Crystal Morphology: Measurement, Modelling and Closed-loop Control

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Crystal Shape

Of critical importance to the end-use properties of the final product e.g. bioavailability

Affects downstream processing filtration, grinding, solid/liquid separations

Dictates other properties e.g. particle size
Observation on Modelling

Crystal morphology prediction only for single crystals: HABIT, Cerius²...

Gap: single crystal morphology – crystal population in a reactor

Is there such a thing ‘morphology for crystal population in a reactor?'
Observation on **Modelling**


PB Modelling: Evolution of Crystal Size Distribution with Time

PB modelling is **Process Scale Modelling**, Useful for Process Design, Optimisation and Control

Size Definition: Diameter of a Sphere Having the Same Volume as the Crystal

Shape distribution?
Observation on **Measurement**

XRD, FTIR, Acoustic Spectroscopy, Raman, FBRM...Providing Little or Limited Shape Information

On-line Imaging: PVM, Perdix, GSK Imaging...

**Image Analysis** as the Bottleneck

Observation on **Morphology Control**

Previous Work: Focused on CSD Control

Closed-loop Control of Shape Distribution: Perceived as too Challenging to Achieve
Objectives

1. “Morphological” PB Modelling the Growth Behaviour of All Crystals in a Reactor; Shape Distribution as well as Size Distribution

2. Demonstrate: Simple Closed-Loop Strategy for Morphology and CSD Control

3. 2D and 3D On-line Characterisation of Morphology of Growing Crystals: Imaging and Image Analysis

4. Future Work
Population Balance Modelling

\[ \frac{\partial n(L,t)}{\partial t} = -G \frac{\partial n(L,t)}{\partial L} \]

- \( n(L,t) \) – the number of crystals of size \( L \) at time \( t \)
- \( G \) – crystal growth rate, m/s

Nucleation and Growth

\[ B = k_b \sigma^\alpha \]
\[ G = k \sigma^\alpha \]

- \( B \) – No. crystals / (m\(^3\)s)
- \( \alpha = \frac{c - C_{sat}}{C_{sat}} \)

Mass and Energy Balances

\[ \frac{dC}{dt} = f(L, G, k, \rho, h) \]
\[ \frac{dT}{dt} = f(L, G, k, \rho, \Delta H, V, U, A, T, T_f) \]
Multi-dimensional (two) PB Modelling

\[
\frac{\partial n(L_L, L_W, t)}{\partial t} + \frac{\partial [G_L n(L_L, L_W, t)]}{\partial L_L} + \frac{\partial [G_W n(L_L, L_W, t)]}{\partial L_W} = 0
\]

\(n(L_L, L_W, t)\) – the number of crystals of length \(L_L\), width \(L_W\), at time \(t\)

\(G_L, G_W\) – crystal growth rates of length and width, m/s

Plate crystals: length \(L\), Width \(W\), thickness 0
Morphological PB Modelling

Size definition of a face: distance from geometric centre

Assumption: symmetrical faces have identical growth behaviour

Potash alum crystal

26 faces:
- 8 \{111\}
- 6 \{100\}
- 12 \{110\}

Three independent faces
- x, y, z
Morphological PB Modelling

\[
\frac{\partial \psi(\bar{x}, \bar{y}, t)}{\partial t} + \nabla \cdot \left[ \psi(\bar{x}, \bar{y}, t) \bar{v} \right] + \sum_{i=1}^{N} \frac{\partial}{\partial x_i} \left[ \psi(\bar{x}, \bar{y}, t) G_i(\bar{x}, \bar{y}, t) \right] = B(\bar{x}, \bar{y}, t) - D(\bar{x}, \bar{y}, t) + R(\bar{x}, \bar{y}, t)
\]

Only Growth

\[
\frac{1}{V_T(t)} \frac{\partial [\psi(\bar{x}, t)V_T(t) \bar{v}]}{\partial t} + \sum_{i=1}^{N} \frac{\partial}{\partial x_i} \left[ \psi(\bar{x}, t) G_i(\bar{x}, t) \right] = R(\bar{x}, t)
\]
Comparisons of crystal shape evolution: Magenta – without GRD  Black – with GRD for growth rates of faces \{100\} and \{110\}

*AIChE J. 54(9), 2321-2334(2008)*
Evolution of individual face \{100\}

- $x \rightarrow \{111\}$
- $y \rightarrow \{110\}$
- $z \rightarrow \{100\}$

Evolution of face 110

- $x \rightarrow \{111\}$
- $y \rightarrow \{110\}$
- $z \rightarrow \{100\}$
Evolution of growth sector boundaries

Magenta, Green - without GRD

Red, Black - with GRD

AIChE J. 54(9), 2321-2334(2008)

*AIChE J.*, 54(9), 2321-2334(2008)
Hot-stage Images

b1, b2 & b3 – 80, 100 & 120s (5°C/min)

c1, c2 & c3 – 200, 240 & 280s (3°C/min)

Predicted Crystal shape (3°C/min) 240s

Qualitative agreement between prediction with GRD and experiment
Shape Optimisation and Control

Simulation

Cooling or Supersaturation Profile; Impurity; Solvents. Parameters

MPB

Crystal Shape and Size Distributions

Optimisation

Optimum Cooling or Supersaturation Profile

MPB

Desired Crystal Shape and Size Distributions
Shape Optimisation and Control

Faceted Growth Rate

\[ G_1 = f_1(\sigma, \text{size}) \]
\[ G_2 = f_2(\sigma, \text{size}) \]
\[ G_3 = f_3(\sigma, \text{size}) \]

Initial Shape Distribution

Target Shape Distribution

Supersaturation Profile Leading to Desired Shape Distribution

Morphological PB Model
Optimisation Algorithm
Shape Optimisation and Control

Optimum T or \( \sigma \) Profile, Leading to Desired Shape and Size Distributions

While Tracking T or \( \sigma \) Profile can be easily achieved by manipulating cooling water flowrate – simple feedback PID closed-loop control
Shape Optimisation and Control
Shape Optimisation and Control

Tracking $T$ or $\sigma$ Profile cannot guarantee the desired shape and size distributions; real-time sensing and predictive control is needed.
- 0.5 L batch reactor

- Camera speed: up to 30 images/s

- Field of view from 105\(\mu\)mX140\(\mu\)m
Challenges to Image Analysis

Original Image  Low threshold  High threshold
A Multi-scale Image Segmentation Method Using Wavelets

- Accuracy
- Robustness
- Speed

Chem Eng Sci 60(4) 1053-1065 (2005)
Morphological closing
Region filling
Morphological opening

Removal of objects with less than 200 pixels & add grey scale
(g) Morphological opening

(h) Segmented objects after removing those with less than 200 pixels

(i) Original grey scale intensity superimposed

*J Process Control, 15(7), 785-797 (2005)*
3-D shape from 2D images: camera model

Shape descriptors

Descriptors

Database retrieval using shape features

AIChe J. 52(6) 2297-2305 (2006)
**StereoVision Imaging**

Stereo DVM cameras

Interface box for control of stereo angles, focus, synchronisation of camera snapshots and light sources, and image recording

PC with software for Image management, analysis, and 3D shape construction

Crystal growth cell (temperature controlled)

Stereo angle ($\theta$)

Camera head

Light source

X-Y stage
Morphology Prediction
Multi-dimensional Population Balance Modelling
Computational Fluid Dynamics

On-line 3D Imaging
Image Analysis
Shape Recognition
Faceted Growth Rates & PB

Model-based Morphology Control

200 Litre Reactor, donated by AstraZeneca
200 Litre Reactor, donated by AstraZeneca
Move to 200 Litre Reactor
On-going and Future Work

1. Use of Impurity / Solvent for Shape and CSD Control

Seeded crystallization producing β form L-glutamic acid, L-phenylalanine as habit modifying impurity

\[ G_W = (-0.51 + 2.15\sigma - 2.22\sigma^2) \]

\[ G_L = 0.025\beta^{1.4}(1 - 4.9 \times 10^{-9} \times (5.3 \times 10^{27} C_{\text{impurity}}^{3.6})^{1/2}) \]
L-glutamic acid

1,2,3,4,5 --- The evolution of CSD with impurity

I,II,III,IV,V --- The evolution of CSD without impurity

(The effect of impurity is to hinder the faceted growth in L direction)
2. **Future Project:** Formulation of Habit Modifying Impurities / Solvents and Design of Crystal Morphology: Integrating High–throughput Technology with Multi-scale Modelling

![Diagram](image_url)

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