

## Shape – The Final Frontier

Xue Z Wang\*, Caiyun Ma and Kevin J Roberts

*Institute of Particle Science and Engineering, University of Leeds, Leeds LS2 9JT, UK*

### Abstract

Organic crystals grown from solution are known to exhibit multiple morphology and habits which are of great importance to the end use properties of the product such as the bioavailability and down stream processing such as in filtration and drying. The crystal morphology can also dictate other quality measures such as size. This paper reviews recent developments in on-line crystal morphology measurement and control using on-line imaging and image analysis. On-line imaging was found to be able to capture with high fidelity crystal shape and polymorphic transitions in real-time. The images were analyzed using a multi-scale image analysis method to extract the crystals from the image background. Preliminary results on estimating crystal growth rates and kinetics parameters for different facets for rod-like crystals were presented. The paper also reviewed recent developments in morphological population balance (PB) modelling which can provide the evolution of the shape and distributions of sizes in all crystal face directions in a reactor. Finally, the perspectives for automatic morphology control which require integration of crystal morphology prediction, morphological PB modelling, on-line 3D imaging and image analysis for shape characterisation as well as computational fluid dynamics are outlined.

**Keywords:** crystal morphology and shape, imaging, image analysis, population balance

### 1. Introduction

The shape, size and polymorphic forms are properties of great importance to crystalline drug products. It is known that certain crystal morphological forms and habits have been related to difficulties in dissolution rate, process hydrodynamics, solid-liquid separations, drug tableting, storage and handling, or in milling and grinding. Although there has been a large amount of research work on on-line measurement of other quality measures such as the size and concentration using various spectroscopy techniques including ultrasound, infrared, near infrared, Uv spectroscopy, X-ray diffraction and Raman spectrometer, the literature on monitoring crystal morphology is scarce. This paper presents recent advances towards developing an enabling technique for real-time measurement and manipulation of the morphology of growing crystals through integrating on-line imaging, image analysis and morphological population balance modelling. The paper also proposes a framework and highlights challenges and future research needs for model predictive control of crystals morphology.

### 2. Morphology Measurement: Imaging and Image Analysis

Laser diffraction techniques were investigated previously for the recognition of non-spherical particles with only limited success mainly due to the difficulty in obtaining a single-particle pattern in mixtures. Use of attenuation acoustic spectroscopy, Raman spectrometer, NIR and X-ray diffraction techniques though can detect polymorphs, but they cannot give detailed quantitative shape information. Several recent studies have demonstrated the effectiveness of on-line imaging as an instrument for monitoring the

shape of the crystals (Wilkinson, 2000, Patience and Rawlings, 2001, Calderon De Anda, et al., 2005a, Calderon De Anda, et al., 2005b, Calderon De Anda, et al., 2005c). In our work, an on-line imaging instrument developed by researchers at GlaxoSmithKline was investigated to monitor the onset as well as polymorph transitions during cooling crystallization of L-glutamic acid, an effective multi-scale image analysis technique for segmentation of the crystals from the complex background of image frames was developed, and subsequently shape descriptors, classification techniques and novel process monitoring charts were derived. Fig. 1 shows the on-line imaging system mounted on the outside wall of a 5 liter batch reactor which is able to take maximum 30 images per second of the pixel resolution of  $480 \times 640$ . Fig. 2 shows polymorphic transition captured in real-time during the cooling crystallization of L-glutamic acid.

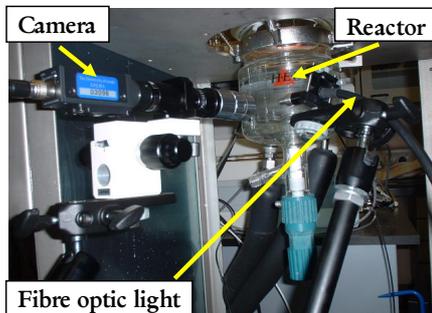


Fig. 1 The on-line imaging system mounted on a 5 litre batch reactor.

On-line images of slurries with particles suspended in a solution pose much greater challenges to image analysis than images of particles obtained with off-line equipment. The major challenges lie in the fact that the slurries in a stirred reactor are in continuous motion, and that the variation of distances from the camera lens of particles captured in a snapshot makes some particles rather vague compared to others. In addition, the light effect and temporal changes of hydrodynamics within the reactor may lead to varied intensity in the image background. As a result a multi-step multiscale approach was developed which proved to be effective in extracting objects from the image background for images obtained by the GSK on-line microscopy system, as well as for the Lasentec's PVM probe (Barrett, 2002), as demonstrated by Fig. 3.

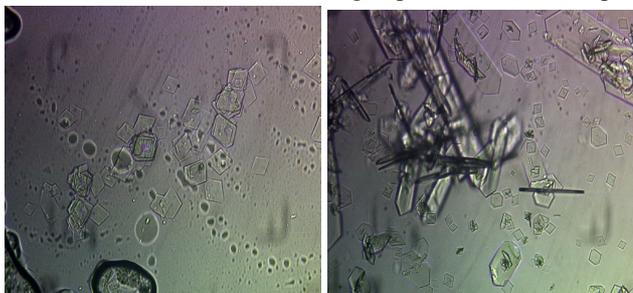


Fig. 2 Polymorph transition for L-glutamic acid captured in real-time, from  $\alpha$  form (left) to  $\beta$  form. The right figure shows mixed  $\alpha$  and  $\beta$  indicating transition being taking place.

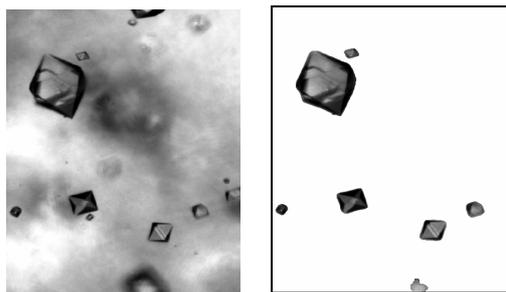


Fig. 3 crystal images were effectively extracted from the background of an image frame obtained by the Lasentec PVM imaging system.

### 3. Faceted Crystal Growth Rates and Kinetics

Given that the fundamental process of crystal growth and its associated kinetic control is surface controlled, the use of a single scalar parameter, particle size, usually defined as a volume equivalent diameter, i.e. based on a spherical assumption of particle shape can be misleading for a number of practical crystallization systems, notably pharmaceutical products, where faceted particles defined by non-unity aspect ratios. Hence, measurement of the growth rate for each individual crystal surface in real-time and within processing reactors could open the way for the development of more effective processes and product quality control. Using on-line imaging and image analysis, a preliminary study was conducted on the estimation of the growth rates of rod-shaped crystals in two dimensions for  $\beta$ -form L-glutamic acid in cooling crystallization under a cooling rate of  $0.10^\circ\text{C}/\text{min}$  (Wang, et al., 2007). The length and width of each rod-shaped crystal were measured every 60 seconds, ranging from 100 to nearly 200  $\mu\text{m}$  in length and from 30 to 45  $\mu\text{m}$  in width, and the values were used to estimate growth rates on both directions (Fig. 4). The growth rate in length was found to be 4 to 6 times greater than for the width. The  $\{101\}$  plane was found to be the fastest growing surface of the morphology studied and an attempt was also made to estimate its growth-kinetics parameters from measurements of length, whilst it was harder to estimate kinetics from measurements of width for other crystal faces. In the temperature range between  $68.34^\circ\text{C}$  to  $67.51^\circ\text{C}$ , the length growth rate is estimated as between  $2.440 \times 10^{-8} \sim 2.995 \times 10^{-8}$  m/s, while the growth rate for the width is between  $0.558 \times 10^{-8} \sim 0.502 \times 10^{-8}$  m/s. The capability to measure crystal growth rates in different directions could be used to estimate the

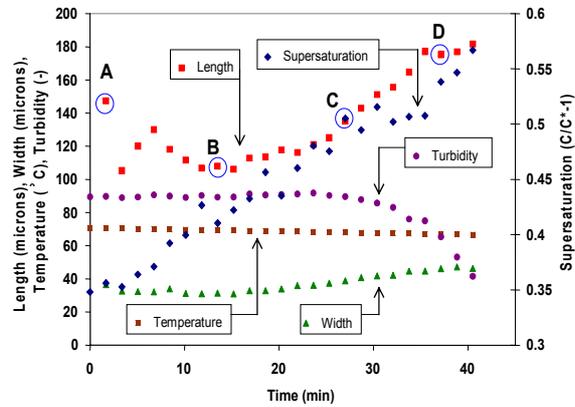


Fig. 4 Crystal length evolution, plotted against supersaturation, temperature and turbidity. Each point represents the average of previous 60 seconds containing 300 images.

Fig. 5 Morphology of potash alum crystal and the schematic diagram of three size characteristic parameters (x, y, z) used in polyhedral PB model

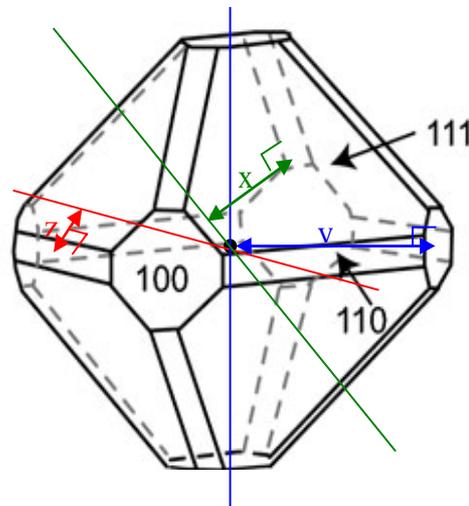


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parameters associated with growth kinetics in multi-dimensional directions. If a semi-empirical kinetic model is used,  $R = k\sigma^n$ ,  $k \approx 1.761 \times 10^{-7}$  m/s, and  $n \approx 2.61$ . It was assumed for  $\beta$  L-glutamic acid, the growth rate in length is very close to the growth rate of the faces  $\{101\}$ .

#### 4. Morphological (or polyhedral) Population Balance Modelling

Modelling the growth and dynamic evolution of crystal size distribution within a crystallizer using population balance (PB) has been mainly based on a size definition of volumetric equivalent diameter thus inherently ignoring the shape of crystals. Recently there are a few researchers who have reported two dimensional, i.e. length and width, PB modelling for rod-like crystals. Puel et al. (Puel, et al., 2003a, Puel, et al., 2003b) developed a two-dimensional PB model to simulate the time variations of two internal sizes of crystals, and consequently of a characteristic shape factor. Similar approach was used to investigate the two-dimensional growth of potassium dihydrogen phosphate by Ma et al. (Ma, et al., 2002) using a hybrid of the upwind discretisation and the Lax-Wendroff method, and by Briesen (Briesen, 2006) employing coordinate transformation method, instead of performing a direct discretisation of the two size parameters, to reduce model size under certain assumptions. We used on-line estimated growth rates for performing two dimensional PB modelling for rod-like  $\beta$  form L-glutamic acid. (Ma, et al., 2007, Wang, et al., 2007)

We have recently extended the work and proposed a new model to predict the population distributions for all identified independent crystal faces, which is a unique methodology to integrate population balance with crystal morphology. (Ma, et al., 2008, Ma and Wang, in press, Wang et al., 2008) The critical inputs for the new population balance model are the accurate growth rates for each crystal faces which can be estimated using on-line imaging and image analysis. From the predicted growth of facets at different times during crystallisation process, many important crystal properties such as shape and growth rate can be evaluated.

A simple and well-known compound, potash alum ( $KAl(SO_4)_2 \cdot 12H_2O$ ), as shown in Fig. 5, was selected as a first attempt to test and validate the polyhedral population balance model. A potash alum crystal has total 26 main habit faces in 3 main faces,  $\{111\}$ ,  $\{110\}$  and  $\{100\}$ , for which a geometric centre can be found (Fig. 5). The normal distance from each crystal face to the geometric centre represents one dimension in the polyhedral PB model, therefore rigorously speaking the polyhedral PB model should have twenty six size dimensions. However, if some faces, such as the eight  $\{111\}$  faces are symmetry-related, and suppose these symmetry-related faces have identical surrounding growth environments and the same growth rate value, then they can be treated as a single dimension, denoted as dimension  $x$  in PB modelling. Similarly, the six  $\{100\}$  faces and the twelve  $\{110\}$  faces will form the second and third independent dimensions,  $y$  and  $z$ , respectively. Therefore, the morphological PB modelling of crystal growth can be modelled based on these three independent faces. For simplification, if we ignore the effects of both primary and secondary nucleation, and also aggregation and breakage, the polyhedral PB equation can be formed as,

$$\frac{1}{V_T(t)} \frac{\partial}{\partial t} [\psi(x, y, z, t) V_T(t)] + \frac{\partial}{\partial x} [G_1(x, t) \psi(x, y, z, t)] + \frac{\partial}{\partial y} [G_2(y, t) \psi(x, y, z, t)] + \frac{\partial}{\partial z} [G_3(z, t) \psi(x, y, z, t)] = 0$$

where  $V_T$  is the total volume of suspension,  $\psi$  is the number population density function

in the suspension,  $G_1$ ,  $G_2$ ,  $G_3$  are the growth rates in x, y and z directions, and  $t$  is time. The growth rate data for each independent facets of potash alum are obtained from literature. Fig. 6 shows crystal shape variations at different times. It can be seen that with the current growth rates of each face, faces  $\{100\}$  and  $\{110\}$  eventually disappear and the crystal will become the pure octahedral, diamond-like form. Fig. 7 shows the size distribution of three dimensions at three different time points.

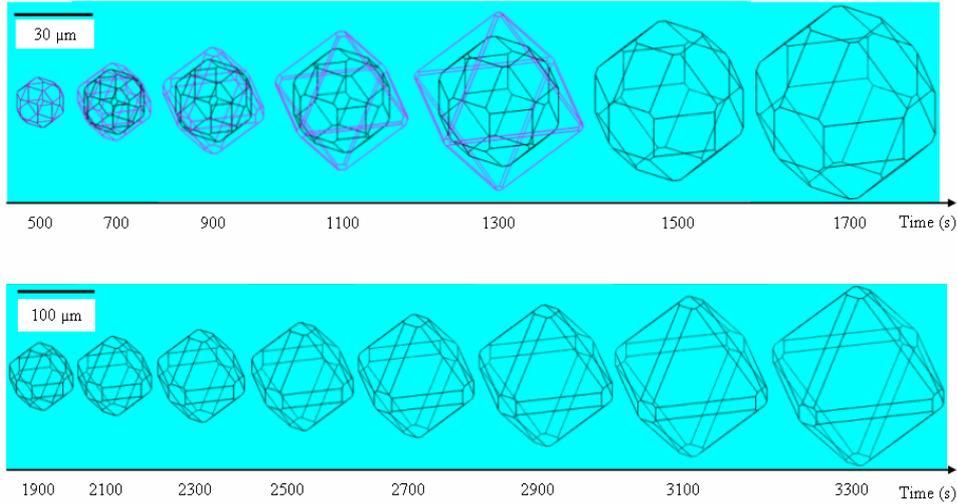


Fig. 6 Modelled morphological evolution with time

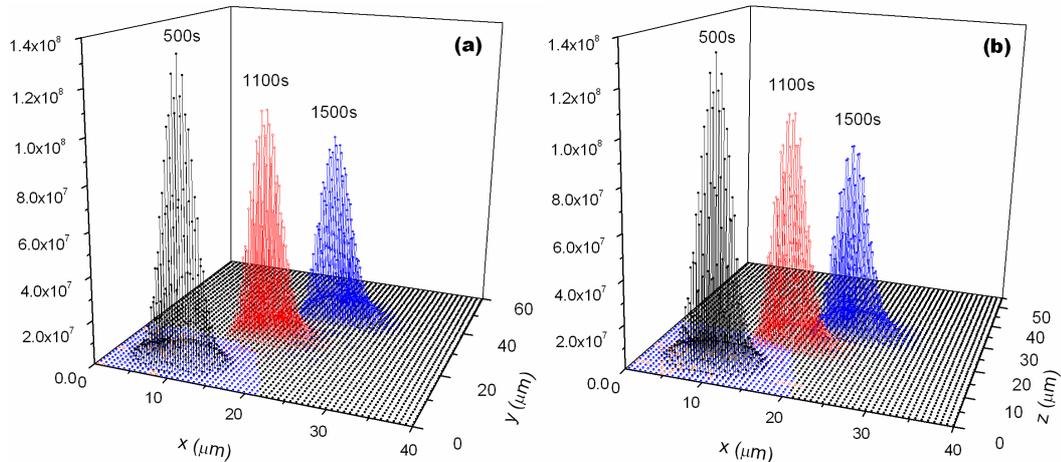


Fig. 7 x-y and x-z population distribution plots at crystallisation times of 500 (black), 1100 (red) and 1500 (blue) seconds with (a) (110) face located at its corresponding mean values and (b) (100) face located at its corresponding mean values.

### 5. Perspectives for Shape Control

Recent advances on imaging and image analysis for real-time measurement of crystal morphology together with development on morphological population balance modeling make it possible in principle to carry out automatic model-predictive control of crystal morphology. Fig. 8 shows a roadmap towards such a goal detailing the main

components needed. On the right hand-side of Fig. 8, through on-line imaging, real-time image segmentation analysis, the real-time size distribution for each face of the crystals for a given polymorph can be estimated. The growth rate for that face can then be calculated based on the size of the current value and the value of a previous time instant. On the left hand side of Fig. 8, based on the initial morphology information of the crystal, morphological PB modelling can be carried out which gives predicted evolution of crystal size distributions for all faces, therefore can be built into the model-predictive framework.

## 6. Final Remarks

Recent developments in on-line shape measurement as well as in morphological population balance modeling opens the way for developing model-predictive control of the morphology as well as size of crystals grown from solution. This will need integration of on-line 3-D shape measurement, modeling of morphology, multi-dimensional PB modeling and CFD.

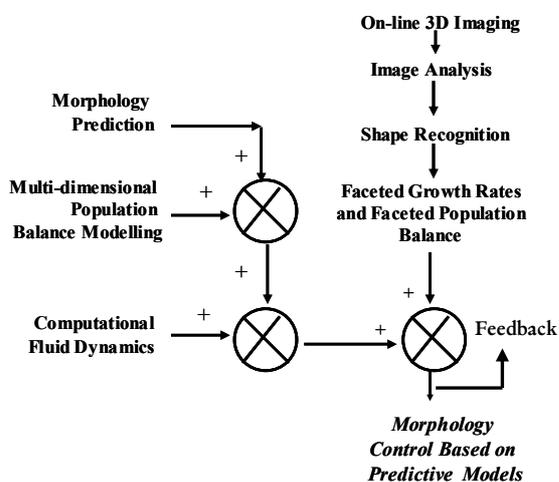


Fig. 8 Components for model predictive control

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