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On-line measurement of the real size and shape of crystals in stirred tank crystalliser using non-invasive stereo vision imaging

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HIGHLIGHTS

- Crystal size and shape in a stirred crystalliser is measured using on-line 3D imaging.
- Off-line sample analysis shows on-line 3D imaging gives more accurate size than 2D.
- For needle like crystals, on-line 2D imaging typically under-estimates the length by 2/3.
- On-line 3D imaging and image analysis is also used to derive faced growth kinetics.

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ABSTRACT

Non-invasive stereo vision imaging technique was applied to monitoring a cooling crystallisation process in a stirred tank for real-time characterisation of the size and shape of needle-like L-glutamic acid (L-GA) β polymorphic crystals grown from solution. The instrument consists of two cameras arranged in an optimum angle that take 2D images simultaneously and are synchronised with the lighting system. Each 2D image pair is processed and analysed and then used to reconstruct the 3D shape of the crystal. The needle shaped L-GA β form crystal length thus obtained is found to be in good agreement with the result obtained from off-line analysis of crystal samples, and is about three times larger than that estimated using 2D imaging technique. The result demonstrates the advantage of 3D imaging over 2D in measurement of crystal real size and shape.

1. Introduction

Crystallisation is an important operation widely used in industry to produce various particulate products such as pharmaceuticals and fine chemicals. The size and shape of crystals are key quality measures (Lovette et al., 2008) that should be measured on-line in real-time for the purpose of effective process optimisation and advanced control. The most widely studied process analytical technology (PAT) for on-line and real-time characterisation of crystal size and shape is focused-beam reflectance measurement (FBRM) that is based on laser light backscattering and measures particle cord length distribution (CLD). CLD can be used to estimate particle size distribution (Li et al., 2014; Mangold, 2012; Nere et al., 2006), but the error can be large if the particles deviate far from being spherical. Effort was also made to extract particle shape information from FBRM CLD measurements such as the imaginative work of (Ma et al., 2001; Yamamoto et al., 2002), but concern remains on the magnitude of error that is introduced in the conversion from CLD to crystal shape. Microscopy imaging is considered as probably the most promising technique for measuring particle shape since one can see the shape of the particles, as a result has attracted much attention in recent years. Calderon De Anda et al. (2005a, 2005b; De Anda, 2005), Wang et al. (2007) and Larsen et al. (Larsen and Rawlings, 2009; Larsen et al., 2006, 2007) used a GSK imaging system with non-invasive high-speed camera to record images and monitor the particle shape and size in a stirred batch crystalliser. Zhou et al. (2011, 2009) used image analysis to automatically extract the maximum possible information from in situ digital particle vision and measurement (PVM) images, which was employed to monitor particle shape and size distribution on-line.

Considering the fact that crystals in a stirred tank crystalliser undergo continuous rotation and motion, characterisation of the

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size and shape of crystals based on 2D images can have big errors unless the crystals are close to sphere. Taking a needle-like crystal as an example for which we are mainly interested in its length. In a three dimensional Cartesian coordinate system, with origin O and axis lines X, Y and Z, a particle can randomly rotate, the probability of the needle-like perpendicular to the camera's optical axis is extremely small over all of the possible orientations. As a result, the 2D imaging technique cannot precisely measure the real size and shape; and the obtained size (i.e. length) is likely to be smaller than the real size.

Li et al. (2006) made probably the first attempt to obtain 3D crystal shape information based on on-line obtained images of crystallisation and presented a camera model for integrating both crystal morphological modelling and on-line shape measurement using 2D imaging. The 3D shape of crystals was predicted using the morphological modelling software HABIT (Clydesdale et al., 1996), then 3D shape rotation and a camera model were used for projecting 3D crystal on a 2D plate to generate a library of 2D images, finally matching between images in the library and the processed on-line images to identify the corresponding crystal with 3D sizes. Wang et al. proposed to use (Wang et al., 2008) two or more synchronised cameras to firstly obtain two or three 2D images of the same moving crystal from different angles and then reconstruct its 3D shape from the 2D images using a 3D reconstruction algorithm. Bujak and Bottlinger (2008) used the same principle to measure particle real 3D shape although their system is for measuring dry particles rather than particles in a slurry. Borchert et al. (2014) proposed an analogous estimation methodology to reconstruct the 3D crystal shape by comparing Fourier descriptors of the 2D crystal projection in pre-computed database with the Fourier descriptors of on-line measured 2D images. However, the size and shape information of crystals collected from a single direction is frequently incomplete, especially for shape estimation. Because of the small crystal thickness, the estimation for the crystal orientation is highly sensitive to the finite image resolution causing an inaccurate shape estimation (Borchert et al., 2014). An additional camera can help provide more accurate 3D shape information of the crystal, which will mitigate this problem and increase the accuracy of shape estimation. Therefore, for suspension crystallisation processes, stereoscopic imaging, i.e., photographing the same particle from multiple view directions, is a promising method to overcome the issue (Bujak and Bottlinger, 2008; Wang et al., 2008). A method of photographing from vertical directions using a single camera but two mirrors the same particles that flow through a cell was presented by Mazzotti and co-workers (Kempkes et al., 2010; Schorsch et al., 2012). The system was further improved based on their early work, i.e., replacing the mirrors with a second camera (Schorsch et al., 2014). Multidimensional particle size distribution is measured using the image acquisition setup. However, the particles are captured by two cameras when they flow through the cell rather than a stirred tank crystallizer. In addition, the concentration of solution is not measured on-line during the crystallisation processes, and kinetics of crystal growth is not presented.

Some other techniques were investigated to characterise 3D crystal shape in recent years such as tomography and optical sectioning. Tomography refers to imaging by sections or sectioning via the use of penetrating wave. Different images can be captured from each direction, and all collected images are used to reconstruct 3D crystal shape (Gonzalez and Woods, 2008; Midgley et al., 2007). Magnetite that ranges from decimetres to micrometres in size were identified and quantified to obtain crystal size distributions (CSDs) using X-ray tomography (Pamukcu and Gualda, 2010). Larson et al. (2002) developed a differential-aperture X-ray microscopy technique to make microstructure and stress/strain measurements with sub-micrometre point-to-point spatial resolution in three dimensions. Another approach for directly measuring 3D crystal shape, optical sectioning is popular in modern microscopy since it allows 3D reconstruction for a sample from images obtained at different focal planes. This technique is employed to analyse rock and mineral (Higgins, 2000; Jerram and Higgins, 2007; Jerram et al., 2009; Ketcham and Carlson, 2001), as it can obtain the inner information of crystal by splitting a 3D object tomultiple2D slices. A non-destructive technique with sectioning is the application of confocal optical microscope, which was reported in detail by Webb (1996). This microscope using optical sectioning technique is successfully applied to reconstruct the 3D shape of final crystal product (Castro et al., 2004; Conchello and Lichtman, 2005; Singh et al., 2012; Wilson, 2011). However, all the methods reviewed above in this paragraph require a sample preparation, which is time-consuming and costly. And these technologies therefore are generally used for off-line imaging of dry samples, not suitable for online measurement of the 3D shape of crystals in a suspension.

In summary, previous work on 3D imaging of the shape of growing crystals has used off-line and slow technique such as confocal microscopy, or been restricted to a small volume vial with no stirring, rather than stirred tank crystalliser. In addition, in previous work of on-line crystallisation imaging, solution concentration was not measured and no attempt was made to derive faceted crystal growth kinetics. Our previous work (Wang et al., 2007) measured solution concentration and derived growth rates but it was based on 2D imaging. In this study, an non-invasive on-line stereo vision imaging system, *Stereovision*^{NI}, was used to measure real crystal size and shape. In a previous study (Wang et al., 2008), a stereo vision imaging configuration involving two synchronised cameras was proposed. The work presented here builds upon the previous idea, focusing on estimating the real crystal size and validation in practical crystallisation process. The instrument, *Stereovision*^{NI} is a product of Pharmavision Limited and is based on fixing two cameras in an optimum angle and that are synchronised with the lighting system. It is non-invasive since it plays the cameras and lighting systems outside the glass walled crystalliser, avoiding some practical problems associated with directing contact with the slurry such as crystals sticking to the camera head. The collected 2D image series of needle-like β-polymorphic L-glutamic acid crystals were processed to reconstruct 3D crystal shape using the *Stereovision*^{NI} software also developed by Pharmavision Ltd. To verify the reliability of this method, the off-line imaging instrument, *Morphologi* G3 from Malvern Instruments Ltd., was applied to analyse the product size (here length) distribution. The results of 3D on-line imaging, 2D on-line imaging and off-line imaging are compared.

2. Experiments

2.1. Materials

L-glutamic acid (L-GA) selected for this study, $C_5H_9NO_4$, is one of the 20 known amino acids. The L-GA crystals are known to have two polymorphs (Davey et al., 1997; Kitamura and Ishizu, 2000), the prismatic α and the needle-like β forms. β-form L-GA crystals was crystallised in this research to demonstrate 3D reconstruction by the stereo imaging technique. Since it is of needle-like shape only one characteristic size, i.e. the length (L) is considered in this article. The solubility of β-form L-GA crystals can be estimated by Eq. (1) (Li et al., 2008), and the relative supersaturation can be calculated by Eq. (2).

$$C^* = 2.204 - 0.07322 * T + 0.00893 * T^2 - 0.000148183 * T^3$$