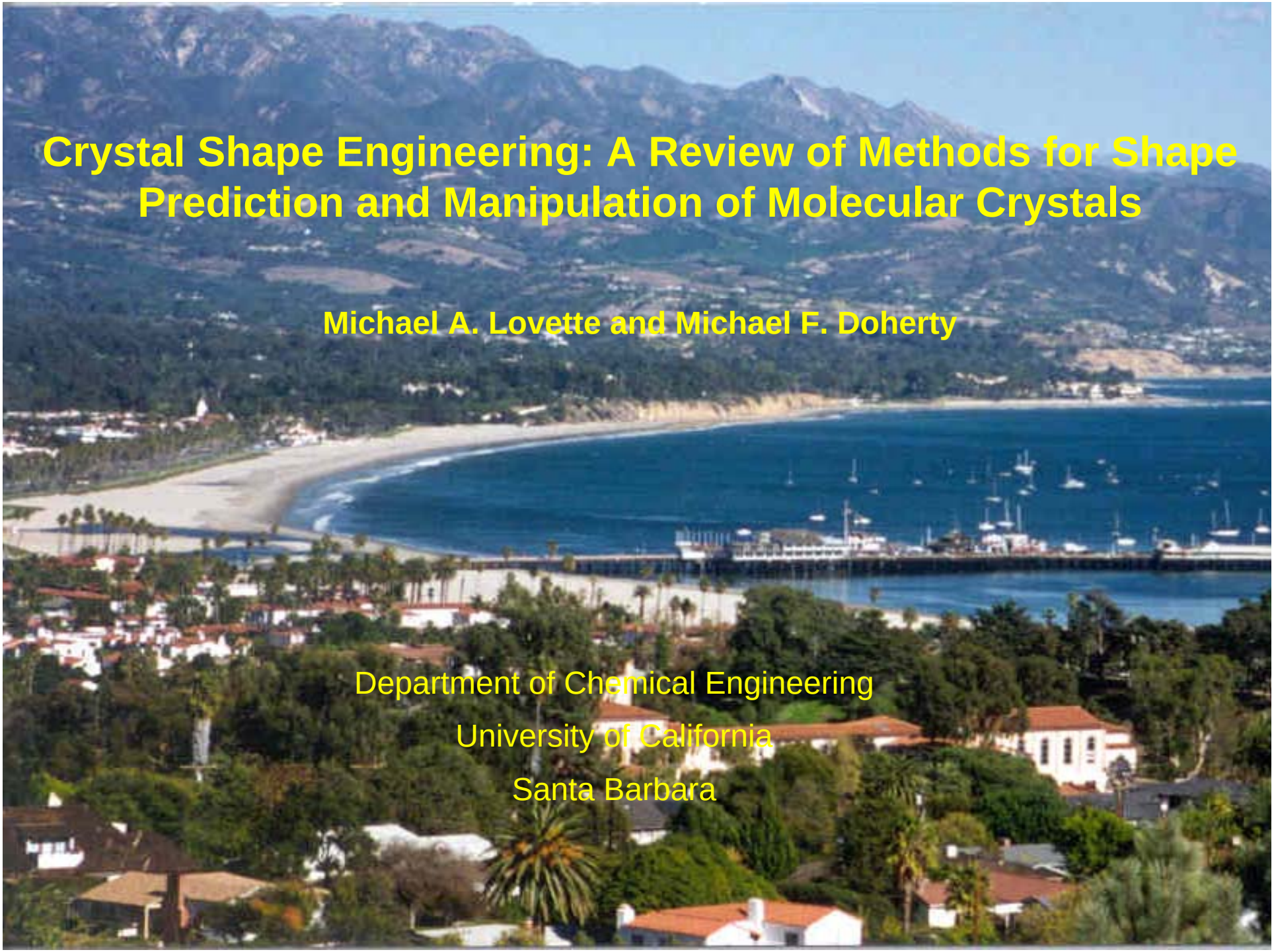

Crystal Shape Engineering: A Review of Methods for Shape Prediction and Manipulation of Molecular Crystals

Michael A. Lovette and Michael F. Doherty

Department of Chemical Engineering

University of California

Santa Barbara

Acknowledgements

People

Daniel Winn
Nancy Lape
Herbert Hofmann
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Sagar Gadewar
Max Muller
Yongchun Zhang
Jacob Sizemore
Ryan Snyder
Andrea Robben
Michael Lovette

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Amgen
Merck
Rhodia
UCSB
NSF:CTS
NSF:MRL
NSF:GRF
PRF
IFPRI

Current Projects in Crystallization

Nucleation and polymorph selection

Andrea Robben Browning

Optimal operating policies for solids processes with recycle

Derek Griffin

Next generation models for dissolution and growth

Ryan Snyder

Shape evolution of Co-crystals

Michael Lovette

Additives and needle crystals

Jacob Sizemore

Importance of 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

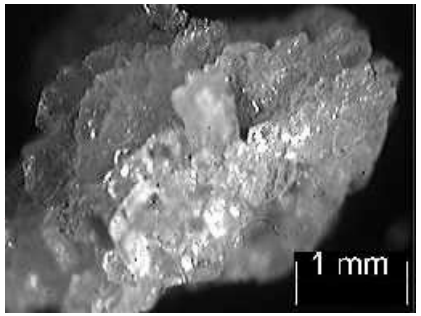
- The ability to predict and manipulate crystal shape enables optimized product & process design

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

Succinic Acid

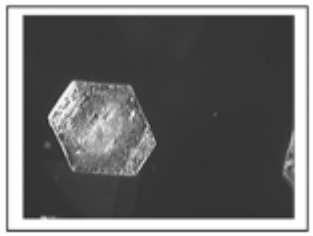


C
(g/L solution)

~5 g/L solution
(Qin & Rasmusm)

Metastable

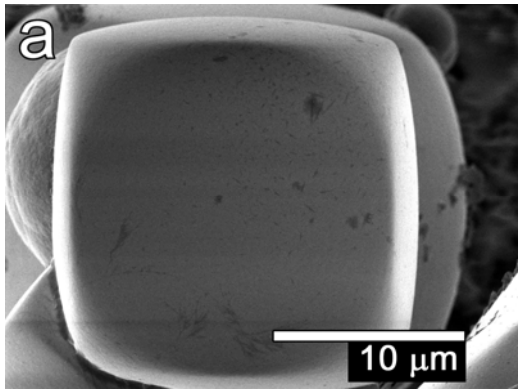
2.2 (°C)
Hofmann & Doherty



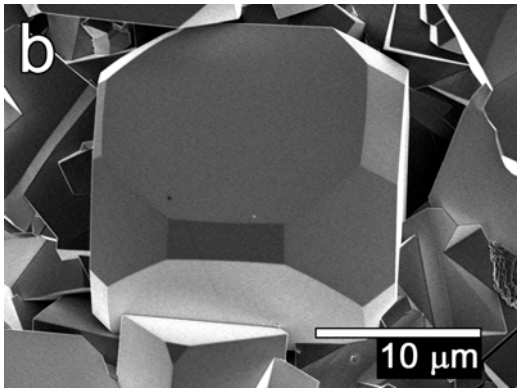
24 (°C) 30 (°C)

T
(°C)

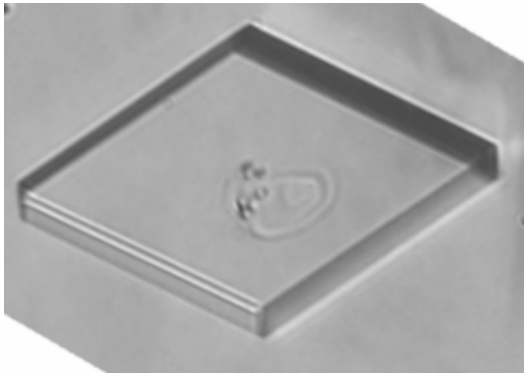
Crystals Form in Various Shapes



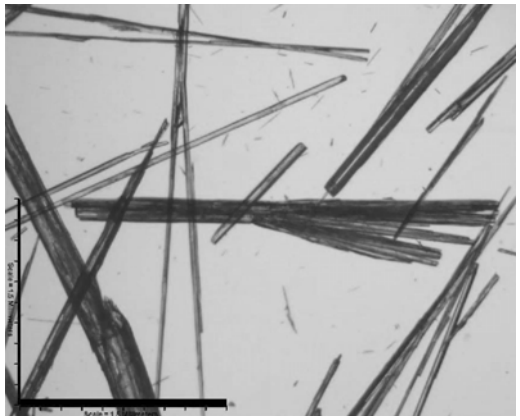
Zeolite



Zeolite

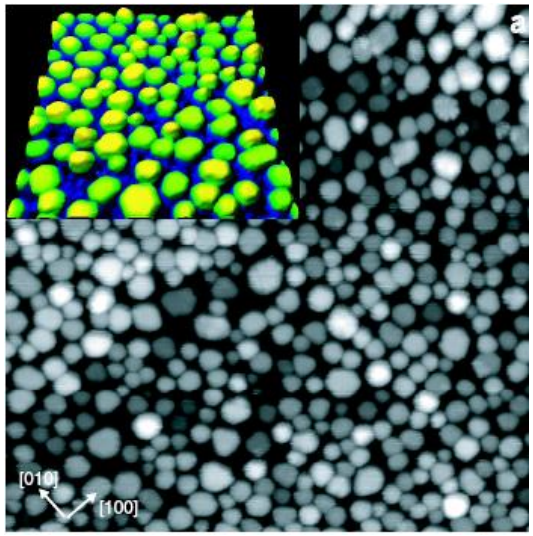


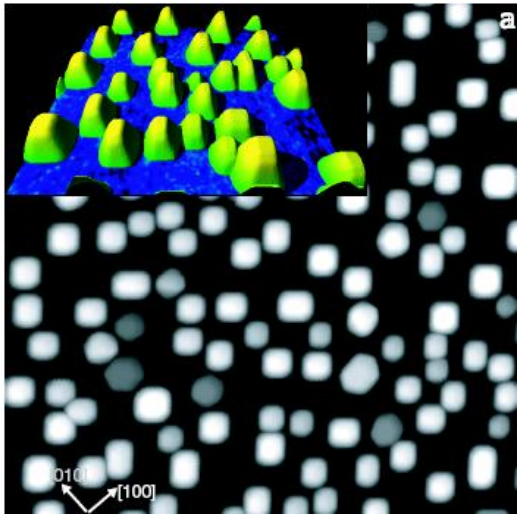
Succinic acid

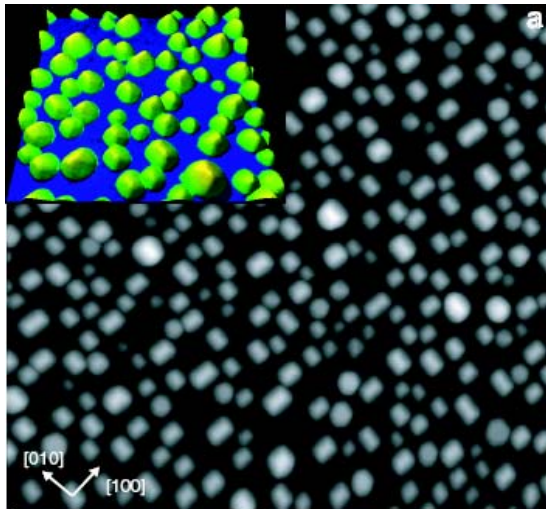


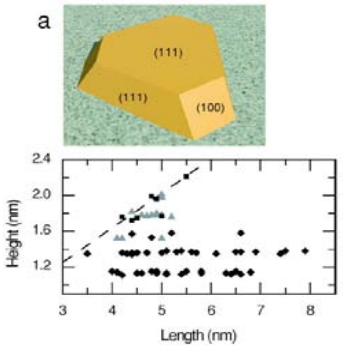
PABA

Non-equilibrium growth shapes of Pd nanocrystals supported on $SrTiO_3$ (001) – Silly, Castell et al. *Phys. Rev. B, 72,* 165403 (2005)

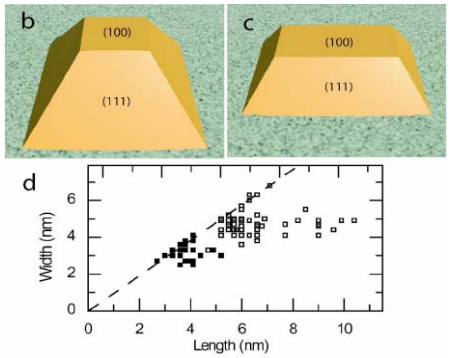




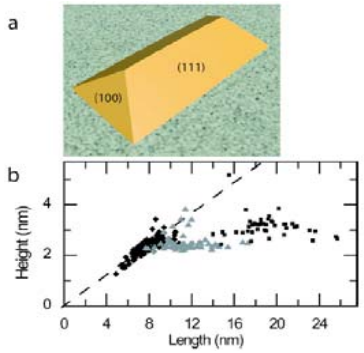




Substrate T = room temp
Anneal T = 650ºC
Surface treatment #1



Substrate T = 460ºC
Anneal T = 650ºC
Surface treatment #1



Substrate T = room temp
Anneal T = 650ºC
Surface treatment #2

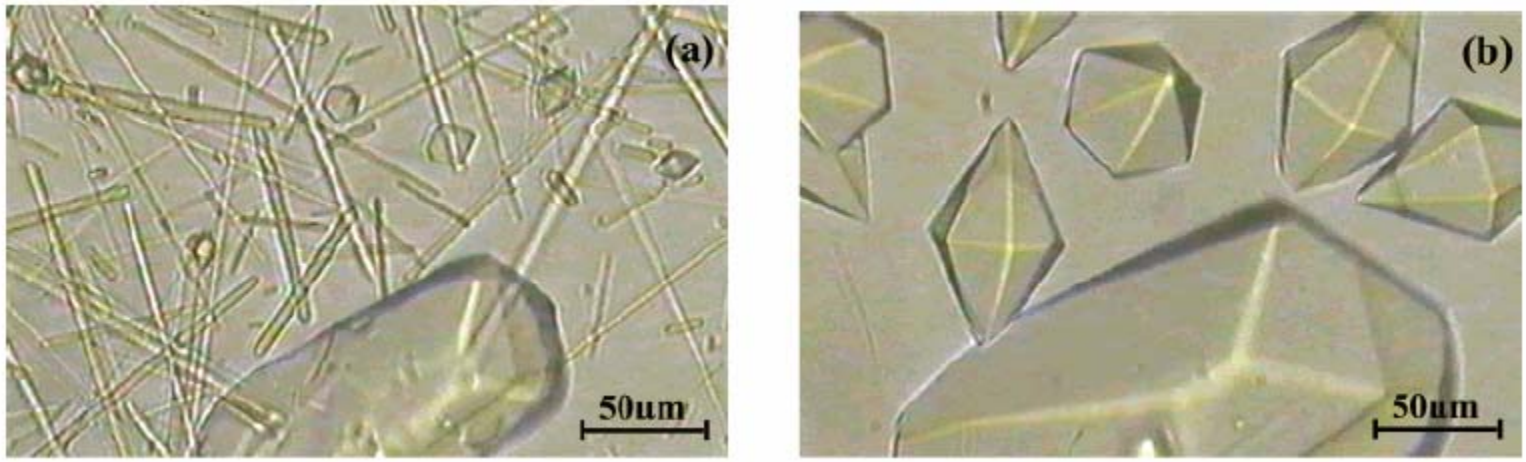
Polymorphism

- 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.

Needles Transform to Bipyramids



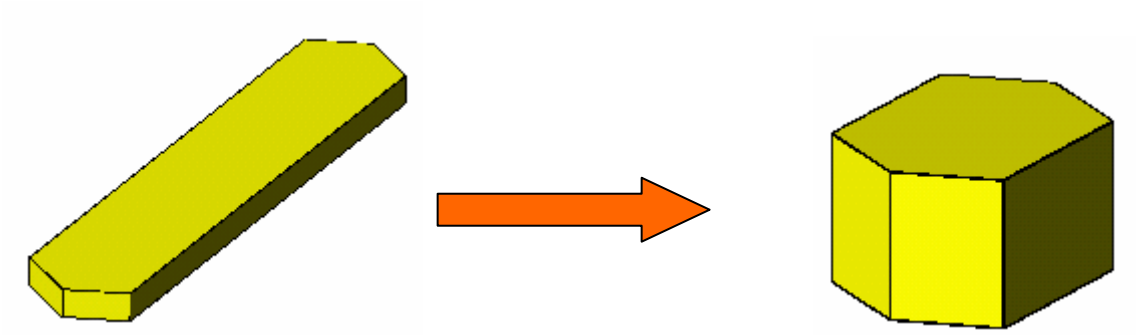
The less stable polymorph (needles) dissolves as the more stable polymorph (bipyramids) grows – Veesler et al. (2004)

Similar observations have been made by Davey and co-workers (Ferrari et al., 2003) for beta-glycine (needles) to alpha-glycine (coffins) and for dihydroxy benzoic acid Form 1 (cubes) to Form 2 (needles)

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

Gordon and Amin Patent: Upjohn/Pfizer

United States Patent [19]

Gordon et al.

[11] **Patent Number: 4,476,248**

[45] **Date of Patent: Oct. 9, 1984**

[54] **CRYSTALLIZATION OF IBUPROFEN**

[75] Inventors: **Roger E. Gordon**, Portage; **Sanjay I. Amin**, Oshtemo Township, Kalamazoo County, both of Mich.

[73] Assignee: **The Upjohn Company**, Kalamazoo, Mich.

[21] Appl. No.: **517,116**

[22] Filed: **Jul. 25, 1983**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 470,820, Feb. 28, 1983, abandoned.

[51] **Int. Cl.**^{3} **C07C 51/42**

[52] **U.S. Cl.** **562/494**

[58] **Field of Search** 562/494

[56] **References Cited**

U.S. PATENT DOCUMENTS

FOREIGN PATENT DOCUMENTS

820267 1/1975 Belgium 562/494

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Kirk-Othmer-Encyclopedia of Chem. Technology, 2nd Edit., (Supp. vol.), John Wiley & Sons, (1971), 889-910.

Derwent Abstract 38877x/21 of Japan 5 1041-338 dated Apr. 7, 1976.

Derwent Abstract 38878x/21 of Japan 5 1041-339 dated Apr. 7, 1976.

Primary Examiner—Paul J. Killos

Attorney, Agent, or Firm—John T. Reynolds

[57] **ABSTRACT**

Ibuprofen is crystallized from a $\delta H \geqq 8$ liquid such as a C_1 to C_3-alkanol, e.g., methanol, containing solutions thereof to obtain ibuprofen crystals which are equant (cube, sphere or grain) in shape, which ibuprofen crystals have larger average partile size, higher bulk density, lower bulk volume and improved flow properties compared to previously known bulk ibuprofen crystalline materials.

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

[56] **References Cited**

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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

FOREIGN PATENT DOCUMENTS

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54-115314	9/1979	Japan .
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

Equilibrium Crystal Growth & Shape

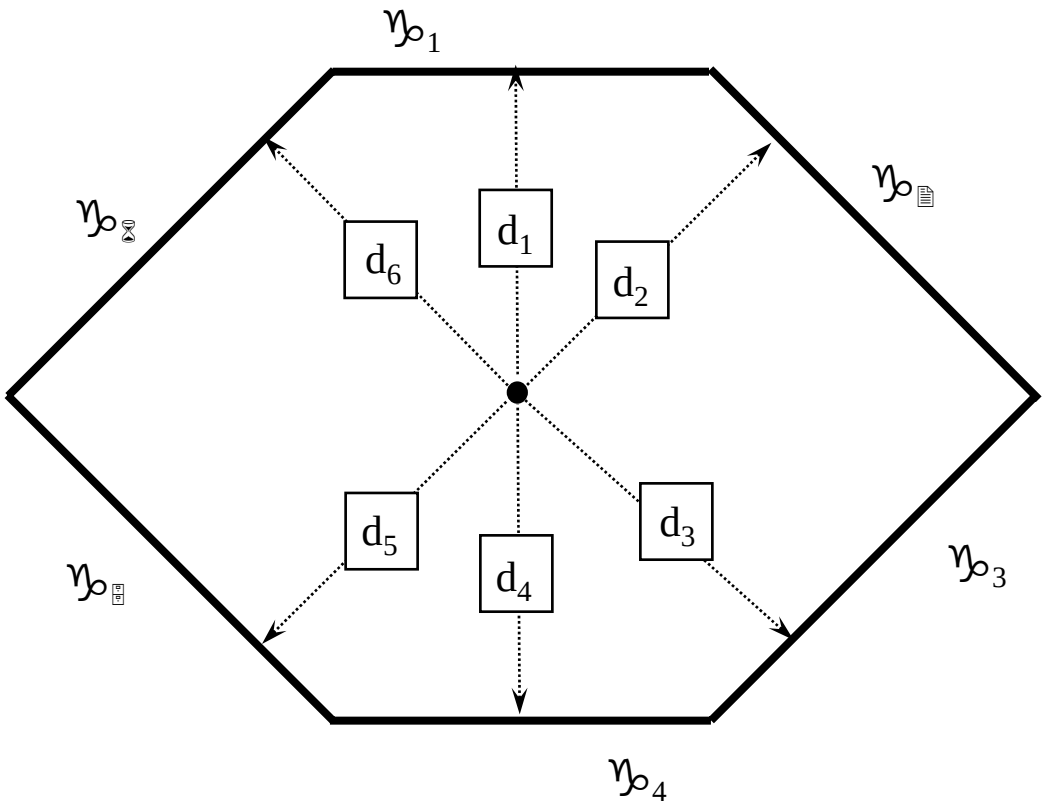
- Idealized shape at infinitesimal supersaturation and looooooooooong times
- Gibbs equilibrium condition for shape of facetted crystals (1877-78)

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

- 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



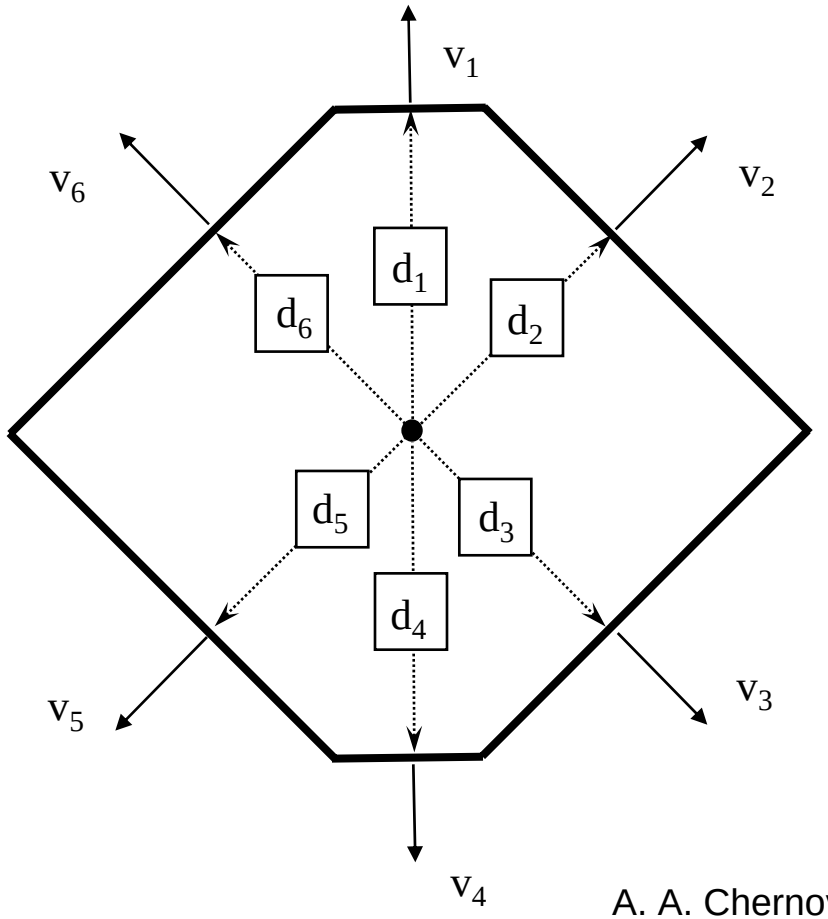
$$\frac{\gamma_1}{d_1} = \frac{\gamma_2}{d_2} = \cdots = \frac{\gamma_i}{d_i}$$

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

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)

Relative Growth 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
  - 2D nucleation model

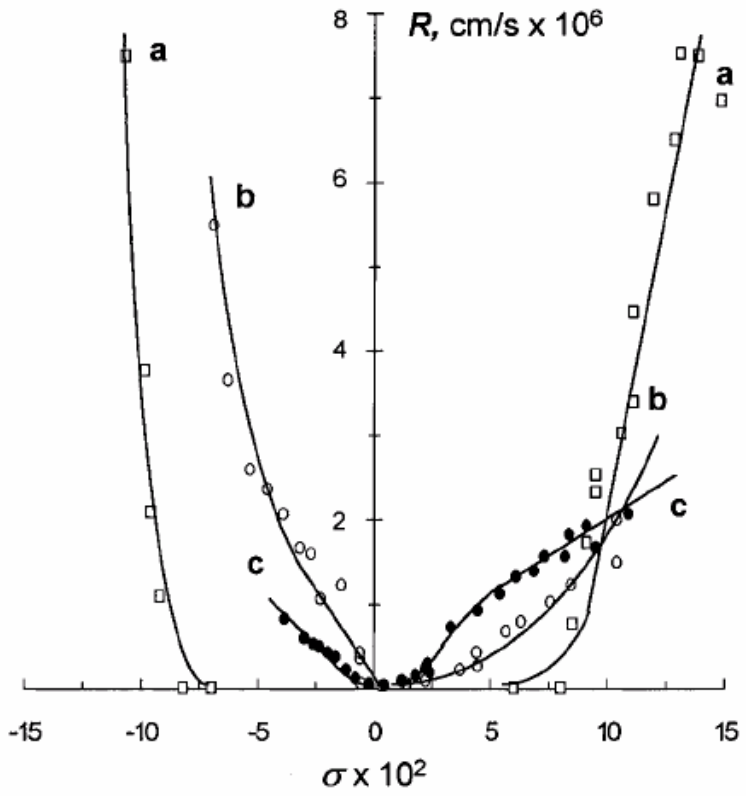
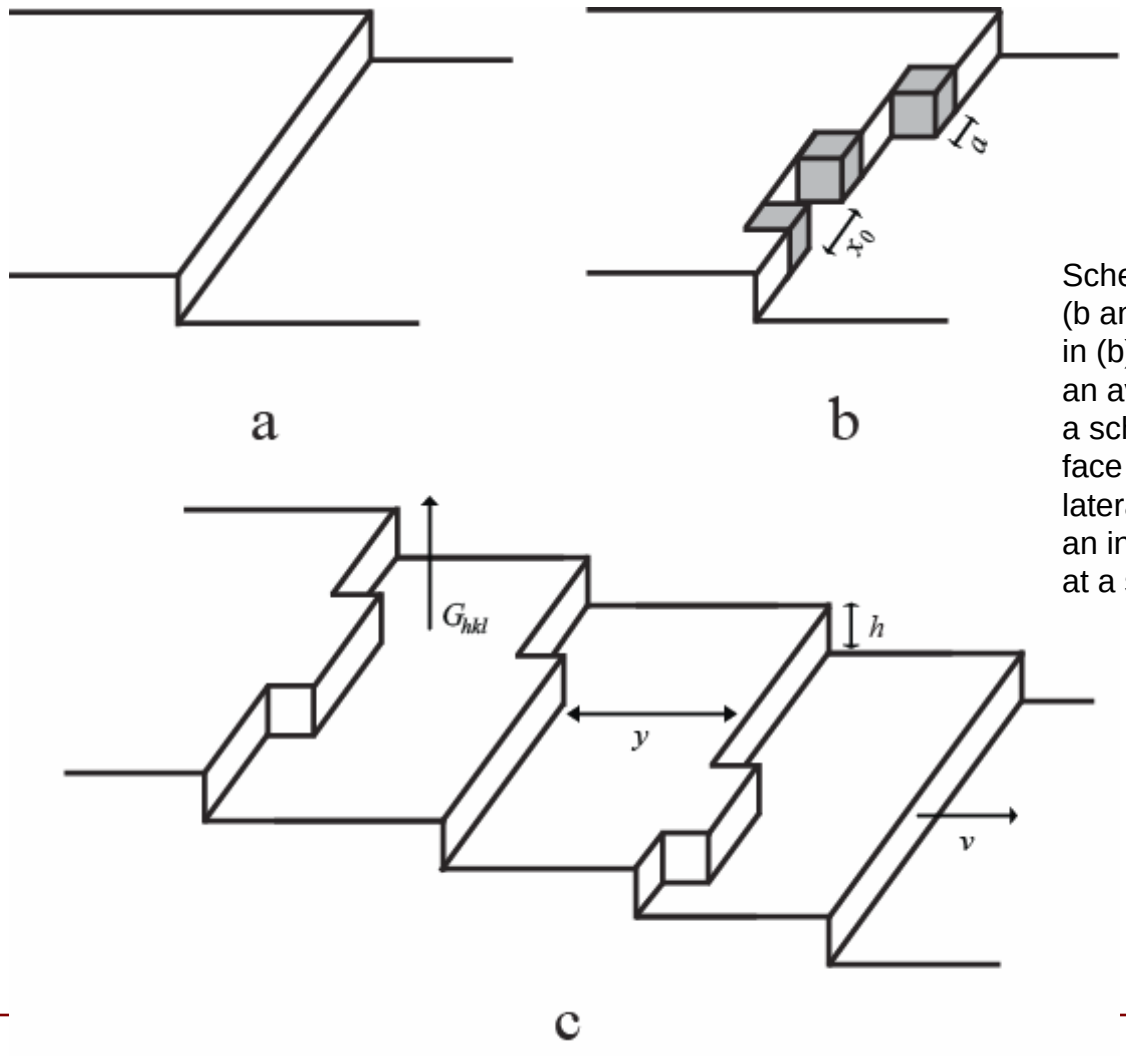


Figure 6. Dependence of normal growth rate R on supersaturation σ for the following faces: (a, □) {110}; (b, ○) {20$\bar{1}$}; (c, ●) {001}.

Crystal Shape and Growth Models

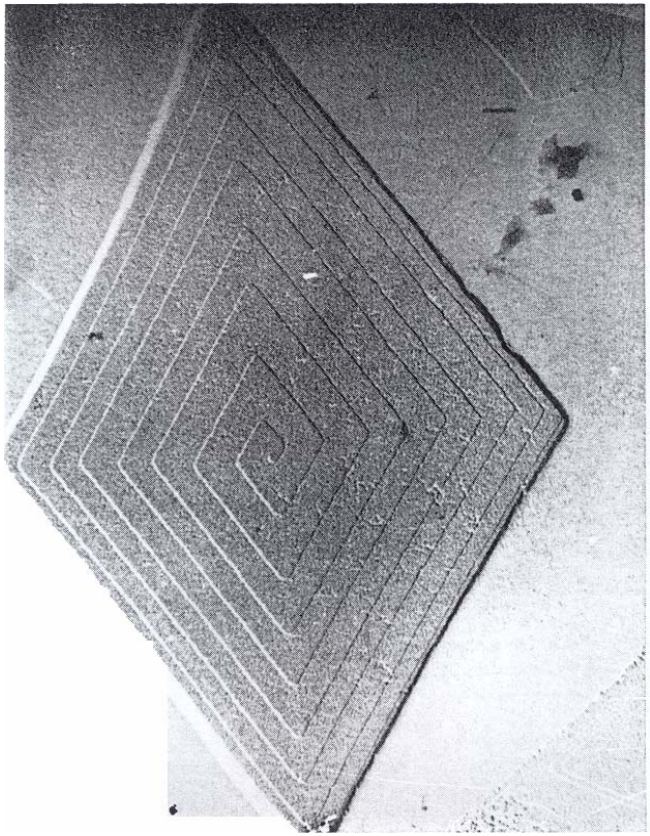
- Crystals grow by the flow of steps across the faces
- Sources of steps
  - 2-D nuclei - birth and spread model
  - spirals growing from screw dislocations
- Sources of edges – strong bond chains (PBC's)
- Sources of docking points for solute incorporation – kinks on edges (missing molecules along bond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

Flow of Steps Across Crystal Face

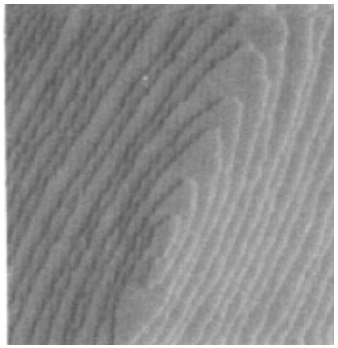


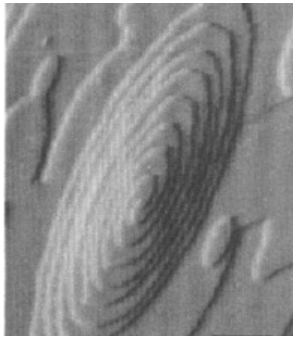
Schematic of step edges at (a) 0K and (b and c) above 0K. The grey squares in (b) represent kink sites separated by an average distance of x_0. Image (c) is a schematic of layered growth of the hkl face growing at a rate, G_{hkl}, through the lateral spreading of steps separated by an interstep distance, y, with a height, h, at a step velocity of v.

Spiral Growth of Organic Crystals

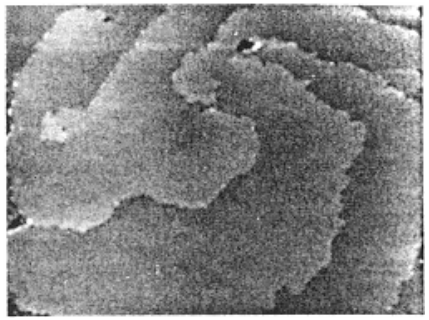


First electron micrographs of spirals: long chain paraffin n-hexatriacontane, $C_{36}H_{74}$ x 16000 (Dawson and Vand, *Proc. Roy. Soc*., 1951)



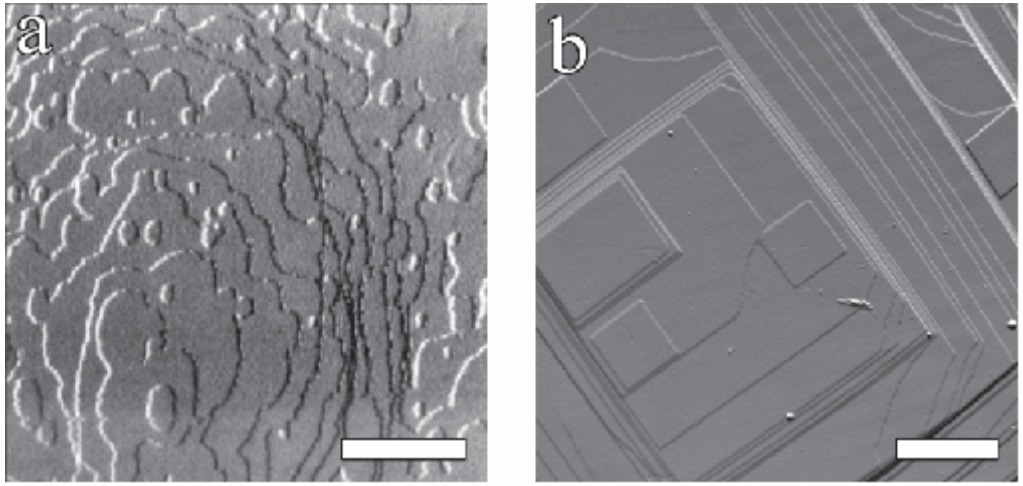


AFM images of spiral growth on hen egg white lysozyme surface (Durban, Carlson and Saros, *J. Phys. D: Appl. Phys*., 1993)



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

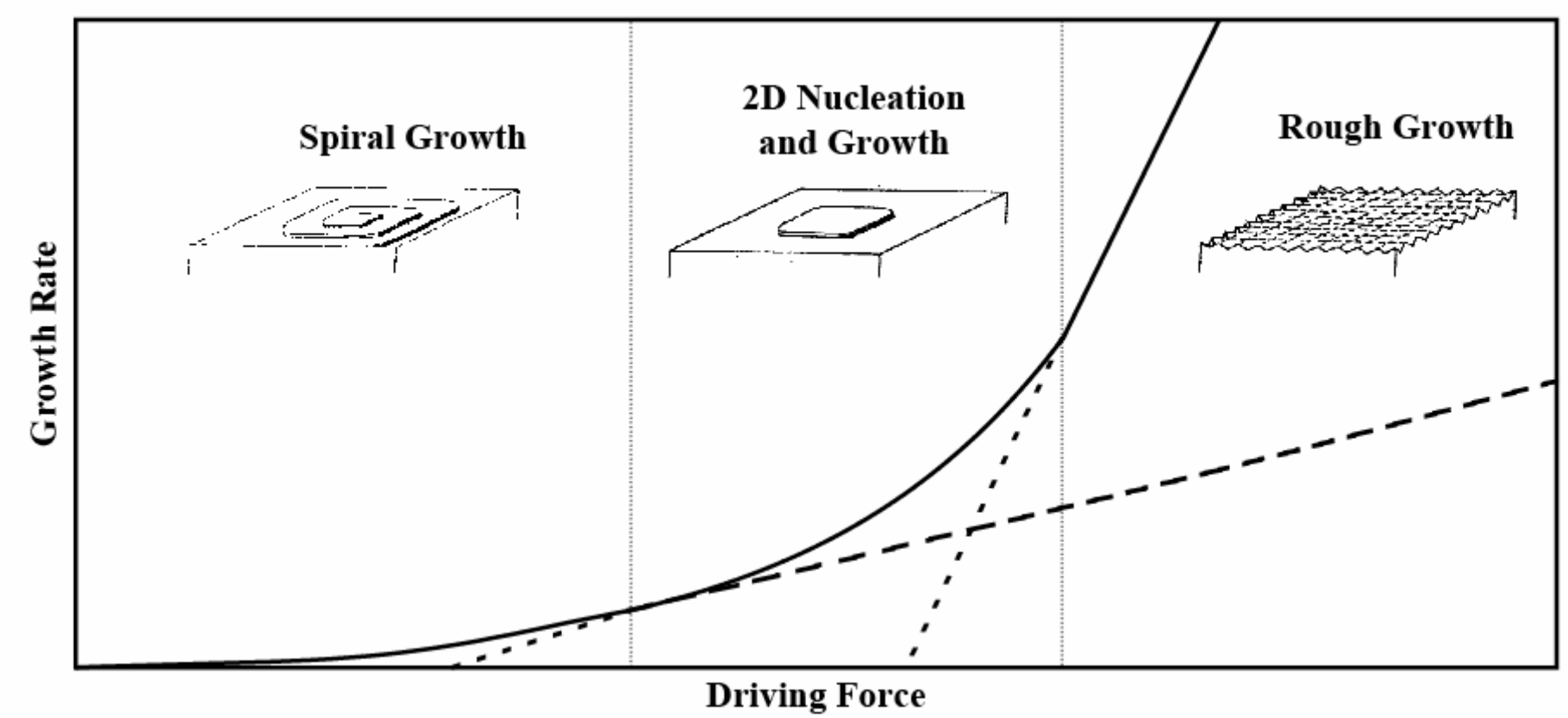
2D Nucleation Mechanism



AFM images of (a) thaumatin and (b) zeolite A growing by the 2D nucleation and growth mechanism with new layers forming on top of complete and incomplete layers.

Image (a) was adapted from Malkin (1995). The scale bars correspond to 2 micron.

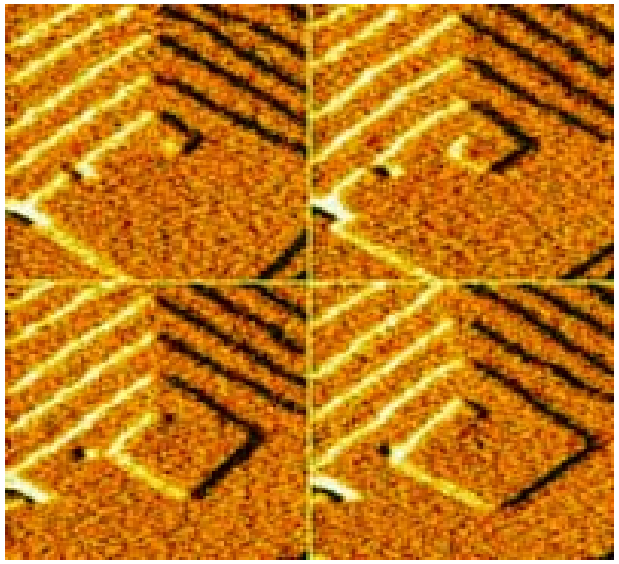
Growth Mechanisms



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.

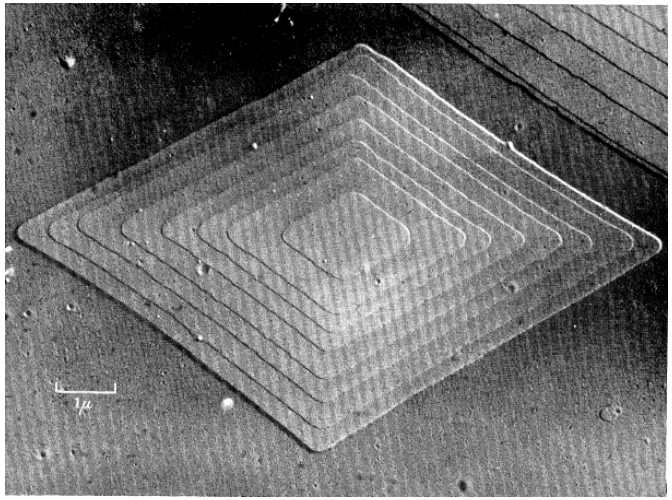
Step Formation

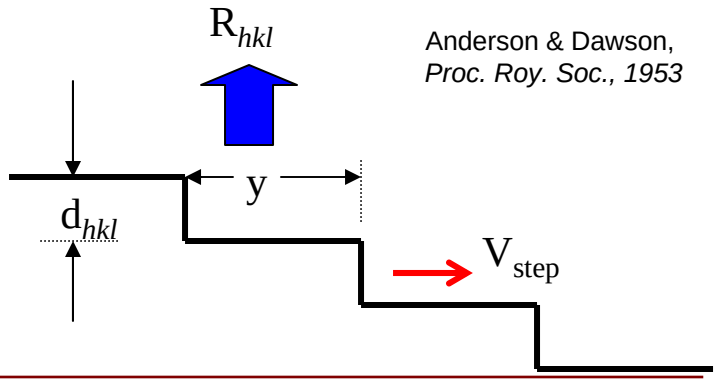
Spirals from a Screw Dislocation (BCF) on Calcite



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

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



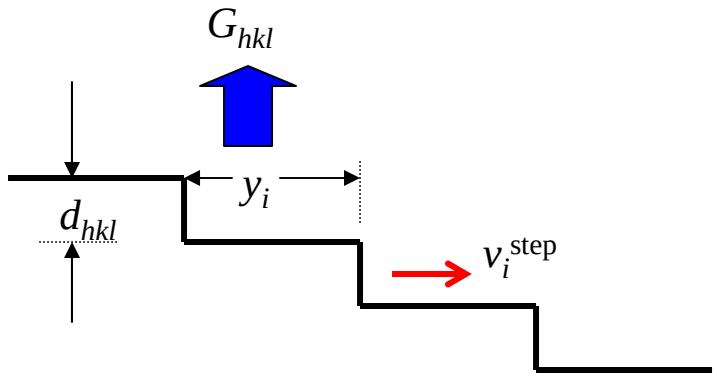


Anderson & Dawson, *Proc. Roy. Soc., 1953*

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

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

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

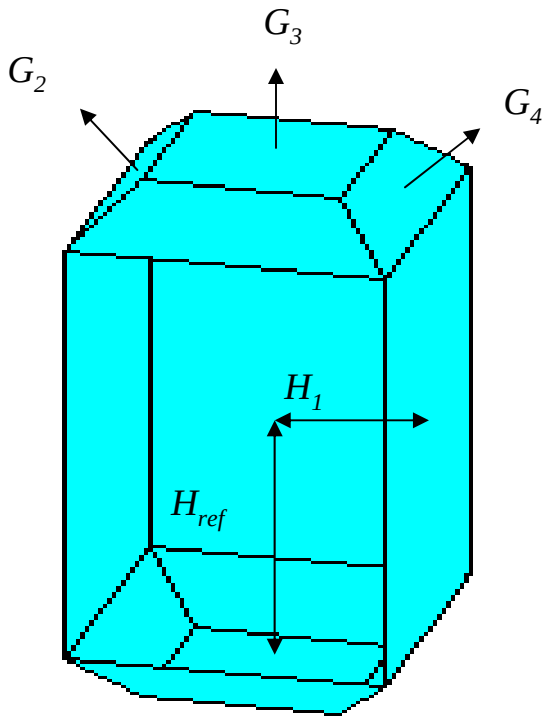
Solid State and Solvent Effects

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

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

Shape Evolution Model



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

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

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

eigenvalues = -1

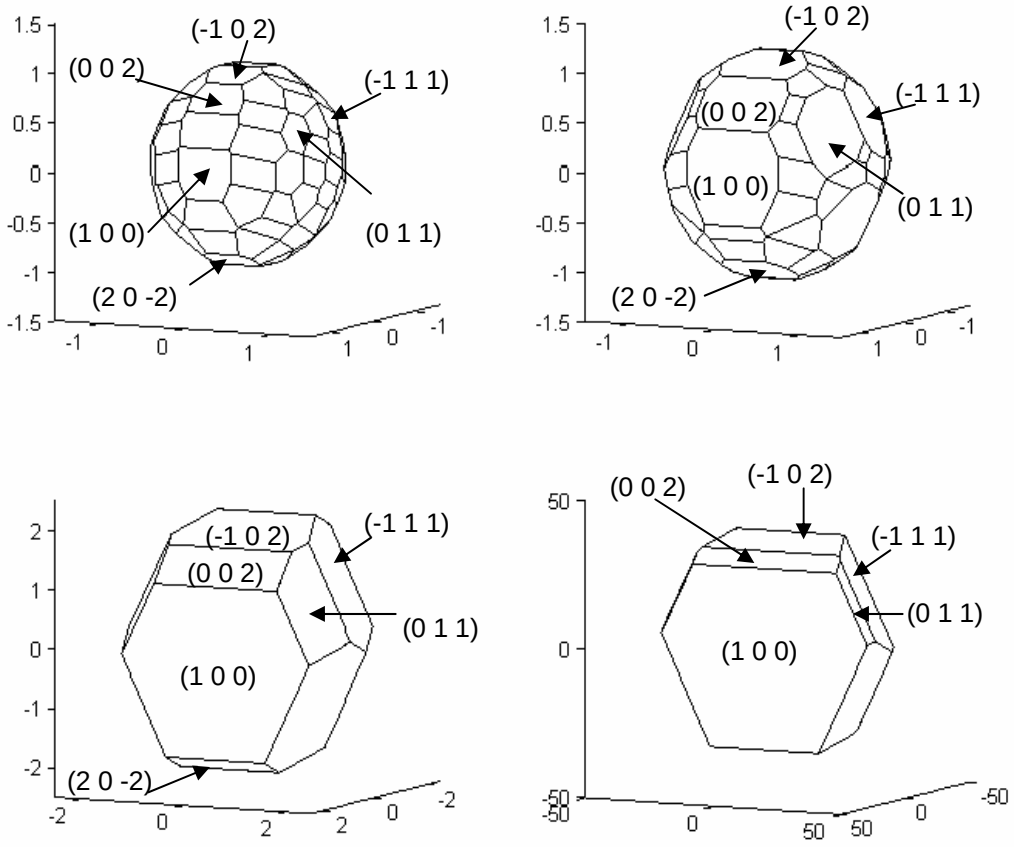
Stable Steady State

$$R_i - x_i = 0$$

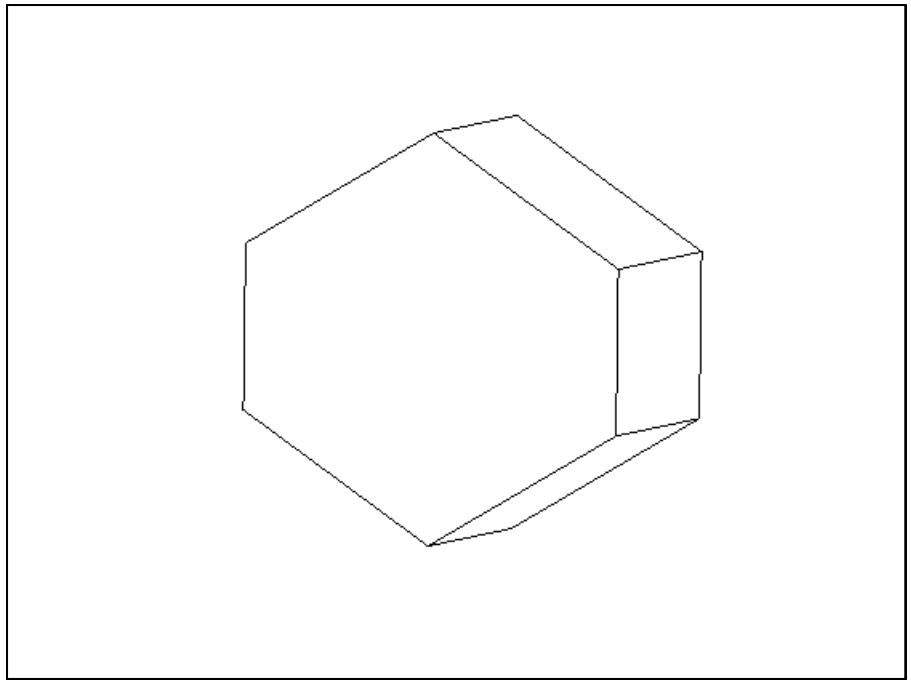
Unique Steady State

Zhang, Sizemore and Doherty, "Shape Evolution of 3-Dimensional Faceted Crystals," *AIChEJ, 52*, 1906 (2006)

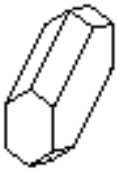
3-D Shape Evolution: Adipic Acid



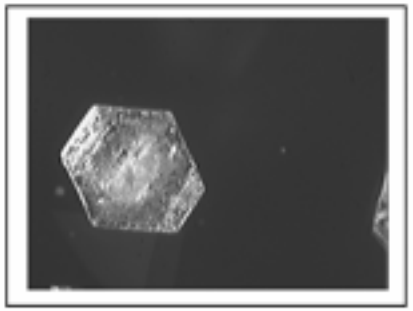
Shape Evolution from Equilibrium-Shaped Seed



Seed Shape:



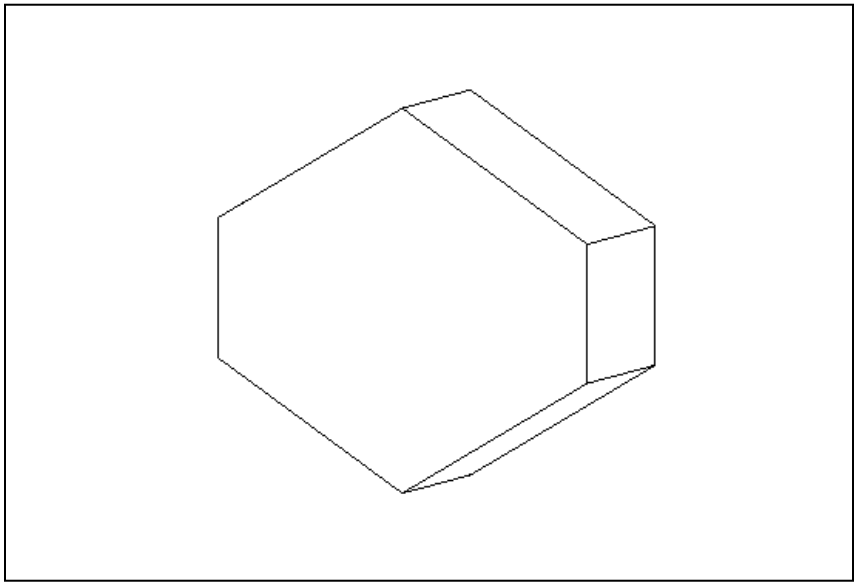
Experiment:



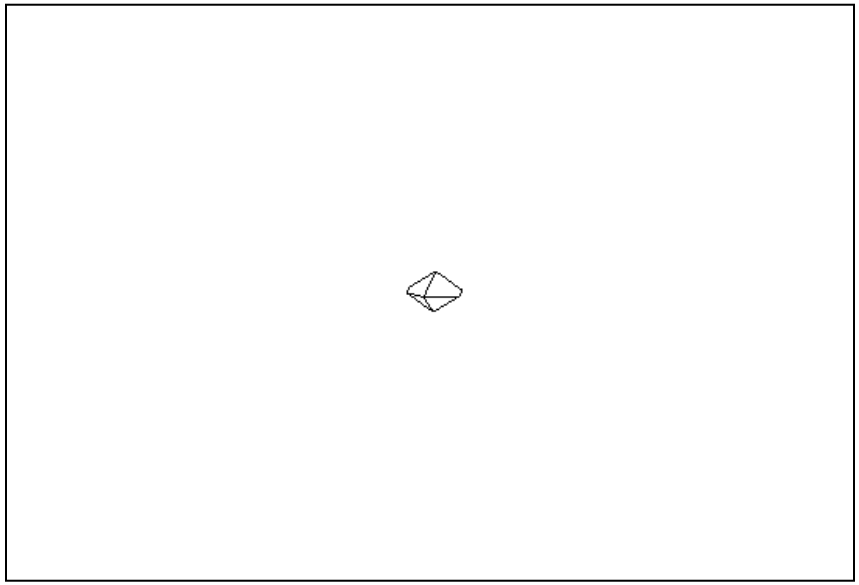
- Evolution of a succinic acid crystal grown out of water from a seed (here chosen as the equilibrium shape) to its steady state shape.

Succinic Acid in Water

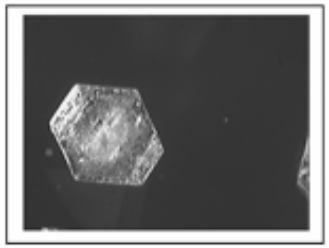
Growth



Dissolution



Growth Seed



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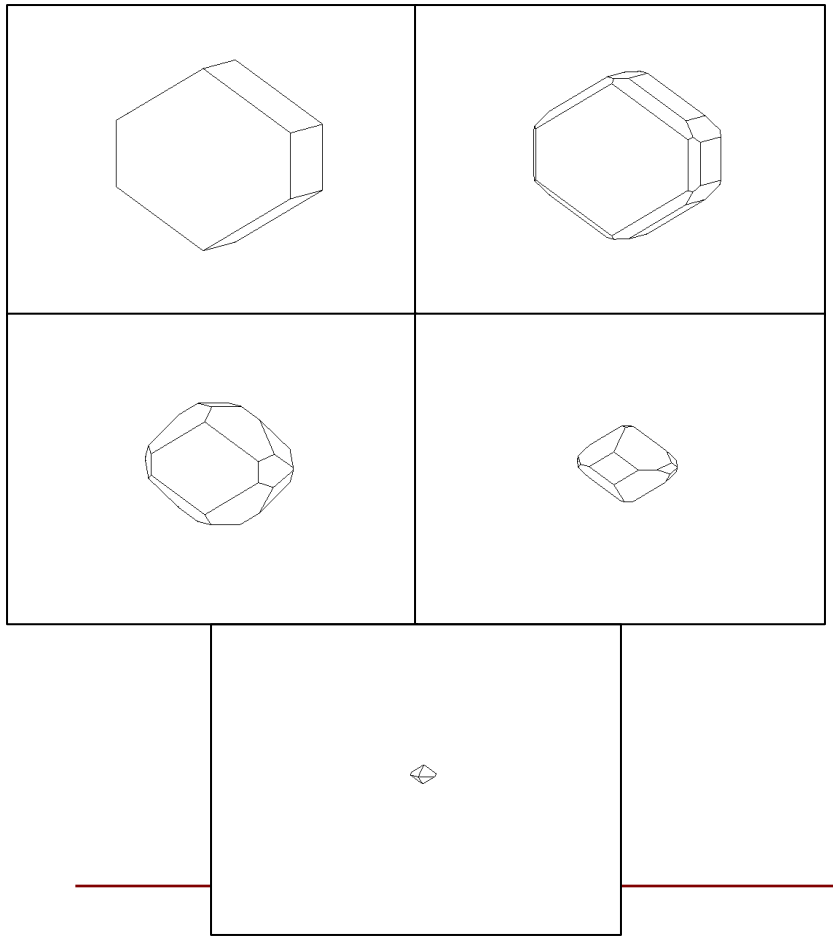
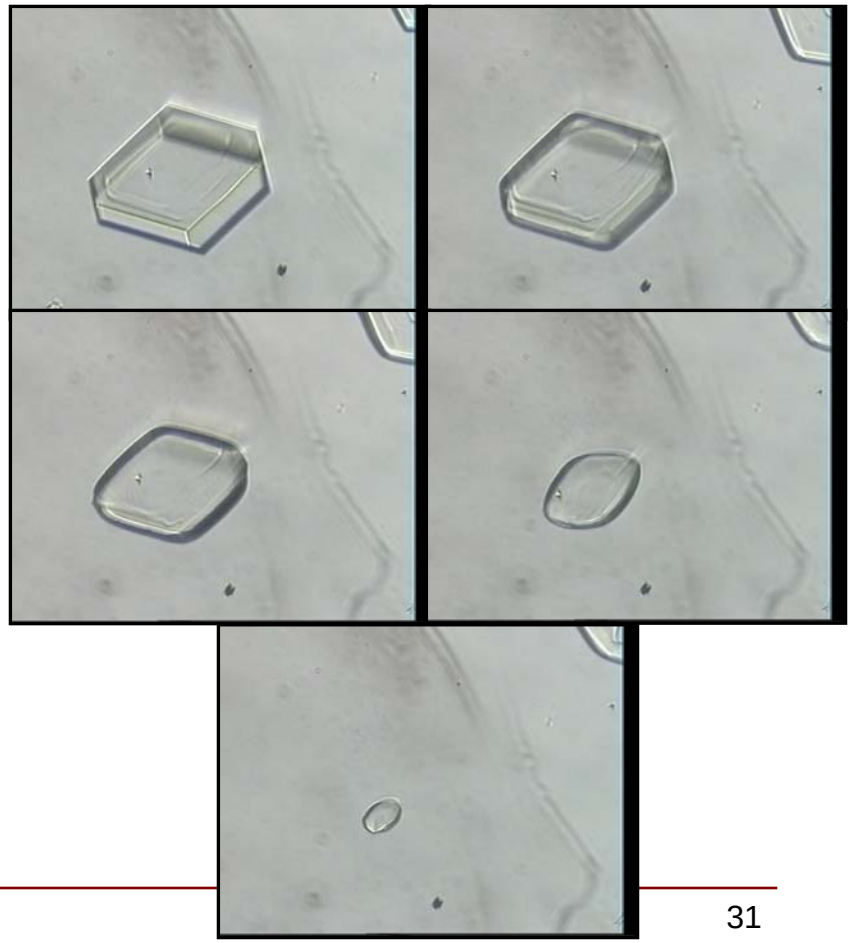
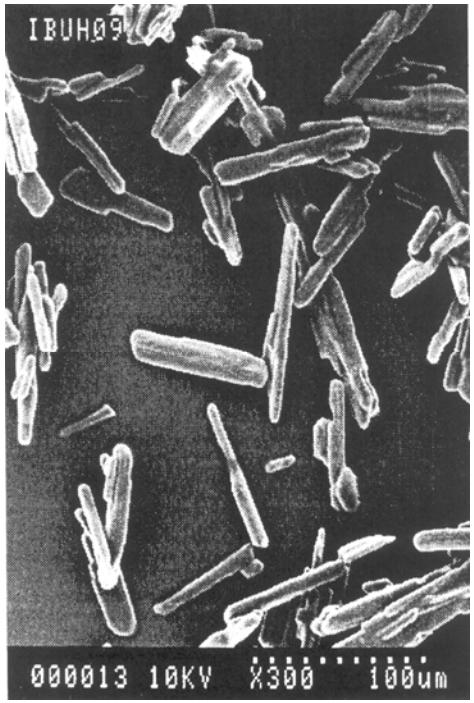
Dissolution Dynamics



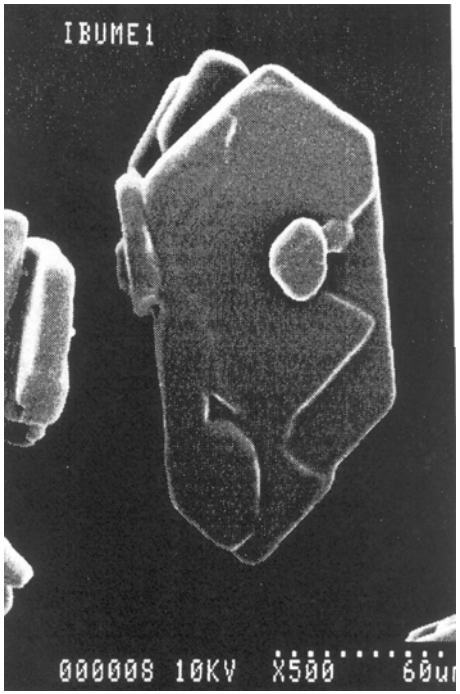


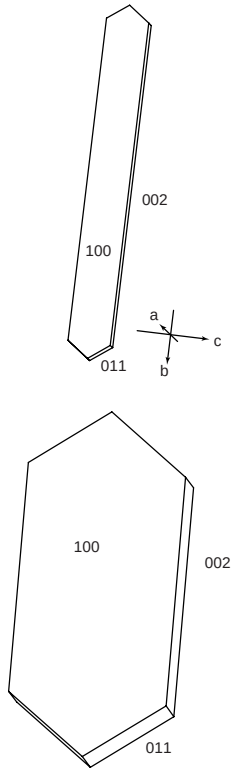
Application - Ibuprofen



Storey & York (1997)
Ibuprofen grown from hexane

Storey & York (1997)
Ibuprofen grown from methanol

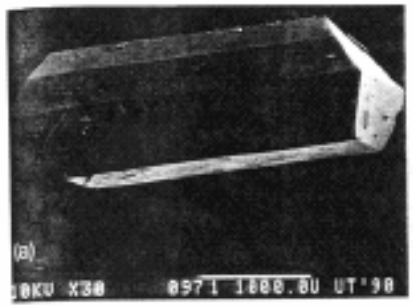




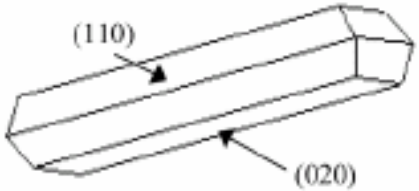
Predicted – ibuprofen grown
from hexane (top) and methanol (bottom)

Application – alpha glycine

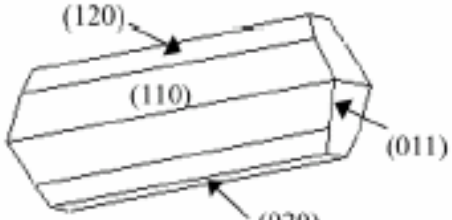
alpha-glycine grown from aqueous solution



(a)



(b)



(c)

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

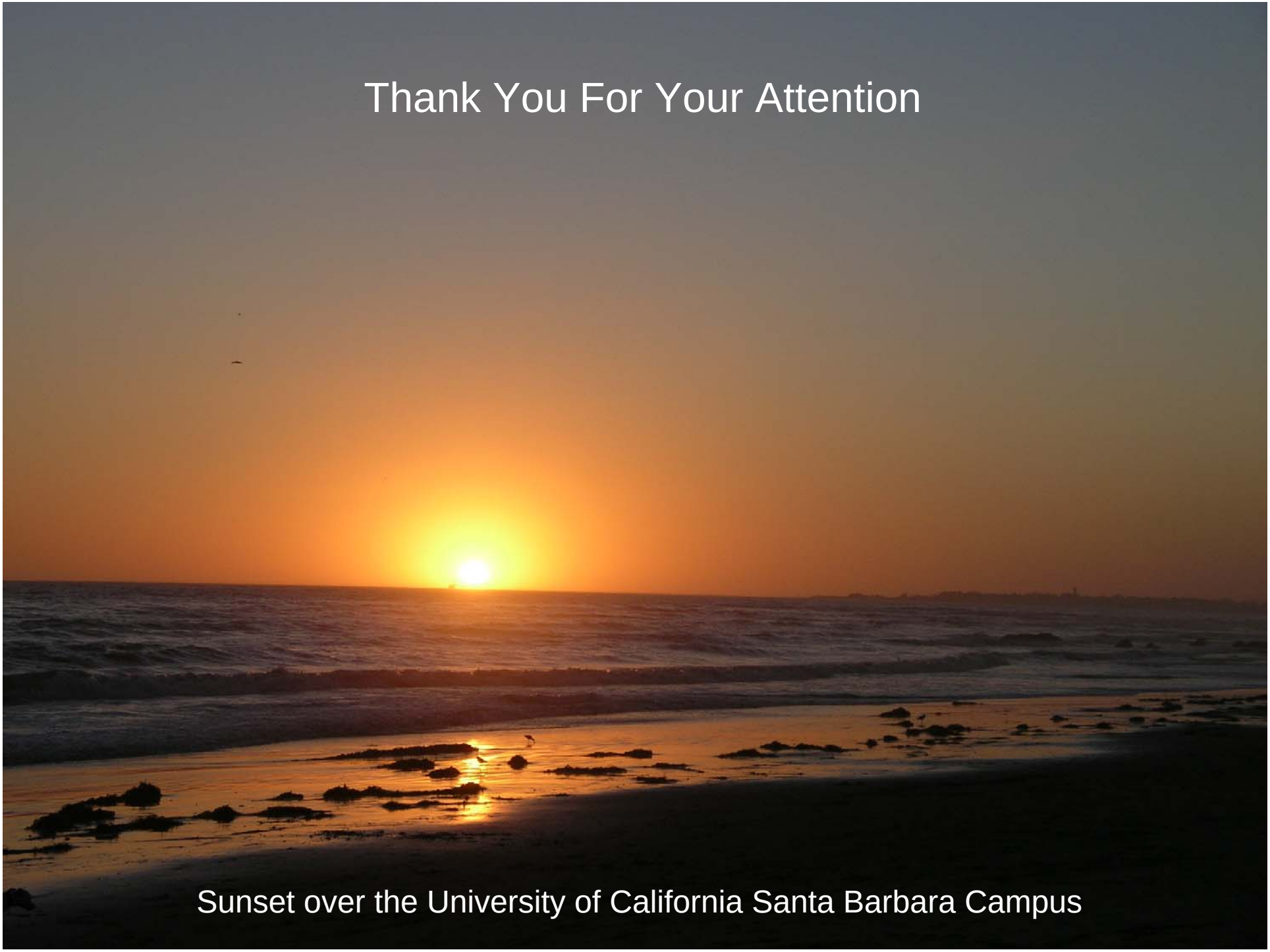
Prediction – Bisker-Leib & Doherty, *Crystal Growth Des*., (2003)

(b) dimer growth unit

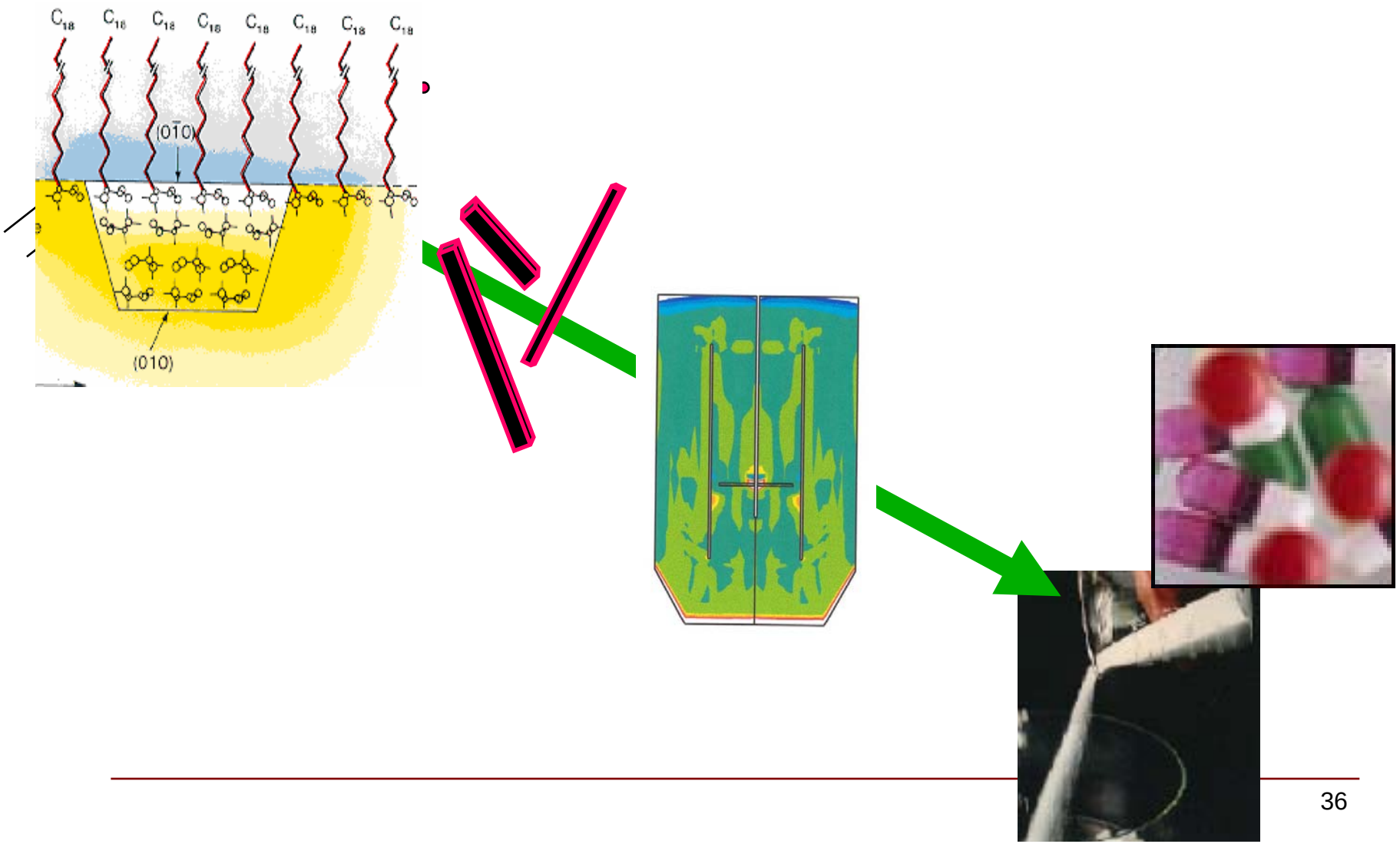
(c) monomer growth unit

Opportunities

- Improving the model
  - Complex bond chains, growth units, kinks – **pharma molecules**
  - Critical edge length – thermodynamic or kinetic?
  - Supersaturation-dependent **relative velocities**
- 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
- Process models & process systems engineering
- Experiments
  - on surfaces for growth model validation
  - for polymorph selection
  - growth units & precursors


Thank You For Your Attention
Sunset over the University of California Santa Barbara Campus

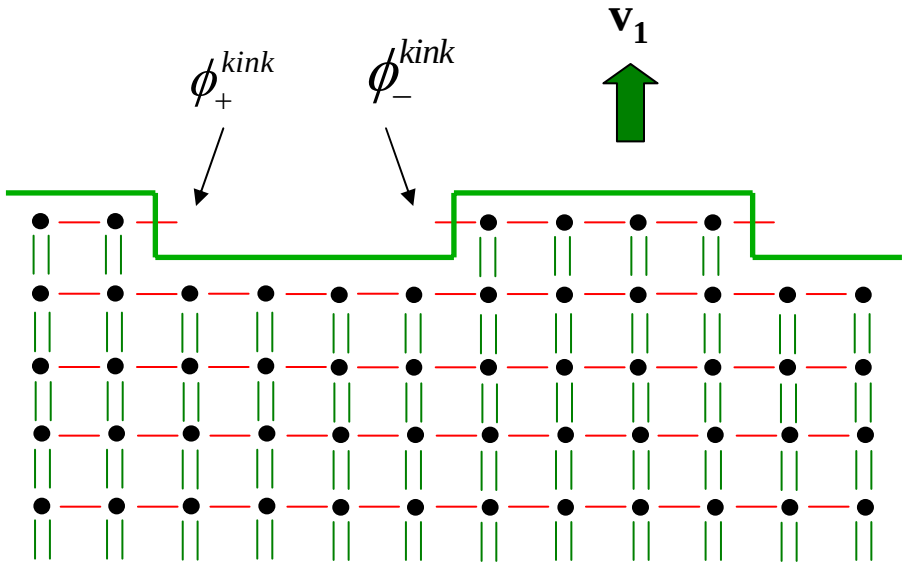
Molecules to Products



Distribution of Kinks

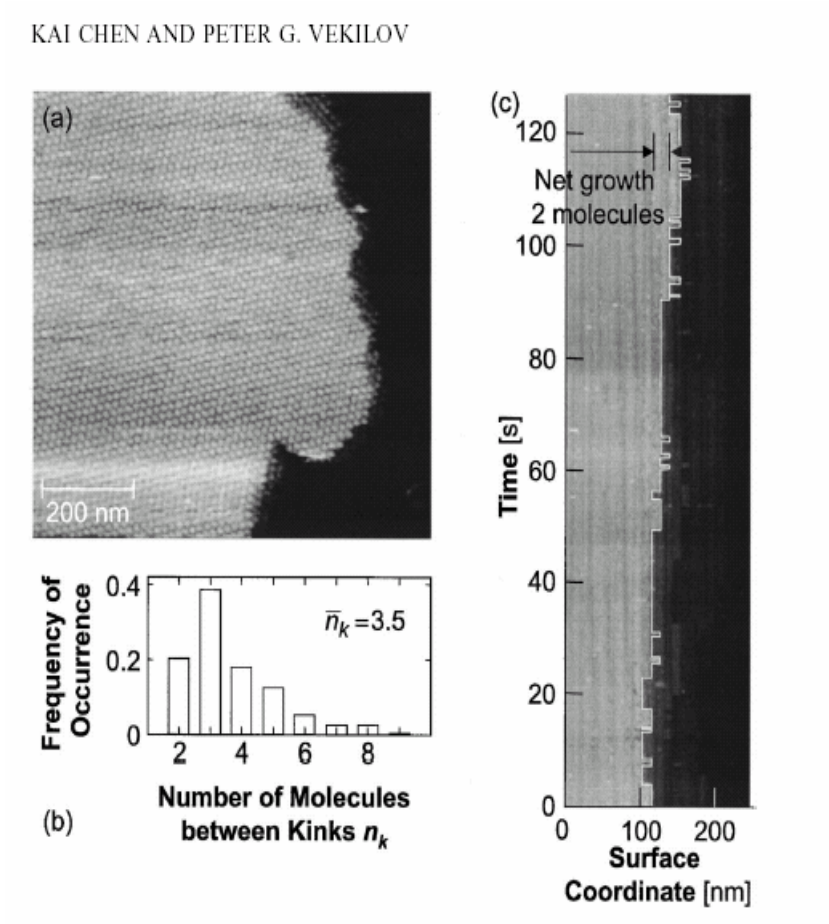
$$p_+ = \frac{e^{-\phi_+^{kink}/kT}}{Q} \qquad p_- = \frac{e^{-\phi_-^{kink}/kT}}{Q} \qquad p_{overall} = p_+ + p_-$$

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



- 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



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)

- Faceted surfaces – new model (ODE's)

  Zhang, Sizemore and Doherty, "Shape Evolution of 3-Dimensional Faceted Crystals," *AIChEJ, 52*, 1906 (2006)