AIChE Letter: Process Systems Engineering

Stereo Imaging of Crystal Growth

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DOI 10.1002/aic.15041
Published online October 7, 2015 in Wiley Online Library (wileyonlinelibrary.com)

Significance

A methodology that directly images the full three-dimensional (3-D) shape of crystals within a crystallizer is reported. It is based on the mathematical principle that if the two-dimensional (2-D) images of an object are obtained from two or more different angles, the full 3-D crystal shape could be reconstructed. A prototype instrument is built and proof of concept study performed to demonstrate the potentials in using the system for 3-D measurement of crystal shape and shape distribution. It is our belief that 3-D measurement of crystal shape represents a significant step forward from existing work of 2-D measurement of crystal morphology and is potentially of great significance to research toward closed-loop control of crystal morphology. © 2015 American Institute of Chemical Engineers *AIChE J*, 62: 18–25, 2016

Keywords: stereo imaging, crystal shape, three-dimensional shape reconstruction, image analysis, crystallization process control

Introduction

Particle shape is known to be extremely important to many pharmaceuticals, biopharmaceuticals, human health products, and speciality chemicals in solid form. In the pharmaceutical industry, particle properties such as dry powder density, cohesion, and flowability, and so forth can be affected by crystal morphology, which plays an important role in a company's ability to formulate drug particles into finished products. Moreover, crystal morphology can affect drug dissolution, potentially affecting finished product bioavailability and, in some extreme conditions, leading to a company to lose the production license of a drug.

Despite its significant potential importance, the direct characterization of particle shape has been quite limited largely relying on off-line instruments. For quite some time, there have been no effective instruments capable of providing real-time information on particle shape particularly with the capability for use during the processing of particles in unit operations such as crystallization, precipitation, granulation, and milling (dry or wet). During the last decades, well-developed and studied process analytical techniques such as acoustic, and mid and near infrared spectroscopy and laser diffraction have been used in process monitoring, these techniques cannot give detailed information on particle shape although some of them have shown to be able to distinguish between different polymorphs with careful spectral data analysis using chemometrics. Overall, the inability in the measurement of particle shape and growth rates in individual faces has greatly restricted the development and implementation of monitoring and control of particle shape for these particle formulation and processing systems.

In recent years, several research groups and industrial companies have found that it is feasible to use on-line two-dimensional (2-D) imaging for particle shape measurement, and initiated research activities.[1–15] Rawlings and coworkers performed research on the measurement of crystal size and shape distributions using on-line video images.[15] Wilkinson et al. from GlaxoSmithKline developed a prototype on-line, noninvasive

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microscopy imaging system[11] for monitoring pharmaceutical crystallization. AstraZenaca[14] tested the use of a commercially available imaging probe named as particle vision and measurement (PVM). In medical and biological areas, miniature CCD cameras were used to develop imaging systems. Gorpas et al.[16] developed a volumetric method, using a binocular machine vision system with a structured light projector, to reconstruct three-dimensional (3-D) tumor surfaces (ca. 10 mm in size). An imaging system using a flow through cell with one camera and two mirrors was developed to obtain 3-D information of crystals grown from solution.[17] A few of three-cameras imaging systems were also developed to characterize 3-D shape of free-falling particles (100 μm ∼ 4 mm)[18] or 3-D information of a wound area.[19] However, all these binocular and three-camera imaging systems are not designed to be used in a reactor for direct measurement of crystal size and shape evolution and the objects to be characterized are normally at millimeter scale, hence not being suitable for micron-sized crystals. Interactive systems that allow users to control and manipulate real-world objects within a remote real environment are known as teleoperator or telerobotic systems.[20] Such systems are often used in medical applications to confirm diagnosis and make surgery. Some 2-D/3-D endoscopes have been developed for these purposes (see for example[20–22]) with the most known ones being da Vinci telerobotic surgical system[21] and ZEUS.[22] Such systems are controlled by surgeons remotely by viewing virtual surgical site with stereoscopic system and controlling stereoscopic camera and robot surgical armaments. However, these imaging systems still have significant limitations in terms of their image processing capabilities and how to link the information for shape monitoring and control. In fact at the moment, they are mainly used to display information to operators and store data onto hard drive. Nevertheless, we believe that with the active research activities internationally and the great interest from instrument companies and end-users, before long the image processing capabilities will improve significantly, thus opening up new commercial opportunities for on-line monitoring and control of crystal size distributions based on shape evolution.

Despite the several research and development programs internationally, all the work on crystal size and shape measurements were restricted to 2-D imaging. Although 2-D shape is already a major step from the traditional characterization of particles based only on a volume equivalent diameter of a sphere, being able to measure 3-D shape will be of much greater scientific and industrial significance. Some microscopic systems such as confocal microscopy are able to provide 3-D information of a particle by scanning many thin sections of the sample.[23] Other techniques can also be used to provide some useful 3-D information of particles off-line such as scanning electron microscopy (SEM) and electron and X-ray tomography. However, these systems are not practical for 3-D on-line measurements due to the very low speed in operation. Mazzotti and coworkers[24,25] designed a flow through microscope with a mirror configuration, hence the passing particles can be viewed from two directions. They applied the system to ascorbic acid crystals for extracting crystal length, width, and depth information. A flow through microscope system was also used to obtain high quality images with regard to particle sharpness.[26] The boundary curve of 2-D crystal projection was used to estimate 3-D shape. Intensive research and development has been performed to obtain 3-D topographical data of objects in robotics and machine vision areas with the objects at meter or millimeter scale. Several optical, noncontact methods have been developed for a wide range of applications, such as moire methods (shadow and projection), fast-Fourier transform approaches, stereo imaging, and so forth. Stereo imaging has the advantage of providing more direct, unambiguous, and quantitative depth information, and it can be used for a very wide range of applications in academic research, industry, and daily life in addition to the applications of 3-D measurement. Most approaches to the application of stereo vision utilize the human vision system to establish a model for the camera system. For stereo imaging system, many different camera-object geometries have been studied and used for specific applications such as the common parallel camera optical axes, the converging (nonparallel) camera optical axes, and so forth. To extract 3-D information from the recorded stereo image pairs for 3-D reconstruction of objects, it is necessary to find disparities among a series of corresponding points between a pair of stereo images taken from the same scene. There are many matching techniques and corresponding algorithms which can be generally divided into three categories: area-based, feature-based, and their combination. In general, feature-based techniques yield a better match more stably and accurately than other techniques. Two types of features commonly used are point-like features such as corners and line segments.[27] Overall, the use of single 2-D images or stereo images for constructing 3-D shape of crystals at micron size scale is still very limited.

In this article, a proof of concept study has been performed to demonstrate the great potentials in using the system for the 3-D measurements of particles at micron scale. The basic mode of the operation is based on the mathematical principle that if the 2-D images of an object are obtained from two different angles, the full 3-D particle shape can be recovered. In the following sections, the methodology of 3-D stereovision imaging system for the characterization of crystal shape is briefly described. Then the stereovision imaging system is developed with some case studies. Finally, some concluding remarks and further development are given.

The Methodology

A two-camera system is proposed, which places two cameras at a predefined angle (stereo angle). The two cameras focus on the same sample volume with the identical camera parameters. The stereo image pairs can be obtained via these two cameras when shuttering at a synchronized instant. The obtained stereo image frames are processed using a multiscale segmentation algorithm[2] or other preprocessing methods. Using corner/edge/line detection,[28,29] the corners, edges, and lines of the crystals from the processed images can be identified. A feature-based matching algorithm (see for example[27]) can be used to identify the corresponding left and right features (corners, edges, lines). The 3-D coordinates of crystal shape can then be reconstructed with the identified corresponding corners, edges, or lines using a stereo triangulation algorithm. The obtained 3-D crystal shape can be further processed for the characterization of crystals such as face growth rates, shape factor, surface area, volume, and size distribution.

Stereovision 3-D imaging system

The schematic diagram of a stereo imaging system is shown in Figure 1. The system can be composed of a reactor or a growth cell for crystal growth under accurate control of heating and cooling conditions and a stereovision imaging system for capturing stereo image frames. The recorded stereo image pairs are stored onto a PC for further image analysis and 3-D reconstruction.

Technique to use stereo cameras (two cameras) for the reconstruction of 3-D vision is directly related to human vision system, that is, two cameras mimics our left and right eyes and 3-D reconstruction software mimics the fast image processing of our brain. Therefore, stereovision technique is not new in any aspect and has been widely used in machine vision such as vehicle and person identification, product manufacturing, and so forth although most of them positioned two cameras in parallel. In chemical processing area, stereovision systems for 3-D reconstruction of particles in micron size scale in reactors are still rare because of the technique challenges when the object size is reduced from millimeters or meters to microns. The proposed stereovision 3-D imaging system in this article is to face the challenges and provide a practical tool for 3-D reconstruction of micron-sized particles in reactors. The built-up stereo imaging system includes a 3-D imaging block (two cameras with two telecentric lenses), a strobe control/pulse generator for synchronizing cameras and lights, a light source, a light controller with strobe triggering pulse for synchronizing cameras and lights, a crystallizer, and a PC with image acquisition software and image processing software for 3-D shape reconstruction, and postprocessing. The imaging system has a spatial resolution of 3.45 μm with the current selection of cameras and lenses. The system can capture up to six frames per second with each image having a resolution of 2448 $\times$ 2050 pixels.

3-D shape reconstruction from 2-D stereo images

With the recorded image pairs, each image is undertaken several image processing steps including preprocessing such as the adjustment of image contrast, edge/corner extraction, and the identification of edge/corner correspondence for 3-D reconstruction. Using the multiscale segmentation method,[2] the crystals from each image of an image pairs can be identified and numbered for further processing. The central coordinates of the numbered crystals are calculated. The paired crystals between the two images in an image pairs can then be found by comparing the central coordinates of the numbered crystals in one image against those in another image with a displacement distance due to the angled stereo cameras. The identified crystal pairs will be further processed to reconstruct 3-D shape. In some cases, crystal pairs may be fully or partially overlapped, which will be discarded as there exist very few algorithms being able to separate overlapped (or aggregated) crystals effectively and accurately at the moment. According to the different features from different crystal shapes such as needle-like, plate-like, rod-like, and so forth, the corner correspondence between the identified crystal pairs can be established. This method can avoid the search of the whole image to obtain the matched corners, hence improving processing speed and quality.

For 3-D reconstruction from 2-D stereo images, in addition to stereo matching to obtain the correspondence of the identified crystal corners in the paired images taken from the same scene, the reconstruction of an object from the correspondence

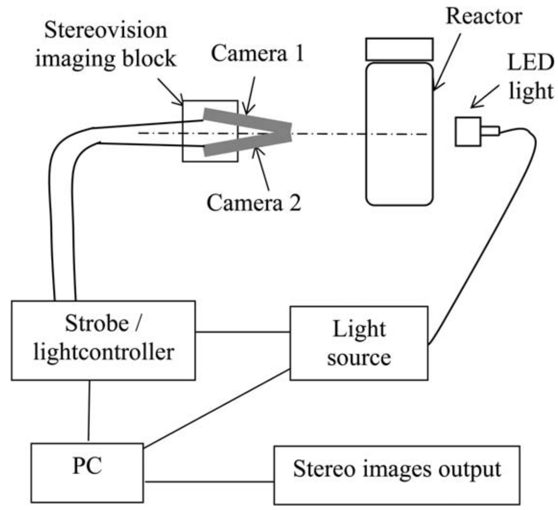

Figure 1. Schematic of the stereovision imaging system.

can be achieved using the triangulation method. For the 3-D coordinates of a corner, the 3-D coordinates (X, Y, Z) of this corner is a function of the coordinates of the two 2-D images (x_1, y_1, x_2, y_2), stereo angle (α), the total distance (L) between a subject and camera, other properties such as resolution (σ), magnification (Δ), and so forth

$$(X, Y, Z) = f(x_1, y_1, x_2, y_2, a, s, D, L, \ \ldots) \quad (1)$$

In the current imaging configurations of the cameras and lenses, the stereo angle between the two camera optic axes is fixed at 22° and the total distance L including the lens working distance, lens length, and camera flange focal distance has a value of 147.726 mm. The magnification of the lenses, Δ, is two times with a resolution σ of 4.65 μm. The obtained equation for the calculation of 3-D coordinates of a corner or point from the two 2-D images is as follows

$$\begin{bmatrix} X \\ Y \\ Z \end{bmatrix} = \begin{bmatrix} a_{11} & 0 & 0 \\ 0 & a_{22} & 0 \\ 0 & 0 & a_{33} \end{bmatrix} \begin{bmatrix} b_1 \\ b_2 \\ b_3 \end{bmatrix} \quad (2)$$

where

$$\begin{bmatrix} b_1 \\ b_2 \\ b_3 \end{bmatrix} = \begin{bmatrix} \dfrac{sin\,\dfrac{\alpha}{2}}{sin\,\alpha} \\ 1 \\ \dfrac{cos\,\dfrac{\alpha}{2}}{cos\,\alpha} \end{bmatrix} \quad (3)$$

$$\begin{bmatrix} a_{11} \\ a_{22} \\ a_{33} \end{bmatrix} = \begin{bmatrix} a_{10} + (x_1 + x_2)\dfrac{\sigma}{\Delta} \\ y_1 \dfrac{\sigma}{\Delta} \\ a_{30} + (x_2 \text{-} x_1)\dfrac{\sigma}{\Delta} \end{bmatrix} \quad (4)$$

with $a_{10} = 74$ mm and $a_{30} = 54.5$ mm. The reconstructed 3-D particles are then used to calculate particle shape descriptors and also perform classification and clustering of particles.

Take a real needle-like crystal (a line segment in theory) as an example, suppose its real length is 1000 μm. However, it can be measured as 1000 μm on a 2-D image only if the line is at an orientation perpendicular to the camera optic axis. If the line has an angle of $\sim 60°$ against the optic axis, it can only be measured as having a length of 850 μm on a 2-D image. Based on the camera model,[4] 2-D images pairs of the line can be computationally generated. With crystal pair identification and edge/corner detection, the coordinates of the end points for the paired lines on the 2-D image can be used to reconstruct the 3-D coordinates of the end points of the line, hence the line in real space. Using our algorithm the reconstructed 3-D line has a length of 991 μm, which is about 1% from the real length of 1000 μm. It can be seen that it will present significant error if the 2-D length of 850 μm for this line is used for further crystal characterization. Furthermore, at the extreme configuration of a line that parallels to the camera optic axis, the line length on a 2-D image will be close to zero. Other methods such as SEM, confocal microscopy can also be used to verify and assess the accuracy of the developed method.

For the image pairs captured from a plate-like crystal in a reactor (Figure 2a), the application of the multiscale segmentation method and the crystal pairs identification procedure will identify the crystal pairs (Figure 2b) for further processing. Based on the features of a plate-like crystal, a parallel fitting procedure is applied to the identified crystal pairs to obtain the 2-D coordinates of the corresponding corners (Figure 2c). Again, due to the plate-like crystal is not orientated perpendicular to the camera optic axis, the reconstructed crystal (Figure 2d) has larger length and width, hence larger area comparing to those from pure 2-D calculations.

For an idealized crystal of L-glutamic acid (LGA) α-form, the same crystal pair identification procedure can be applied to the original 2-D images (Figure 3a) and the identified crystal pairs were then processed with edge/corner detection and correspondence search. The reconstructed 3-D shape of the LGA α-form crystal is shown in Figure 3b. Note that with the help of crystal symmetrical features, the whole crystal shape of LGA α-form can be established from the reconstructed 3-D shape which only represents a half of the real crystal in 3-D space.

The typical stereo images of a sugar crystal are shown in Figure 3c. After performing crystal pair identification, edge/corner detection, and correspondence of the left and right images, the coordinates of the corresponding corners on left and right images were used to obtain the 3-D shape of a sugar crystal (Figure 3d). Again, crystal symmetry can help to establish the whole 3-D structure.

The typical images of potash alum crystals are illustrated in Figure 3e (left and right images). Crystal pair identification, edge/corner detection with some false corners being manually removed, and then correspondence processing were performed. With the corner coordinates, stereo triangulation can be used to calculate the corresponding 3-D coordinates. After that the 3-D shape of the crystal was reconstructed as shown in Figure 3g. For comparison purpose, the nine surfaces of the potash alum crystal on the 2-D image were shown in Figure 3f, each associated with a letter from A to I. By following the habit faces of potash alum crystals, that is, 26 faces in three symmetrical face groups {100}, {110}, and {111}, faces A–I in Figure 3f, g are corresponding to the three face groups: one {100} face – A; four {110} faces – B, D, F, H; and four {111} faces – C, E, G, I. The crystal size in x, y, and z directions were estimated from the 3-D coordinates as 580, 588, and 277 μm, respectively.

A proof of concept study under seeded cooling crystallization conditions was performed using an industrial compound with cuboid-like crystal shape to obtain the crystal growth rates of the individual faces. The captured stereo images from both cameras were processed to reconstruct the 3-D shape of individual crystals, that is, obtaining the 3-D coordinates of all corners of acuboid-like crystal and also the corresponding normal distances (x, y, and z) between the center of the crystal and the corresponding individual faces 1, 2, and 3. The 3-D imaging system recorded the stereo images at a rate of one per second for a period of $\sim$75 min (from the time of seeds being added at 70 min to the end of recording at 145 min). As the motion and rotation of crystals and also the crystal overlapping happened during the crystallization process, in this study, some typical stereo images at a few time instances (75, 90, 100, 110, 120, 130, and 140 min), corresponding to each time point images of a time window of 5 min were selected for processing and 3-D shape reconstruction. The normal distances of individual faces within the 5 min time window formed their distributions which then were used to obtain their corresponding mean normal distances. The mean normal distances of faces 1, 2, and 3 are plotted in Figure 4 with the corresponding fitted results as $x = 1.76\ t - 102.28$ μm, $y = 1.94\ t - 99.02$ μm, and $z = 1.25\ t - 78.35$ μm, where t is the time (min), with fitting R^2 being 0.97, 0.99, and 0.98, respectively. From the linear relationship between the normal distances and crystallization time, the crystal growth rates of three individual faces (faces 1, 2, and 3) for the cuboid-like compound have constant values of 1.76, 1.94, and 1.25 μm/min, respectively.

The 3-D reconstruction speed using the developed method depends on various factors such as quality of images, the complexity of the imaged crystals, and so forth. Typically, reconstructing a 3-D line, or a plate-like crystal, or a more complex-shaped crystal requires from 1 to a few seconds using a desktop PC (duo core 2.0-GHz processor and 3-Gb RAM operating under Windows XP). To reconstruct all crystals from image pairs, the time required also depends on the number of paired crystals identified from an image pairs. In cooling crystallization processes, the sampling times for images and temperature can be very fast (ca. <1 s), but for concentration measurement typically from 30 s or longer. Therefore, the 3-D reconstruction processing time can be in the same order as the concentration measurement using attenuated total reflection – Fourier transform infrared (FTIR) spectroscopy. However, for fast crystallization such as reactive crystallization, high performance PC may be needed to speed up the processes of images and FTIR spectra, hence developing real-time on-line feedback control systems.

Final Remarks

Crystal growth is primarily controlled by its surface chemistry which leads to various growth rates for different crystal faces. During crystallization processes, surface chemistry for each face can also vary with operating conditions. Therefore, to develop real-time shape model predictive control,[30–32] the on-line measurement of faceted crystal growth rates, from

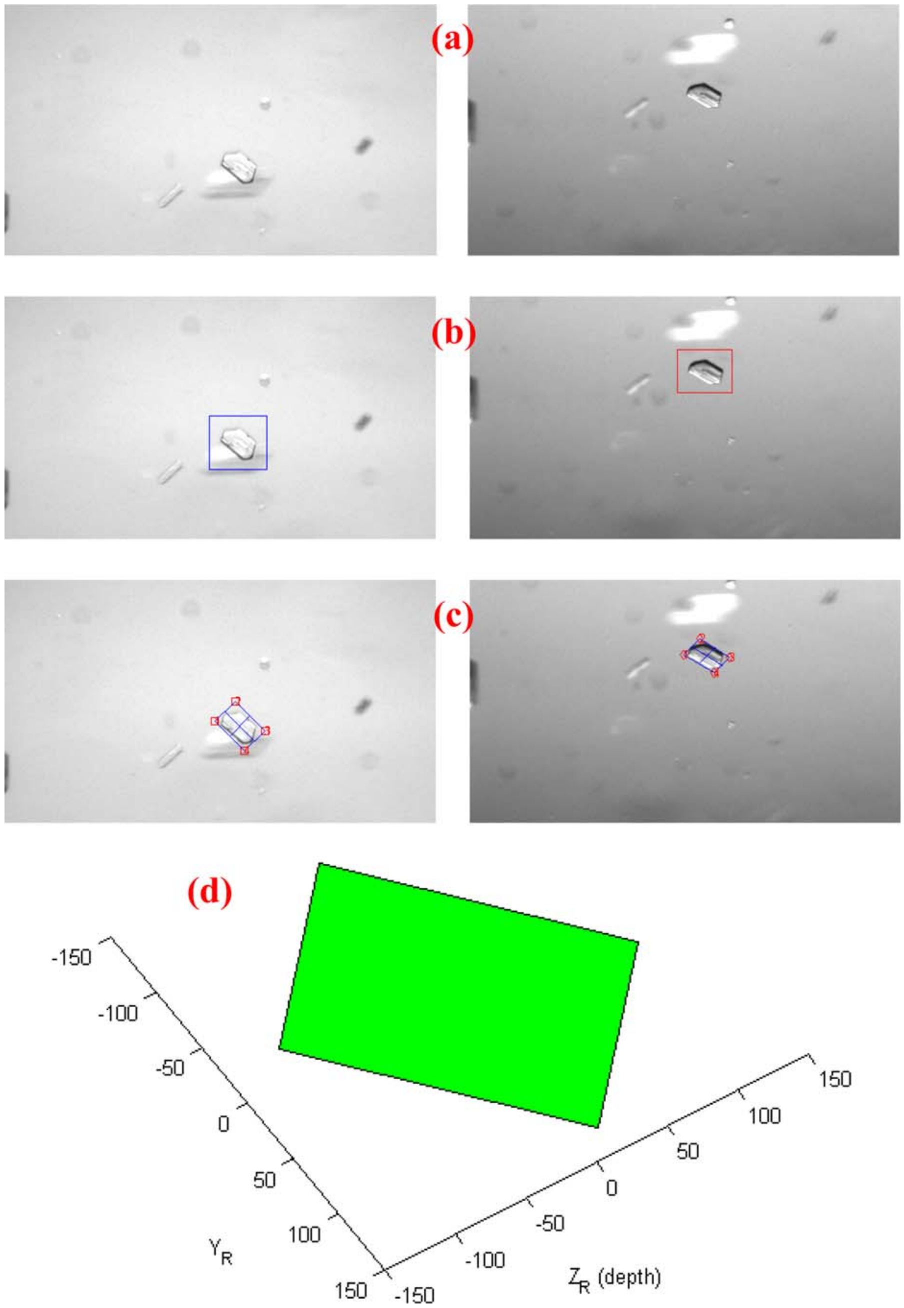

Figure 2. Shape reconstruction procedure demonstrated for a plate-like crystal (a) original image pairs, (b) identified crystal pairs, (c) feature-based edge/corner detection, and correspondence, (d) reconstructed plate-like crystal in 3-D space.

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

crystal shape evolution, during the crystallization process becomes an essential and direct input into the population balance models including the unique morphological population balance model (MPB).[33,34] With real-time on-line measurement of crystal shape/size evolution, together with a proper process optimization and control technique, a real-time, online MPB-based closed-loop feedback control can be developed and applied to practical crystallizers, hence achieving the desired crystal properties of final products including shape and size distributions. In literature such as Kwon et al.,[30–32] by combining PB model with measured faceted growth rates, a predictive control strategy was developed to control crystal shape and size of hen-egg-white (HEW) lysozyme. The online size (or aspect ratio) of HEW lysozyme crystals was obtained from imaging techniques such as PVM and Focused beam reflectance measurement (FBRM) which cannot provide 3-D crystal shape evolution. As shown in the Section on 3-D shape reconstruction, due to the continuous rotation of crystals

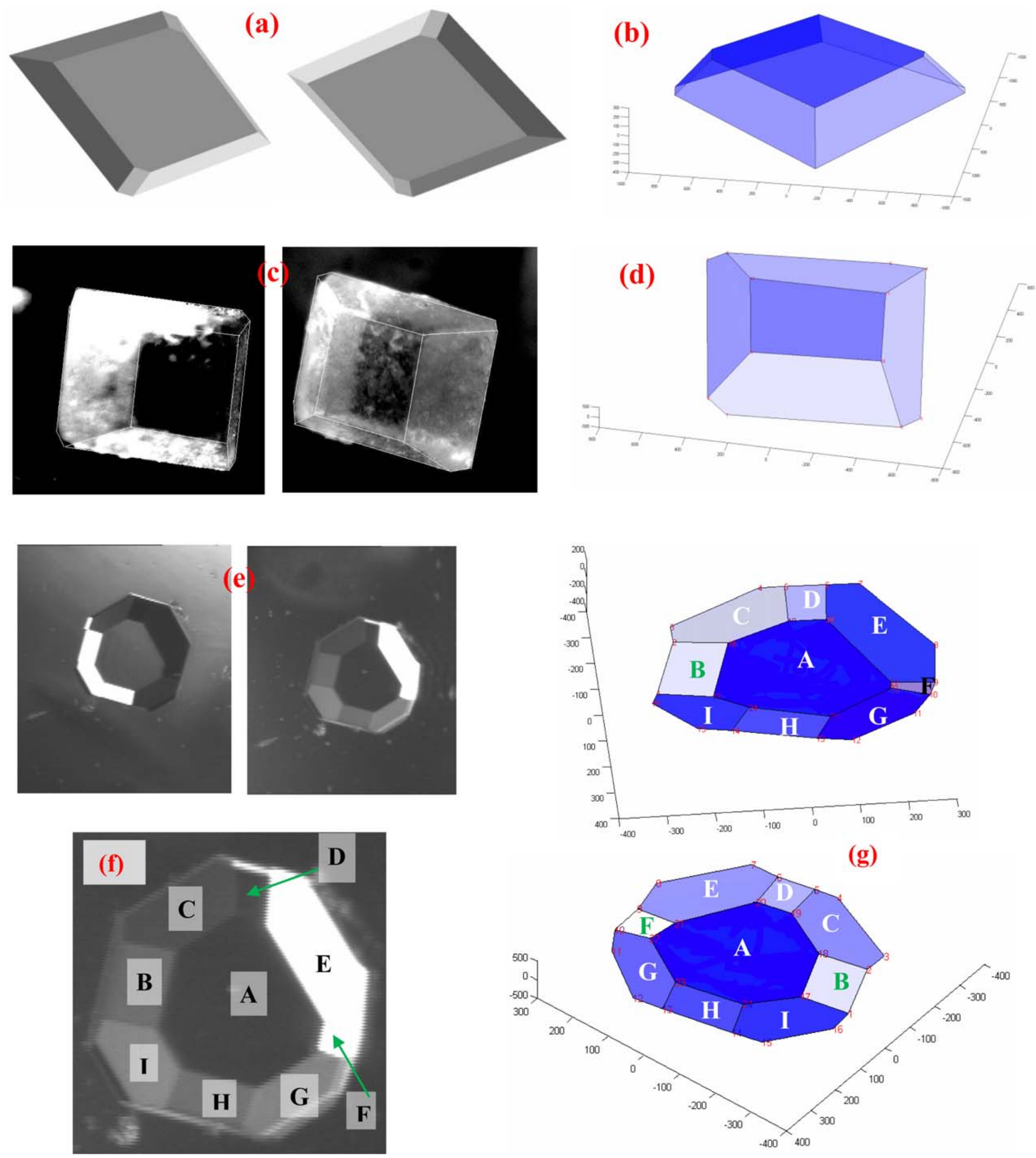

Figure 3. Examples of 3-D shape reconstruction of crystals: L-glutamic acid (LGA) α crystal (a and b), sugar (c and d), and potash alum (e–g) [(a) original 2-D images of a LGA α crystal; (b) reconstructed LGA α crystal in 3-D; (c) 2-D image pairs of a sugar crystal; (d) reconstructed 3-D sugar crystal; (e) 2-D image pairs of a potash alum crystal; (f) a 2-D image with nine faces; (g) reconstructed 3-D crystal with two orientations (nine surfaces on the top part of the crystal: one {100} face – A; four {110} faces – B, D, F, H; and four {111} faces – C, E, G, I)].

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in a crystallizer, the crystal orientation against the camera optic axis may generate great error. Therefore, combining aspect ratio from PVM and FBRM 2-D measurements with crystal morphology may not produce accurate crystal shape and size.

The existing process imaging systems can only record 2-D images and some 3-D systems in machine vision and medical applications have been applied only to large objects and/or the visualization of 3-D images as an assistant to remote microsurgery. The 3-D stereovision imaging system presented in this article is designed to record and reconstruct 3-D shape of particles at micron size scale in reactors. The technique uses two cameras and two telecentric lenses to image different facets of

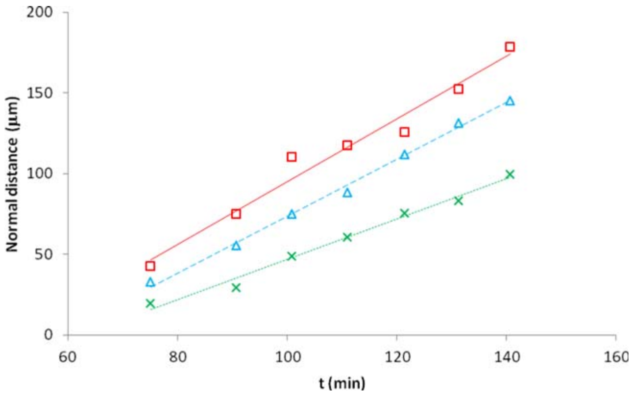

Figure 4. The evolution of the mean normal distances of individual crystal faces during the crystallization process (symbols – reconstructed normal distances with blue triangles for face 1, red squares for face 2, and green crosses for face 3; lines – fitted normal distances with solid line for face 1 ($R^2 = 0.97$), dashed line for face 2 ($R^2 = 0.99$), and dotted line for face 3 ($R^2 = 0.98$)).

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a particle, and then to reconstruct the 3-D shape. The reconstruction of 3-D crystal shape from 2-D stereo images can involve the following steps: raw stereo image preprocessing; corner/edge detection; correspondence establishment; and triangulation for 3-D calculations. The obtained 3-D crystal shape can be used to characterize crystal properties such as face growth rates, shape factor, surface area, volume, and size distribution. The case studies demonstrated that the instrument, together with the developed methodology, is potentially very useful for process and product quality monitoring and control of crystallization processes in academic research and industrial applications including pharmaceuticals, agrochemicals, dyes and pigments, food, detergents, and formulation additives.

Acknowledgments

Financial support from the China One Thousand Talent Scheme and National Natural Science Foundation of China (NNSFC) under its Major Research Scheme of Meso-scale Mechanism and Control in Multi-phase Reaction Processes (project reference: 91434126), and Natural Science Foundation of Guangdong Province (project reference: 2014A030313228) is acknowledged. The research reported in this article has also benefited from previous work supported by the UK Engineering and Physical Sciences Research Council (EPSRC) for the projects of Shape (EP/C009541) and StereoVision (EP/E045707) and by the Technology Strategy Board (TSB) for the project High Value Manufacturing CGM (TP/BD059E).

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Manuscript received Jan. 6, 2015; and revision received Aug. 10, 2015.