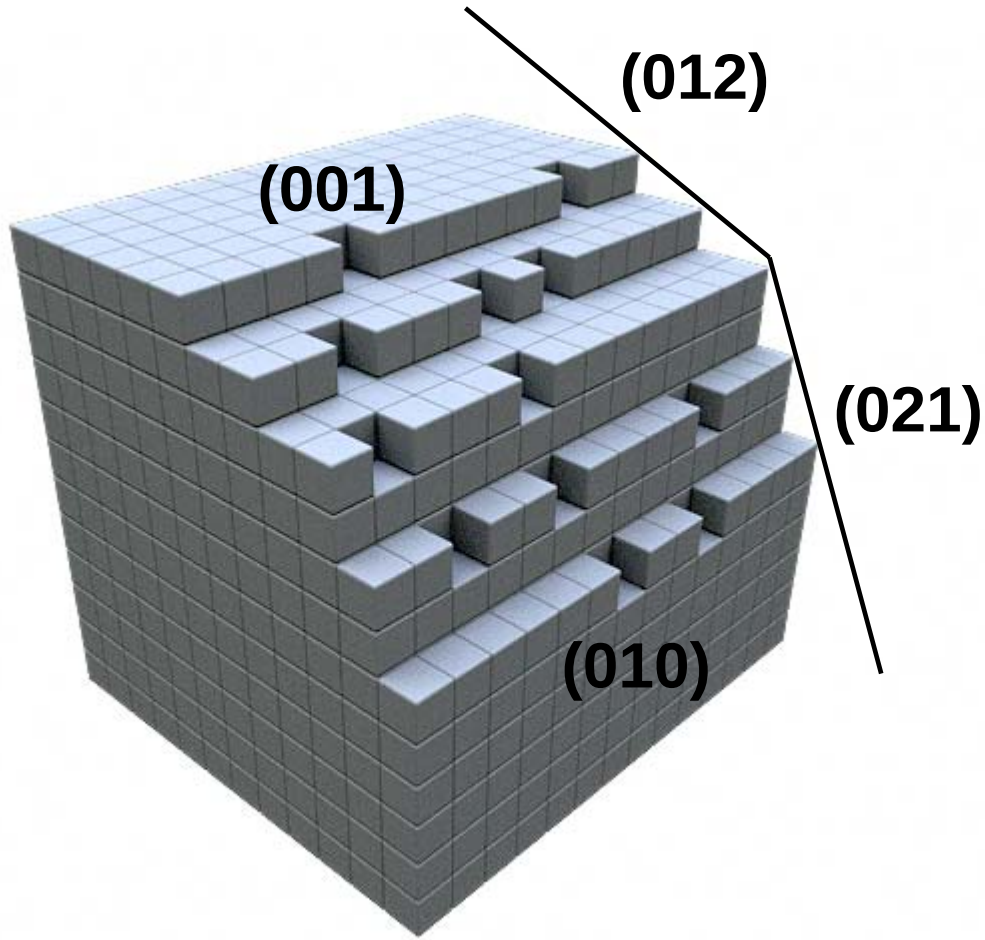
Extra Slides

Dissolution at Crystal Edges – 1 PBC



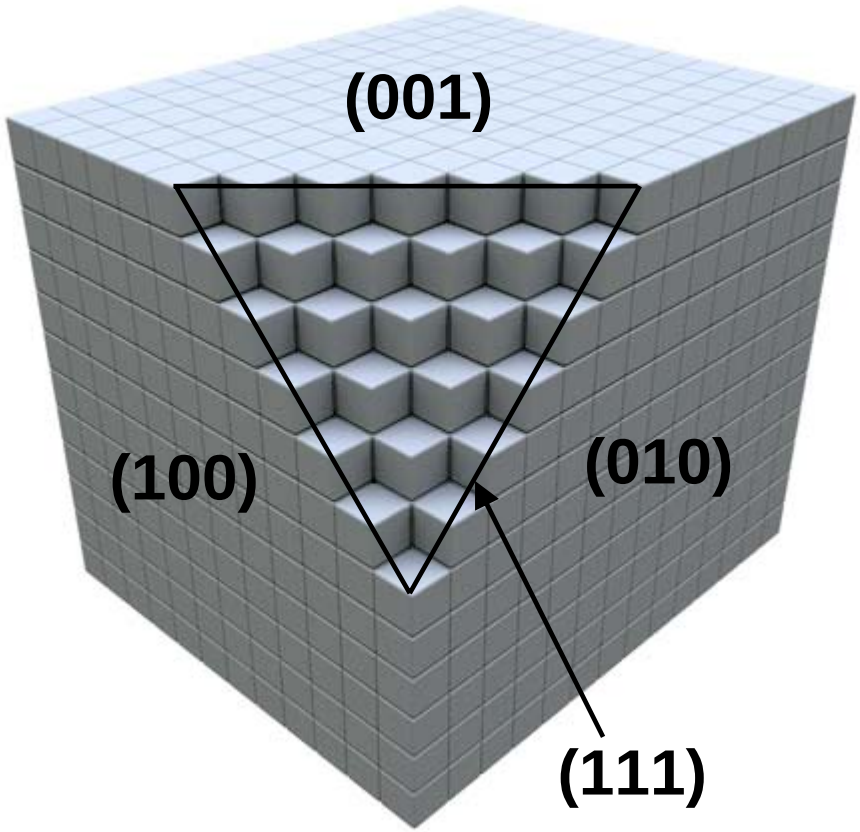
- Faces appear at certain locations in dissolution
  - **Edges**
  - Vertices

Dissolution at Crystal Edges – 2 PBC's



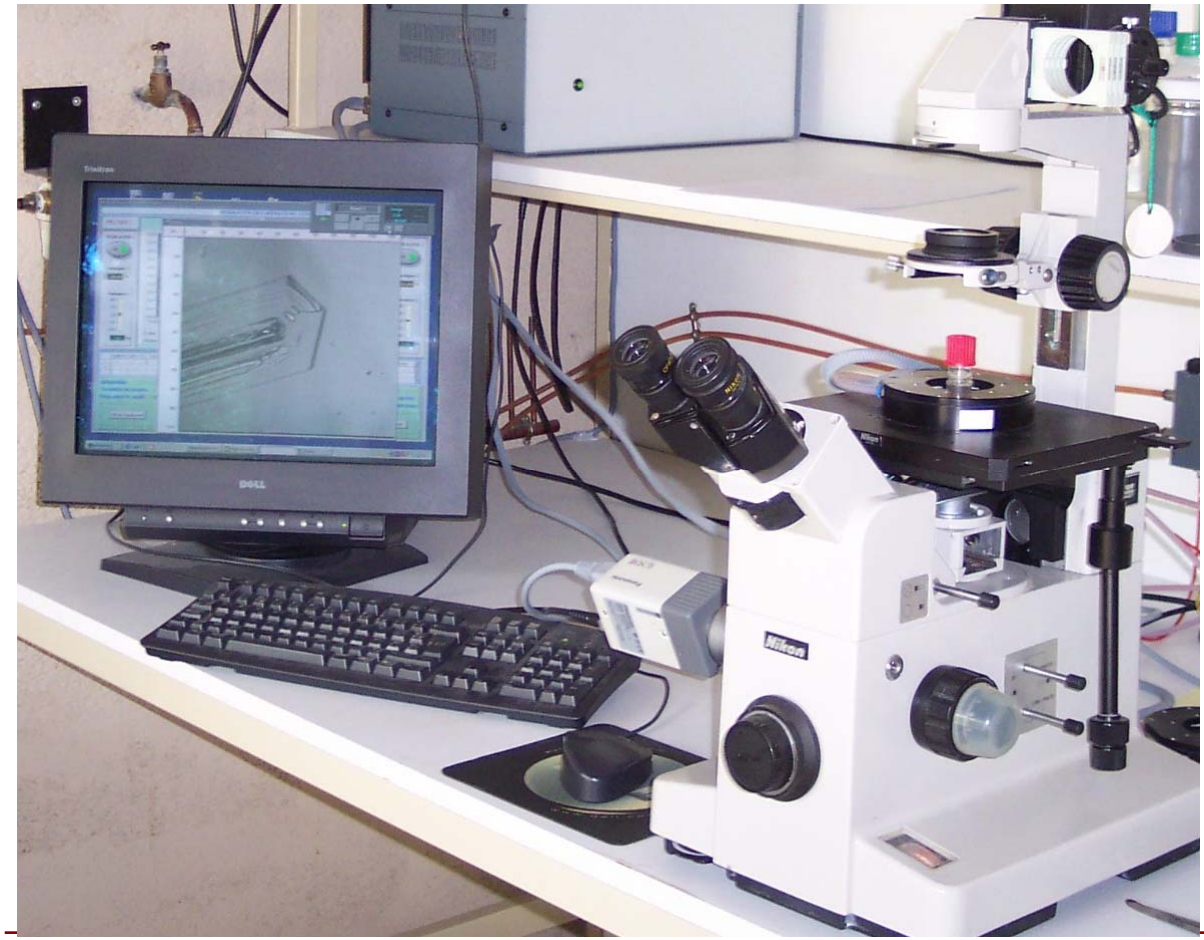
- Faces appear at certain locations in dissolution
  - **Edges**
  - Vertices

Dissolution at Vertices – 0 PBC's



- Faces appear at certain locations in dissolution
  - Edges
  - **Vertices**

Experimental Apparatus



- Peltier Cell
- ~2-3mL Batch Crystallizer