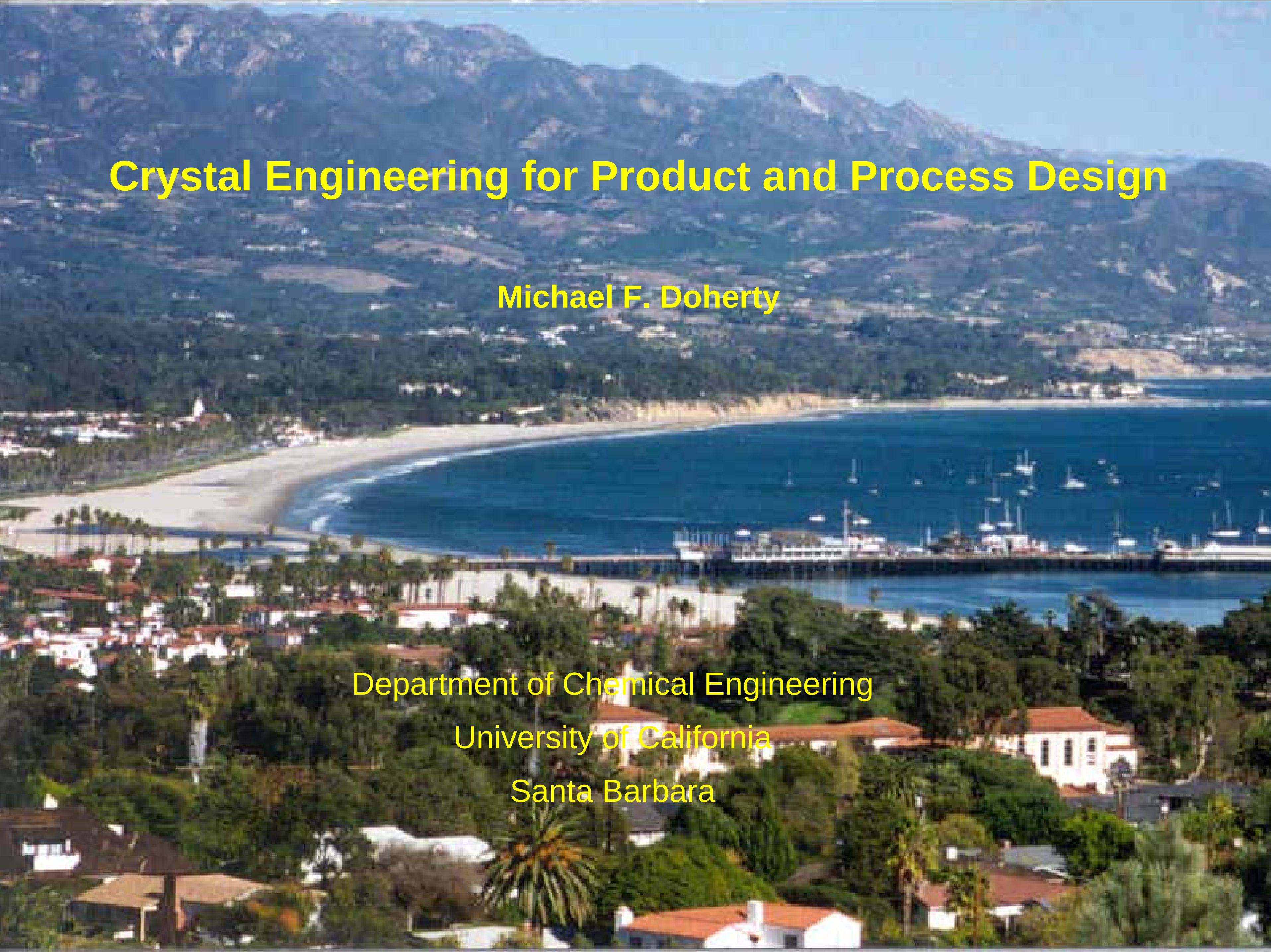

Crystal Engineering for Product and Process Design

Michael F. Doherty

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University of California

Santa Barbara

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 21^{st} century."

Jim Trainham, DuPont

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

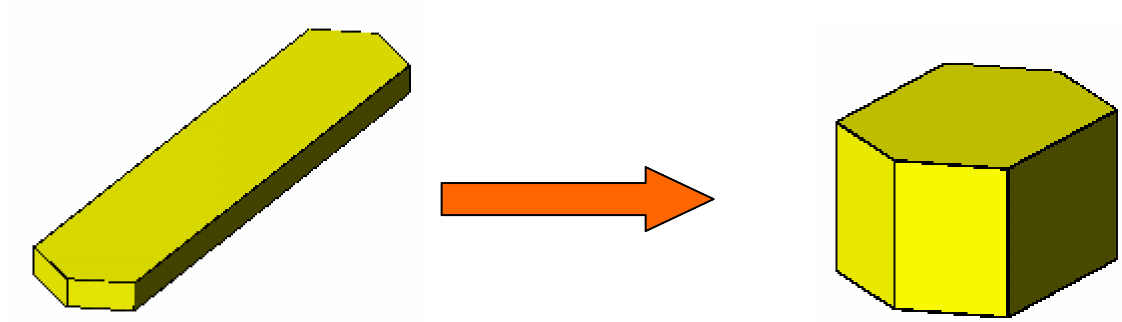
Main Points for Today's Lecture

- Crystals grow in many different shapes
- Shape is an important product quality characteristic (usually want to avoid needles and flat plates, although Ed Cussler wants to make flakes!)
- Often, the desired shapes cannot be obtained during growth
- Better understanding of the mechanisms for growth and for dissolution lead to novel technology for product and process design of crystal shape

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**

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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

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

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

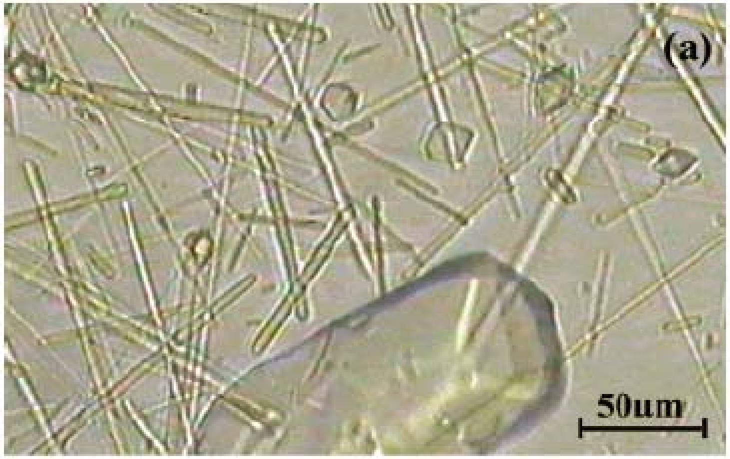
Primary Examiner—Arthur C. Prescott

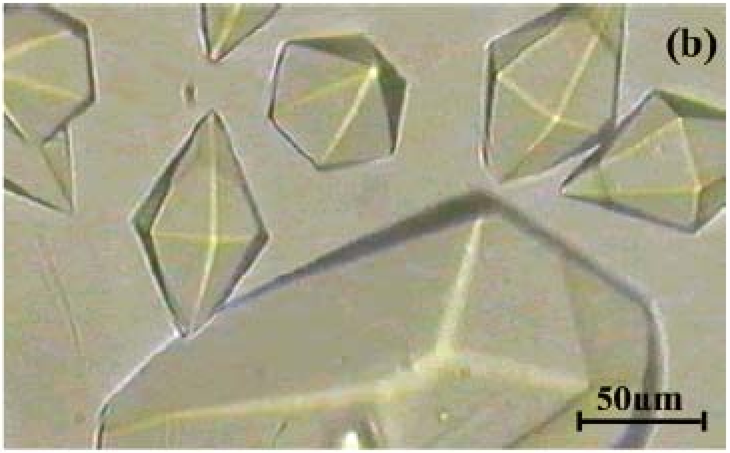
[57] **ABSTRACT**

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

Some Compounds Exist in Multiple Shapes – Different Polymorphs of BPTI





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)

Shape Evolution Models

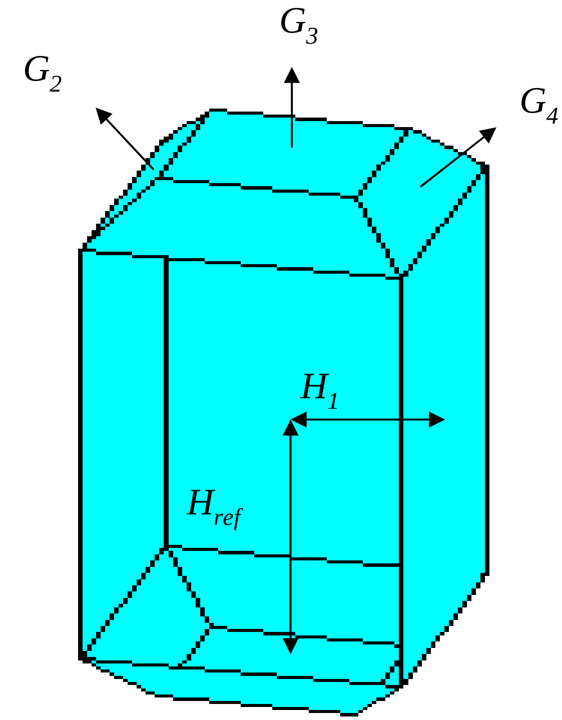
- Curved surfaces – Hamilton-Jacobi equation (PDE)
  - Most general case – involves shocks to model facets
  - Complete mathematical treatment by Lighthill & Whitham, “On Kinematic Waves I & 2,” *Proc. Roy. Soc., 229*, 281 & 317 (1955)

- Faceted surfaces – new models (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*, 1337 (2007)
  - Snyder, Studener and Doherty, “Manipulation of Crystal Shape by Cycles of Growth and Dissolution,” *AIChEJ, 53*, 1510 (2007)

Ingredients for the Model

- Shape evolution model for faceted crystals
  - applies to both growth and dissolution
- Identify the list of candidate planes on the crystal surface
  - growth (easy), dissolution (harder)
- Test to determine which planes are **real** and which are **virtual** at each moment of time
- Select a relative growth rate mechanism
- Test the model against experiments
- Use the model to develop new technology

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)

$$R_i - x_i = 0$$

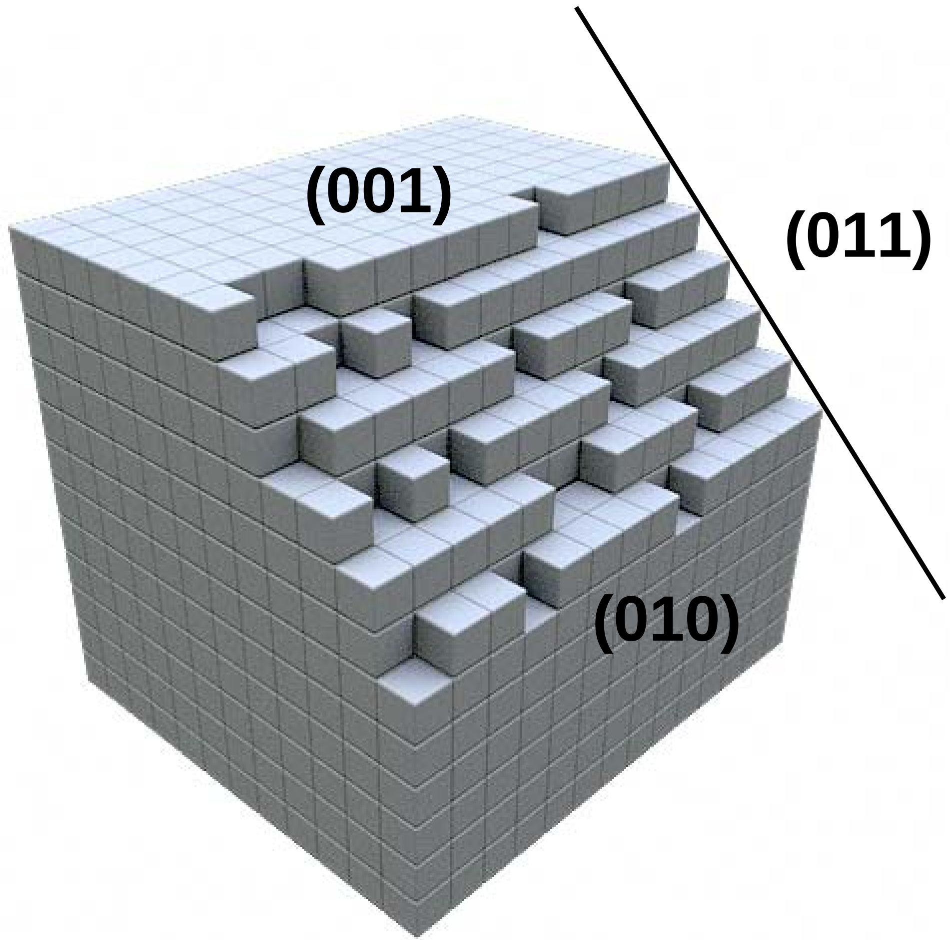
Unique Steady State

(different for growth & dissolution)

Identify List of Candidate Planes

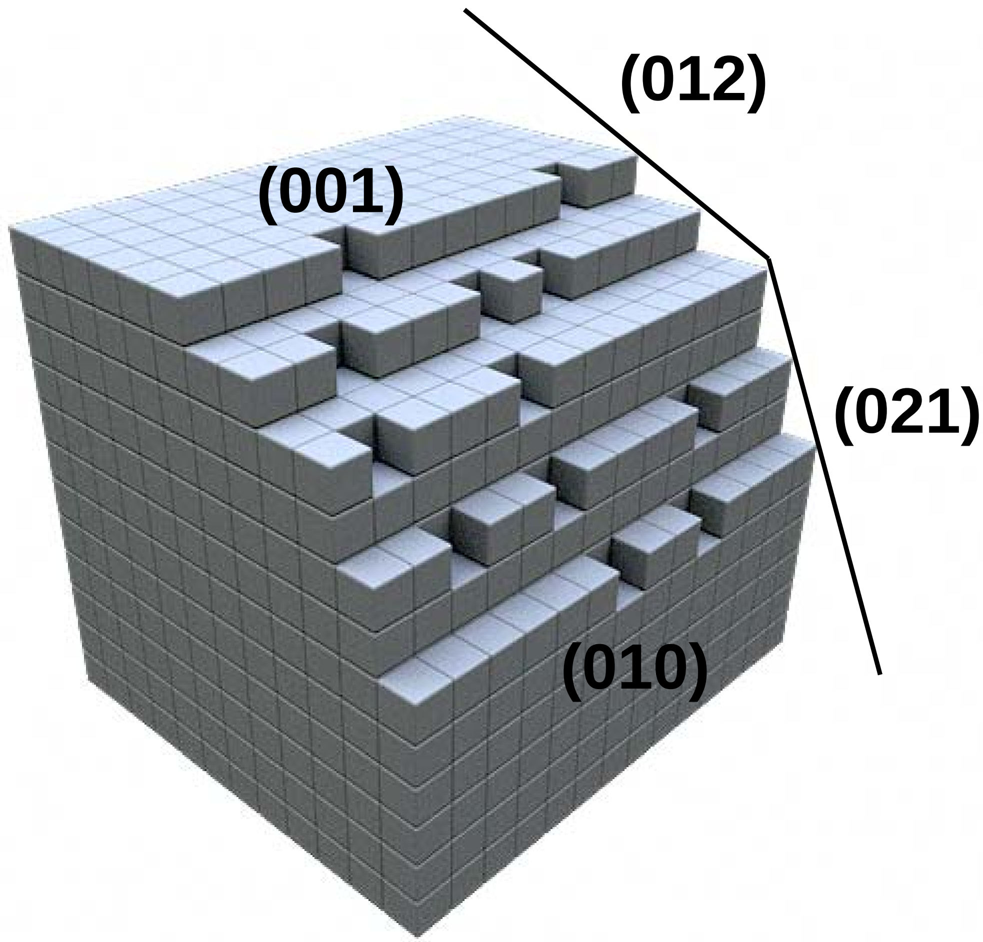
- Growth shape is dominated by SLOW moving faces
  - Include all low index planes in list
- Dissolution shape is dominated by FAST moving faces
  - Higher index planes move faster – need to identify the correct planes and cut off the list (see the papers)
- Selecting the candidate faces is different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

Dissolution at Crystal Edges – 1 PBC



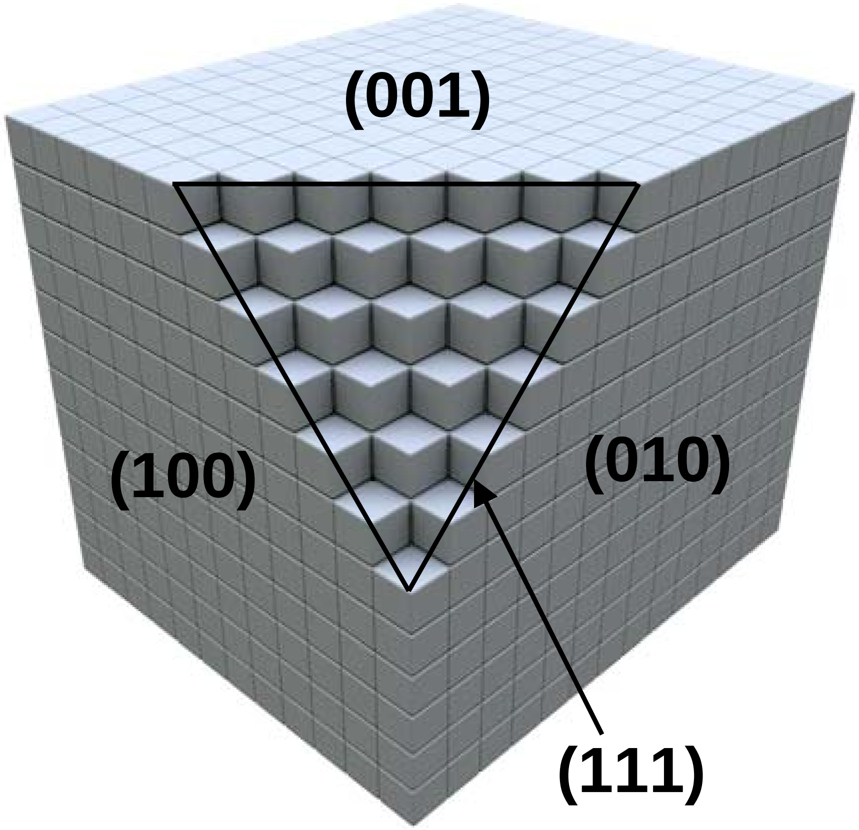
- Faces appear at certain locations in dissolution
  - **Edges**
  - Vertices

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**

Relative Growth & Dissolution Rates

- Experime
  - e.g., th … cetamol crystal

    Shekun… ic Studies of the Growth … phen). I. Growth Kinetics,
- Semi-Me
  - BFDH
  - AE mo
- Mechanis
  - Spiral growth model (BCF, Chernov)

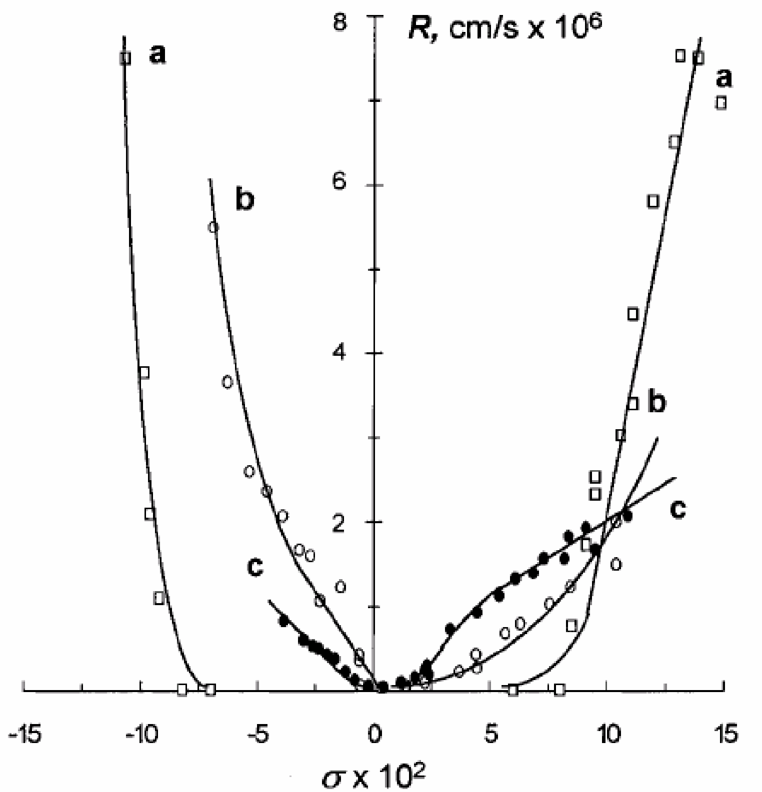
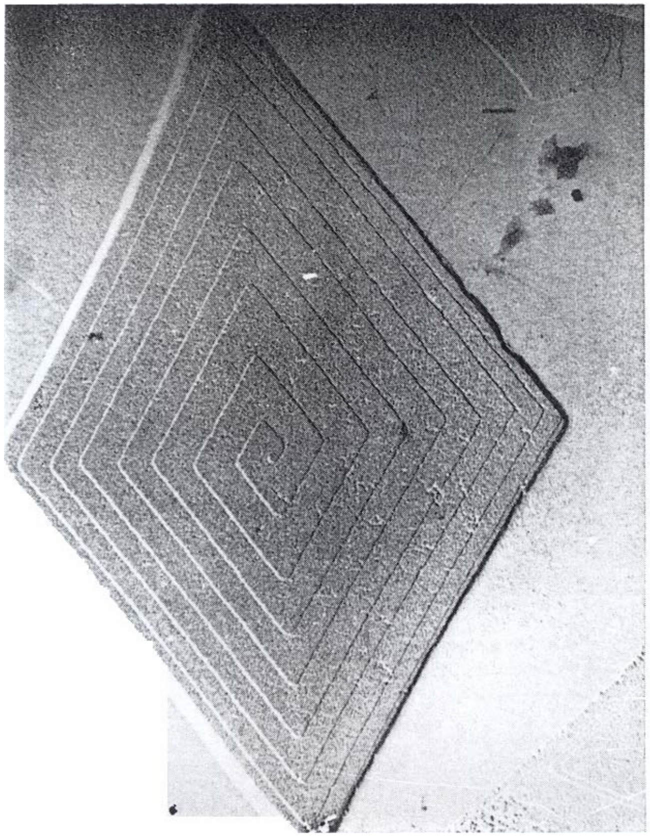


Figure 6. Dependence of normal growth rate R on supersaturation σ for the following faces: (a, □) {110}; (b, ○) {$20\bar{1}$}; (c, ●) {001}.

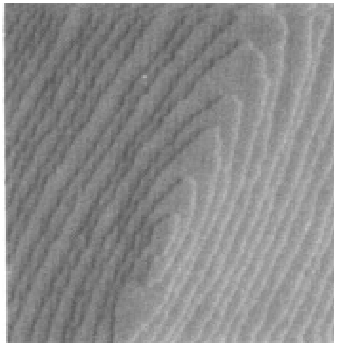
Crystal Growth Models

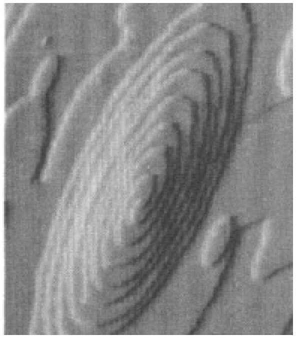
- Crystals grow by the flow of steps across the faces
- Sources of steps
  - 2-D nuclei - birth and spread model
  - spirals growing from screw dislocations
- Sources of edges – strong bond chains (PBC's)
- Sources of docking points for solute incorporation – kinks on edges (missing molecules along bond chains)
- Assume kinks are Boltzmann distributed
- We assume that solute integration at kink sites is rate limiting – fast diffusion

Spiral Growth of Organic Crystals

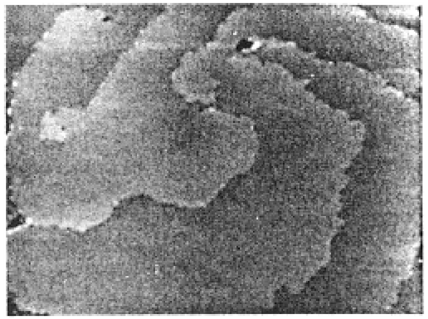


First electron micrographs of spirals: long chain paraffin n-hexatriacontane, $C_{36}H_{74}$ x 16000 (Dawson and Vand, *Proc. Roy. Soc.*, 1951)



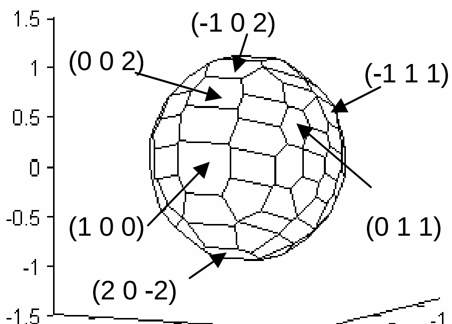


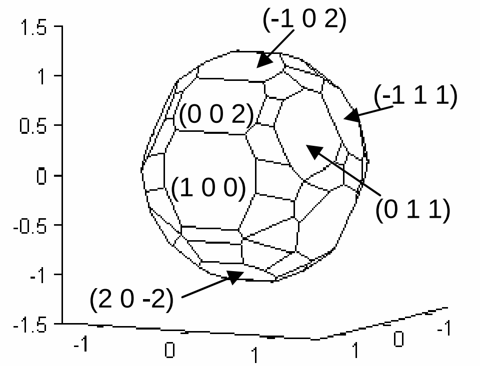
AFM images of spiral growth on hen egg white lysozyme surface (Durban, Carlson and Saros, *J. Phys. D: Appl. Phys.*, 1993)

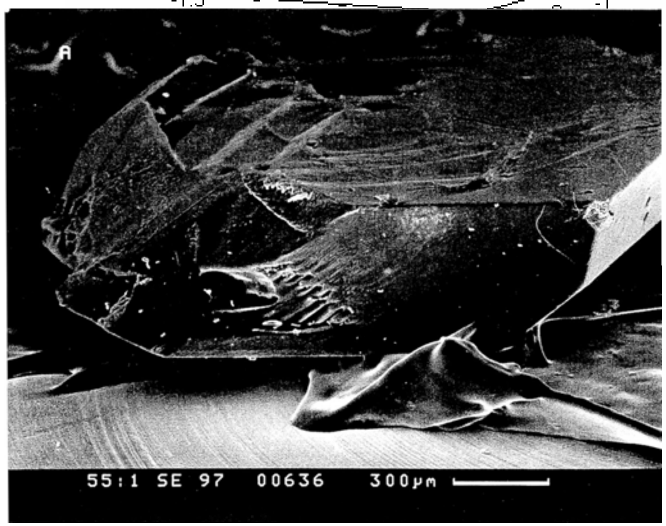


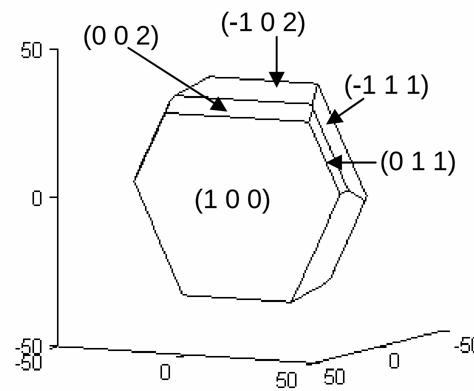
AFM image of spiral growth on a 50μm canavalin protein surface (Land et al., *Phys. Rev. Lett.*, 1996)

3-D Shape Evolution: Adipic Acid



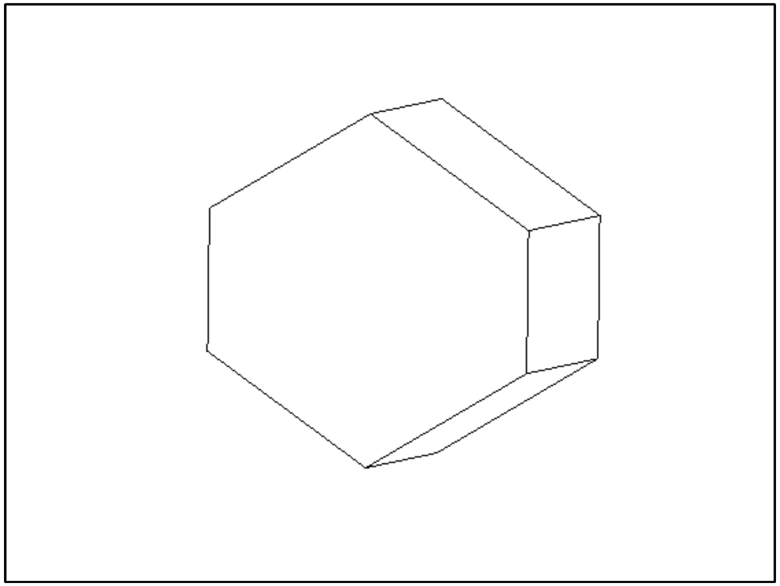


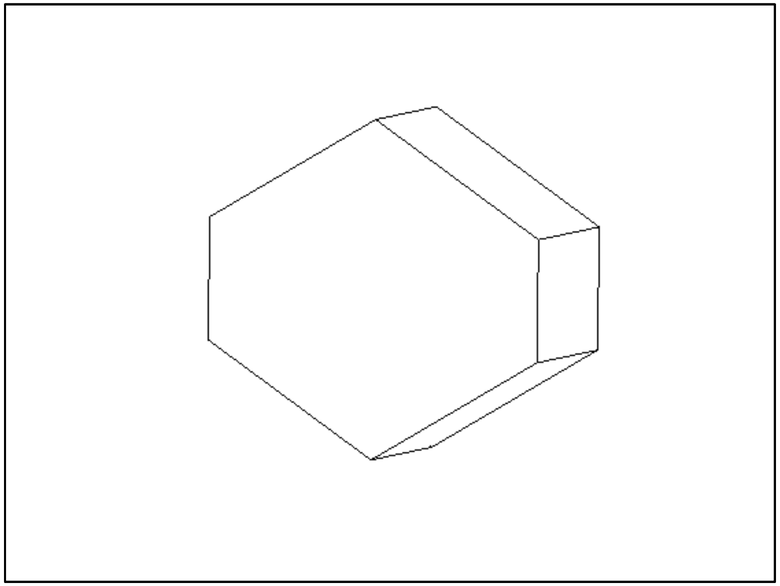




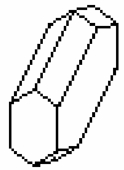
Succinic Acid - Growth in Water from Two Different Seeds

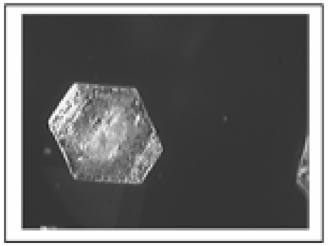
Equilibrium-shaped seed



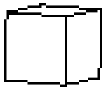


Seed 1:



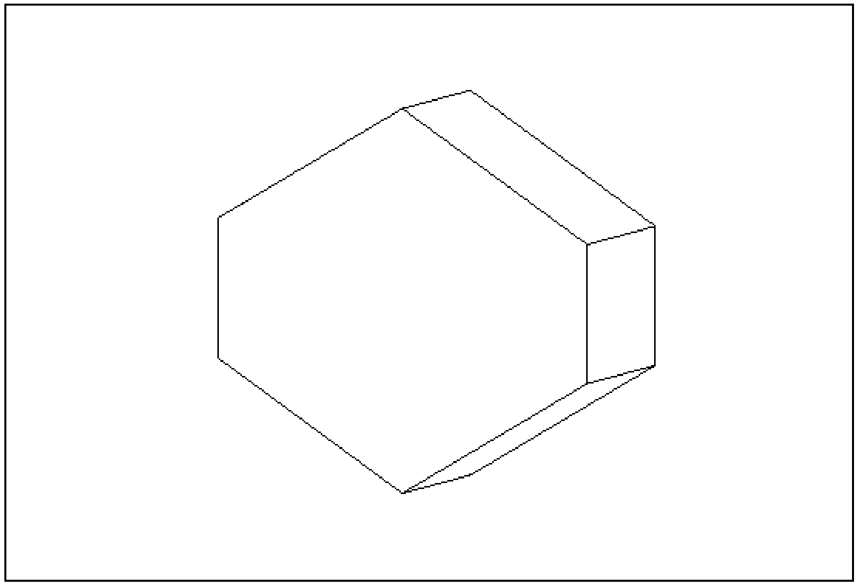


Seed 2:

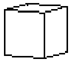


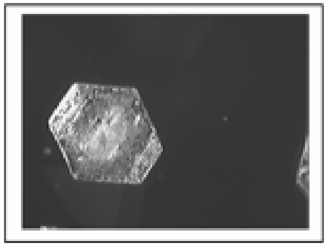
Succinic Acid in Water

Growth

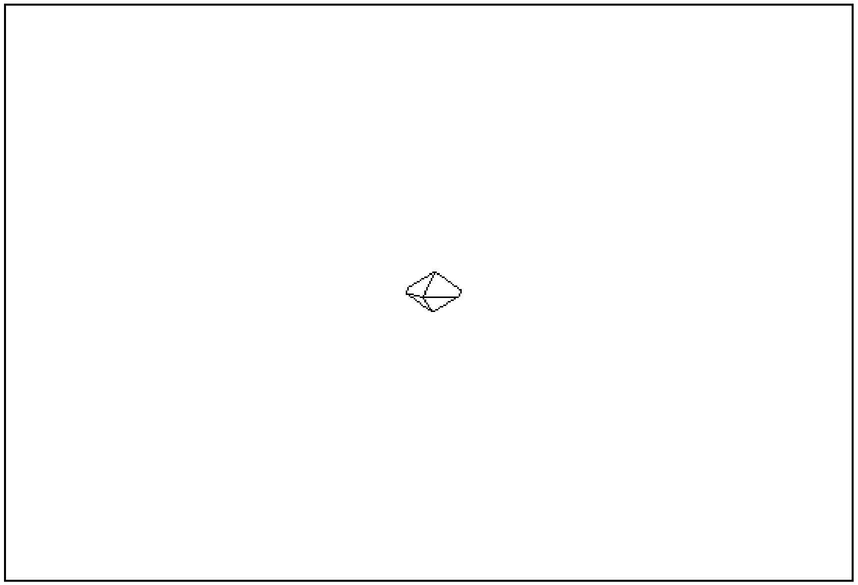


Growth Seed

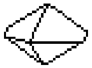




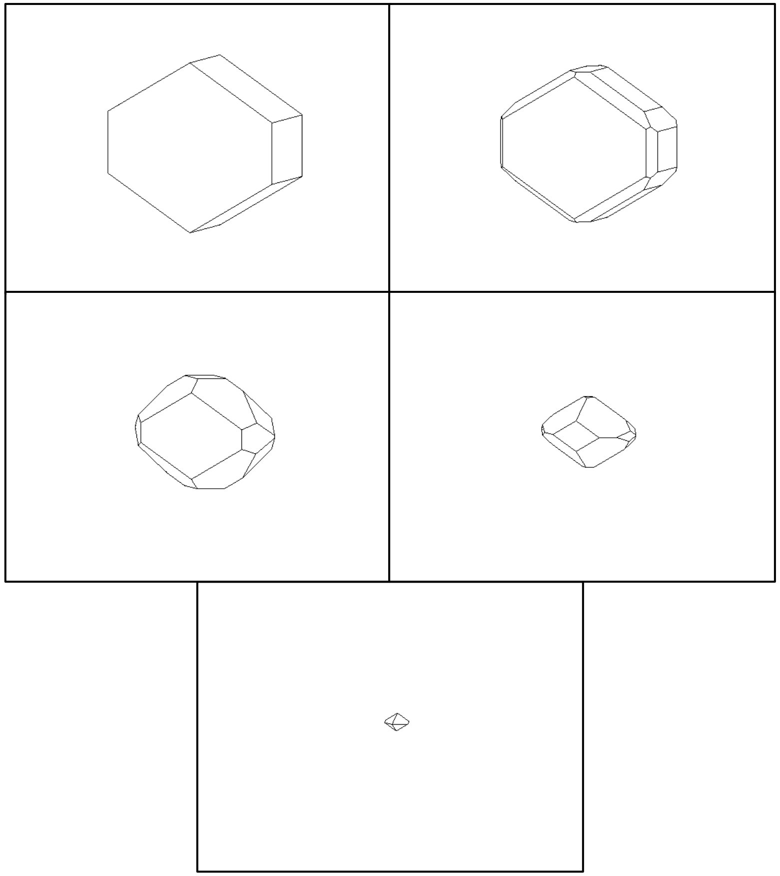
Dissolution

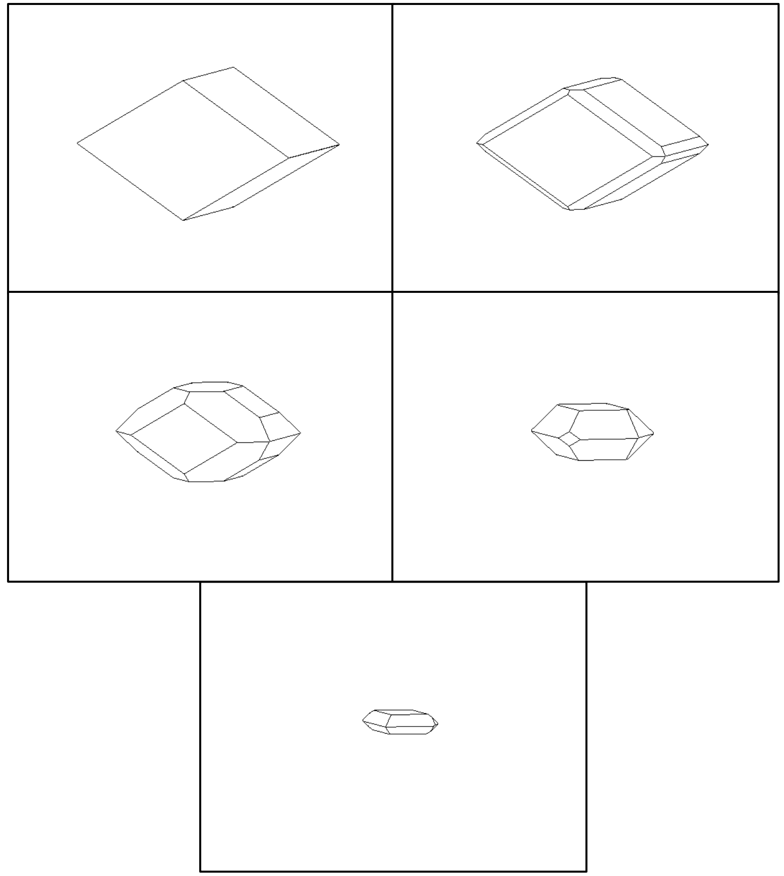


Confirmed by video microscopy



Dissolution of Succinic Acid in Water: Similar Initial Condition but Different End Shape





Dissolution is not the Reverse of Growth

- While dissolution and growth occur via similar mechanisms, the resulting crystal shapes are dramatically different

  - Seed $\xrightarrow{\text{Grow}}$ Growth Shape $\not\xrightarrow{\text{Dissolve}}$ Same Seed

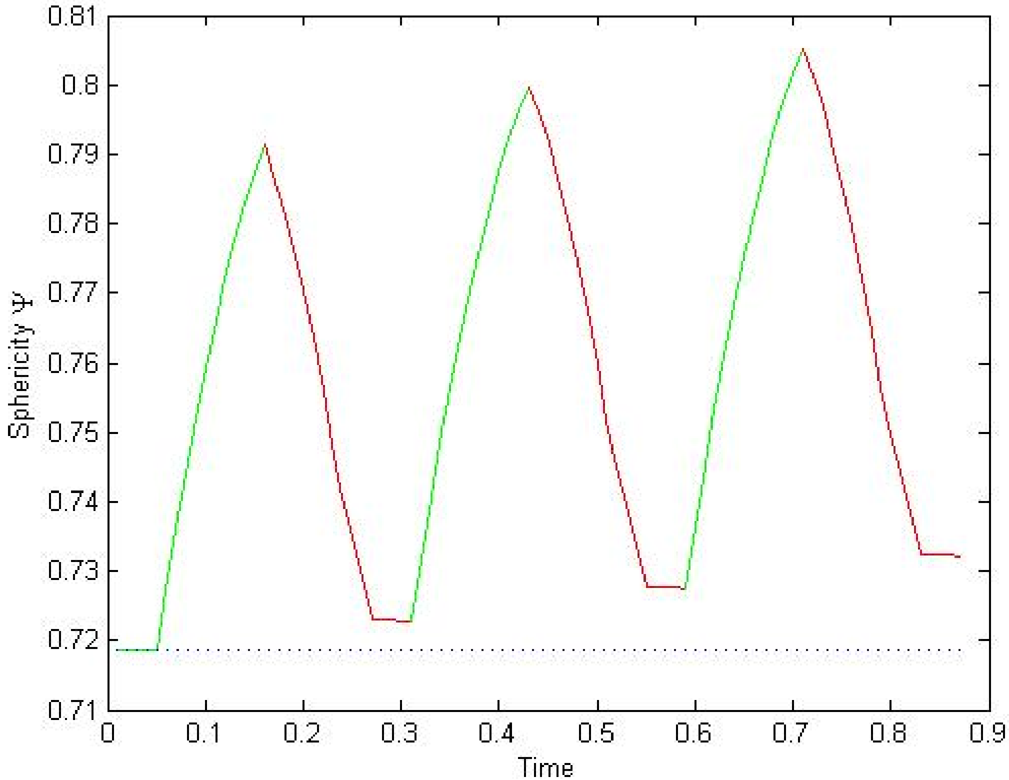
- Final growth shape is independent of the seed
  - Moving towards the steady state of the system

- Final dissolution shape depends on the seed
  - Moving away from the steady state of the system

Changes in Morphology by Growth and Dissolution Cycles

Cycling without disappearance of faces and dissolving 20 % of the material during each period of dissolution…

Notice – sphericity is increasing with cycles - implies shape is changing



(010) and (0-10) Faces: R_G=3.0; R_D=6.0

Green = Growth
Red = Dissolution

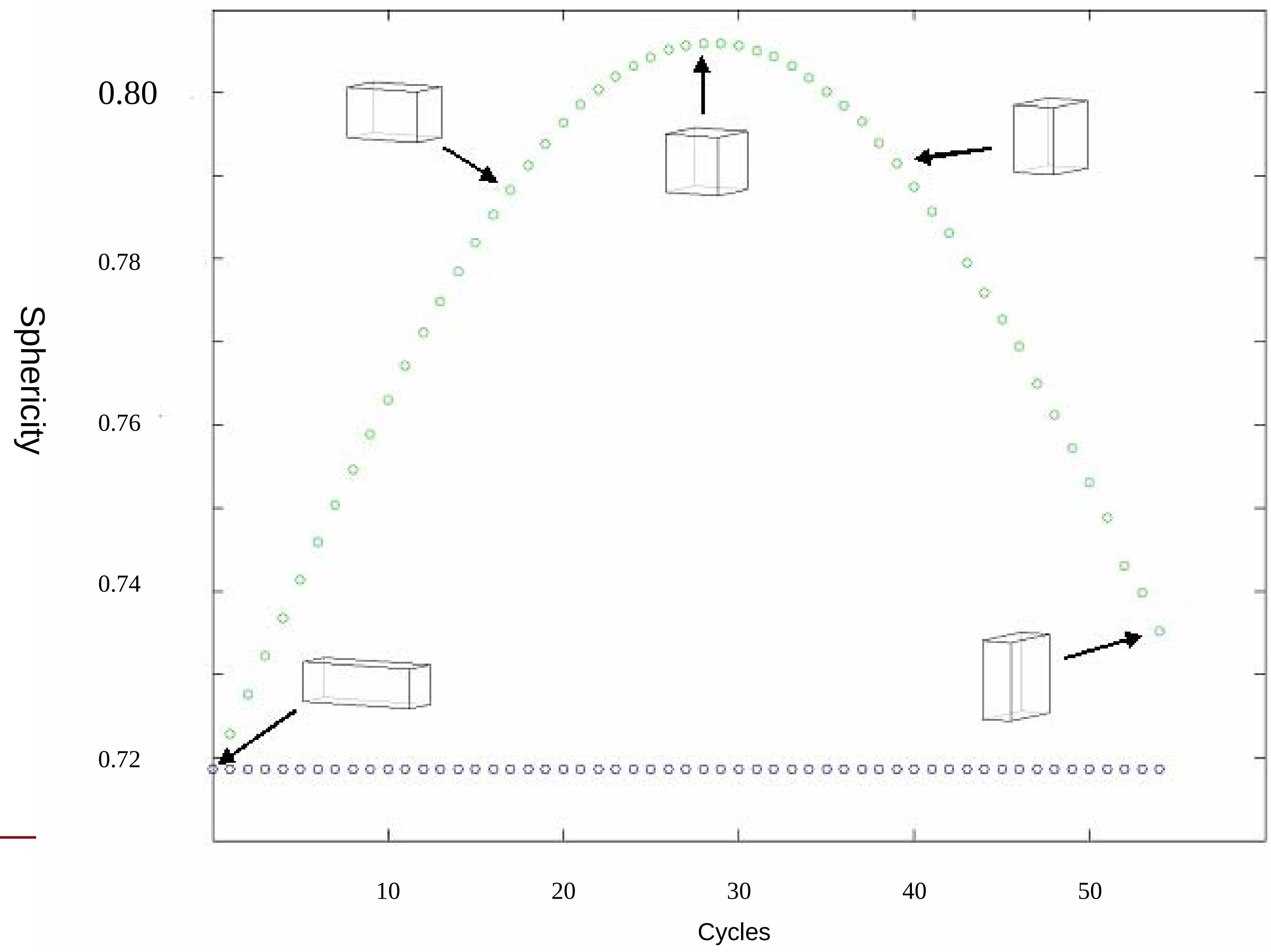
Quantifying Changes in Crystal Morphology

Sphericity is a useful **scalar** quantity to grasp the extent of change made to the crystal morphology after a cycle of growth and dissolution

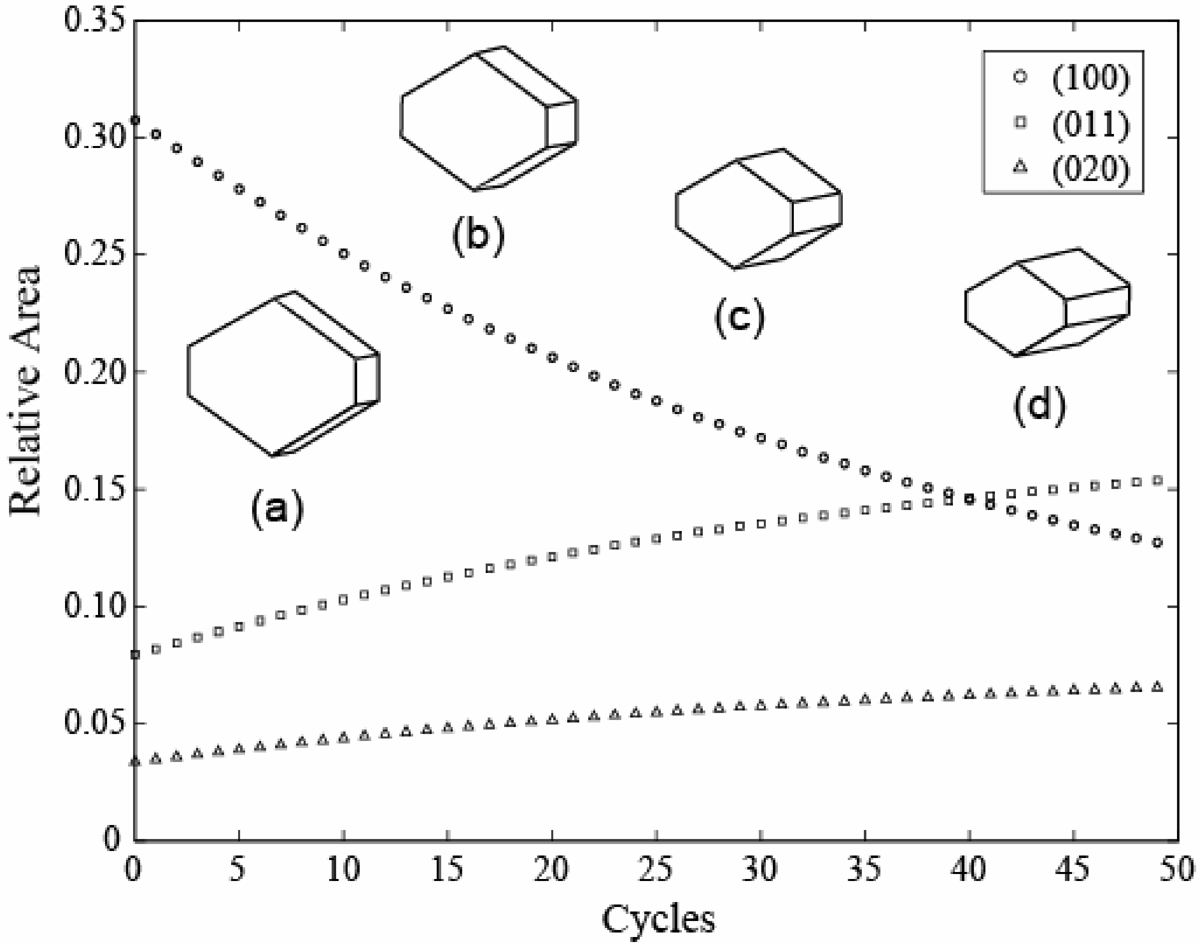
$$\psi = \frac{\text{Surface area of a sphere having the same volume as the crystal}}{\text{Surface area of the crystal}}$$

$$0 < \psi < 1$$

Morphology Manipulation by Cycling Temperature



Process Cycling for Succinic Acid



Cycle

(a) 0th

(b) 11th

(c) 31st

(d) 49th

Next Steps

- Modeling
  - embed the shape evolution model in process models (population balances, mass and energy balances, CFD, batch and/or MSMPR crystallizers, etc)
- Experiments
  - perform cycling experiments in the lab on real crystals and compare with predictions
- Process technology
  - how to design new equipment to obtain multiple cycles in a simple and fast manner?

Sunset over the University of California Santa Barbara Campus