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Multi-scale segmentation image analysis for the in-process monitoring of particle shape with batch crystallisers

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Abstract

The morphological forms and habits of pharmaceutical crystals are important properties that can be affected by minor changes in operating conditions such as cooling rates and supersaturation. As a result the pharmaceutical industry demands on-line techniques for real-time measurement of the dynamic changes of these properties in crystallisers. On-line imaging represents a potentially powerful technique for real-time monitoring of the morphological forms during crystal growth, but a major challenge is the availability of methods for image analysis that need to be tolerant to the quality of on-line images, accurate, fast and robust. This paper describes a multi-scale segmentation methodology for analysis of images obtained for batch cooling crystallisation of L-glutamic acid using an on-line high-speed imaging system developed by the pharmaceutical manufacturer GlaxoSmithKline. The method proves to be able to analyse effectively the on-line images of different crystal morphological forms, and of varied qualities. Application of the methodology to the analysis of images from a different on-line imaging probe and from an off-line slurry sample imaging system demonstrated the capability of generalisation of the method.

Keywords: Process imaging; Image analysis; Crystallization; Shape measurement

1. Introduction

High value-added speciality chemicals such as pharmaceuticals are often manufactured in batch crystallisation processes. For a product in crystalline form, morphology often represents a critically important property not only to the end-use functional properties, but also to downstream processing and handling of the product. It is known that certain crystal morphological forms and habits have been related to difficulties in dissolution rate, process hydrodynamics, handling and storage or in milling and grinding processes. The ability for a substance to crystallise in more than one morphological and polymorphic form, has been the subject of many previous theoretical studies, which led to the development of some software systems, such as HABIT (Clydesdale et al., 1996; Walker et al., 1998), CERIUS-2 (Accelrys webpage) and shape visualisation software SHAPE (SHAPE software webpage). These software systems calculate the attachment energies and the relative growth rates associated with the crystal faces. However, they have not been able to consider all the engineering factors that might affect the crystal morphology. It is known that minor changes in supersaturation, cooling rates, reactor hydrodynamics, pH and impurity in the feed can have significant impact on the crystal product. In addition, there are unexpected factors which can become deterministic, such as wall effects on heat transfer, baffles, and impeller materials and types (Liang, 2002). For these reasons, there is a genuine need to develop on-line techniques for real-time measurement of crystal morphology from nucleation through crystal growth until completion of a batch run.

Laser diffraction techniques were investigated previously for recognition of non-spherical particles, but only have

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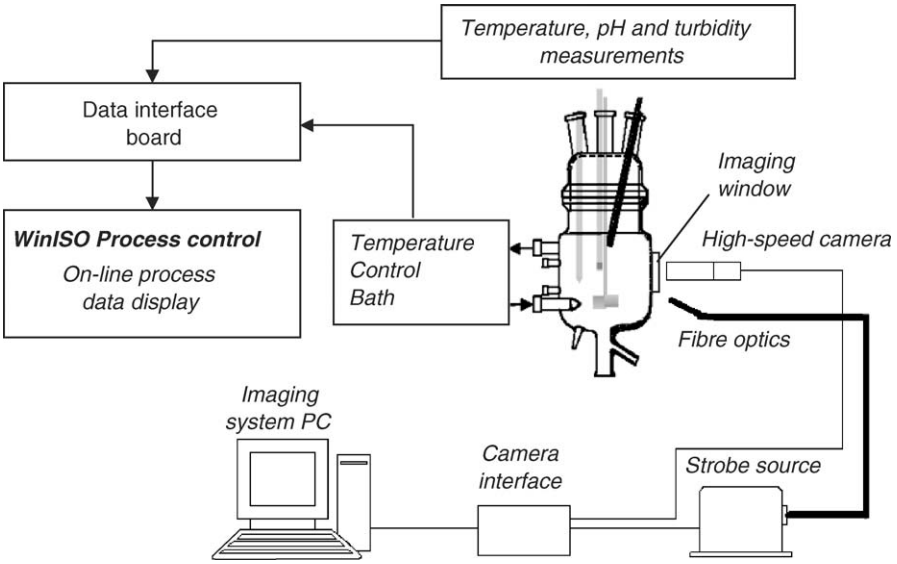


Fig. 1. The experimental system with the on-line imaging system.

achieved limited success. The main difficulty has been in obtaining a single-particle pattern in mixtures due to problems associated with partial scattering of the particles (Yamamoto et al., 2002; Ma et al., 2000, 2001). Mougin (2001) attempted to interpret the ultrasound attenuation spectra in order to identify dynamic changes in morphology during the crystallisation of an organic compound. A correct interpretation was found possible though some additional information needs to be provided which is not always readily available. Studies have also been made to produce crystals with different size and shape properties through supersaturation control using ATR FTIR (Gron et al., 2003; Feng and Berglund, 2002). Modification of temperature to maintain supersaturation values during nucleation and crystal growth helps produce uniform size and shape properties. This practice requires concentration and supersaturation models for the compound to crystallise obtained from calibrations, and the temperature range for control may be limited.

With the rapid progress in high-speed on-line digital imaging sensors, there is a great potential for applying the techniques to real-time monitoring as well as control of shapes and sizes of particulate products such as crystals in the industrial environment. Among the many factors that need to be dealt with in order to achieve such a goal, a major challenge is clearly a technique for image analysis which needs to be accurate, fast, robust and tolerant to the quality of images and noises. Image analysis has been used for some time in chemistry and chemical engineering laboratories for size and shape studies using some commercial software systems. The majority of the commercial tools were developed for analysing images of particles and slurry samples taken off-line and have not been fully tested using images taken on-line. Images taken on-line using high-speed cameras pose much greater challenges to image analysis. A case that can exemplify the challenges for on-line images was reported by Patience (2002) who attempted to use a commercial image analysis software system to analyse images of crystallisation slurries obtained using an on-line imaging probe, the particle vision measurement probe (PVM) of Lasentec (Barrett, 2003; Barrett and Glennon, 2002), but failed. As a result Patience and Rawlings (2001) developed an on-line photo-microscopy system using a stop-flow through cell.

On-line image analysis has to address the following challenges:

- *Tolerance to the quality of images and noises*: Images taken on-line using high-speed cameras are often poor in quality. The objects can have edges of varied degree of clarity due to the varied distances from the lens of the camera. In addition, the background can also have varied intensity characteristics.
- *Accuracy*: The available methods often still need time-consuming manual assistance, e.g. redrawing faint circles, and no available methods are able to perform equally or better than visual inspection. In contrast, in some applications of the medical field and space industry, image analysis can be more accurate than visual inspection. This can be partly attributed to the fact that research in the medical field and space industry is very active while there have been very few publications in process industries.
- *Robustness*: Compared with laboratory conditions, industrial sensors operate in harsh and often varying conditions and at much larger scale. Images from industrial digital sensors can be more challenging than those obtained in laboratories.

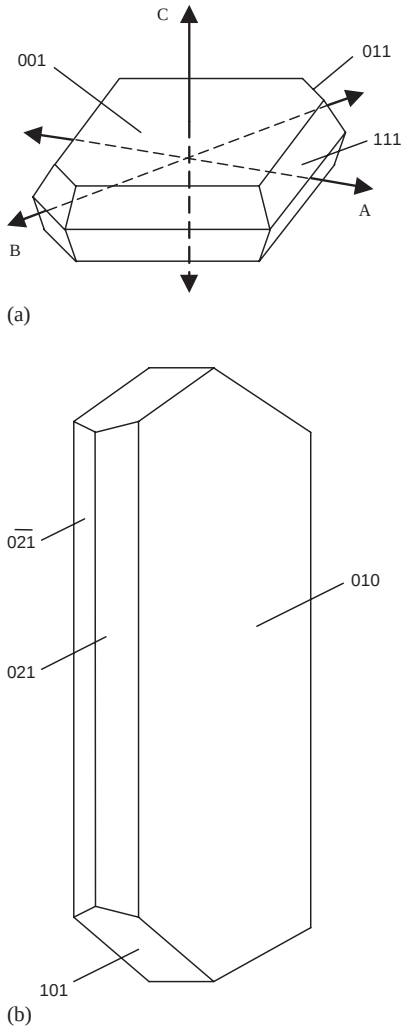


Fig. 2. Morphology of L-glutamic acid α- (a) and β-form (b) (Kitamura and Ishizu, 2000; Davey et al., 1997).

- *Speed*: A single image reflects only the localised spatial and temporal information therefore it is important to consider a number of successive images, e.g., ten, in order to get the statistical information of the process to facilitate control. The minimum requirement on analysis speed depends on the application.

In this paper, we report a multi-scale segmentation methodology for analysis of images obtained for the batch crystallisation of an organic compound, L-glutamic acid, using an on-line high-speed imaging system developed by the pharmaceutical manufacturer GlaxoSmithKline. The rest of the paper is organised as follows. In the next section, the experimental system including the batch crystallisation reactor and the imaging system will be introduced. The methodology employed for on-line image analysis will be described in the third section, and some results will be presented and discussed in Section 4. Conclusions will be made in the last section.

2. The experiment

2.1. System set-up

Experiments were carried out using a glass jacketed reactor of 500 mL, a data interface board, and a PC running WinISO process control software provided by Hazard Evaluation Laboratory Ltd. To control the temperature, a Julabo FP50-HD thermostated bath was employed. Due to the operated temperatures, a condenser was used to circulate water at 6 °C. Reactor stirring was provided using a pitched blade stirrer rotating at a constant speed of 200 rpm. The temperature was measured using a platinum resistance thermometer (PT100), turbidity was measured with an in-house-built turbidimetric fibre-optic probe system. Both signals along with pH values were logged onto the computer system. Observation and recording of the process were carried out in real-time using the on-line imaging system. The on-line imaging system employed in the experiments is a prototype system developed at GlaxoSmithKline, UK (Wilkinson et al., 2000) which has been found being able to detect in real-time crystallisation on-set and dynamic transitions of crystal polymorphs (Calderon De Anda et al., 2005). A schematic diagram of the system is illustrated in Fig. 1. A high-speed CCD camera is employed for image acquisition with a maximum frequency of up to 30 images per second with a typical pixel resolution of 480 × 640 and a field of view from 140 μm to 16 mm. The camera is situated just outside the reactor wall and an imaging window is attached to the external reactor wall to avoid convexity effects on the images. To provide illumination, a strobe light source is used and the light is conducted using a fibre-optic guide. Camera acquisition and flashing light are synchronised to freeze the moving particles by using a camera interface box developed by the GSK researchers. The captured images are sent to a PC running VideoSavant software (IO Industries, Inc.) for acquisition and storage of frames. Users can chose from using one or two fibre-optic light guides, both adjustable in angles and distances. In this work, we found that for our application one fibre-optic light guide gives better results. The system allows to visualise and record in real-time every event occurring throughout the process, capturing the complete history of the crystallisation.

An off-line particle characterisation system using imaging technique is also used in the study. The PharmaVision System 830 (PVS830) from Malvern Instruments, Ltd (Malvern Instruments Ltd. Webpage) is an automatic vision system for analysis of the size and shape of particles. A zoom lens allows analysing particles between 0.5 and 2000 μm. The instrument automatically calibrates itself prior to an analysis by the measurement of both light intensity and precision grating with a known number of lines per millimetre. To perform analysis, the sample is placed on a sample tray under a CCD video camera. A linear actuator connected to a PC moves the camera across the sample tray and the camera takes digitised video images. Particles from the images are

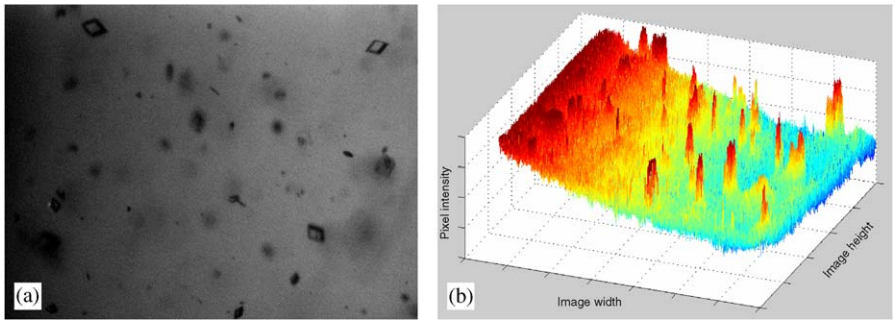


Fig. 3. A sample real-time image and the corresponding 3D pixel intensity plot.

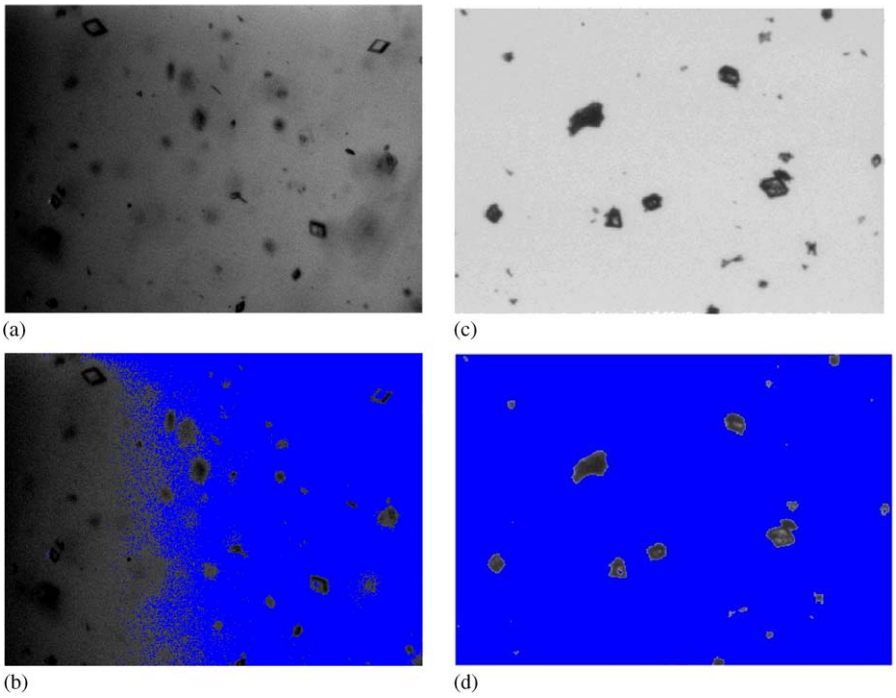


Fig. 4. Threshold method works for the off-line image, (c) to (d), but fail for an on-line image, (a) to (b) due to varied background intensity.

automatically segmented by embedded computer software obtaining a variety of size and shape parameters, such as length, width, mean diameter and roundness, supported by images of all particles for further visual understanding. The performance of the instrument is verified by reference slides certified and traceable to the National Institute of Standards and Technology standards. For the image analysis in the PVS830, a pipette was used to take samples from the reactor solution at several instants during the process. The samples were quickly placed and covered on the sample glass slide of the PVS830 previously calibrated, and images were grabbed and analysed. The time from taking a sample until the image analysis was from 10 to 20 s.

2.2. *Habit and polymorphism of* L*-glutamic acid*

Solutions of 33.3 g of L-glutamic acid (purchased from Aldrich Chemicals) dissolved in 500 mL of fresh distilled water were prepared. The solutions were heated up to 95 °C and kept constant at this temperature until everything was dissolved, then linearly cooled down to 15 °C keeping this temperature until the end of the experiment. Different linear cooling rates of 1, 0.5 and 0.25 °C/min were investigated in the study. The concentration and temperatures of the experiments were chosen to be near to those used in an industrial scale operation.

Thermodynamically, at a constant temperature a crystal in equilibrium with the mother phase exhibits the shape with the minimal overall surface energy. It is therefore expected that those faces providing a higher surface energy will preferably be occupied by new solute molecules, meaning in turn that they will have a higher growth rate. These faces are generally rough and not observed on the final crystal shape, whereas those slow smooth growing faces provide larger area critically defining the final crystal morphology.

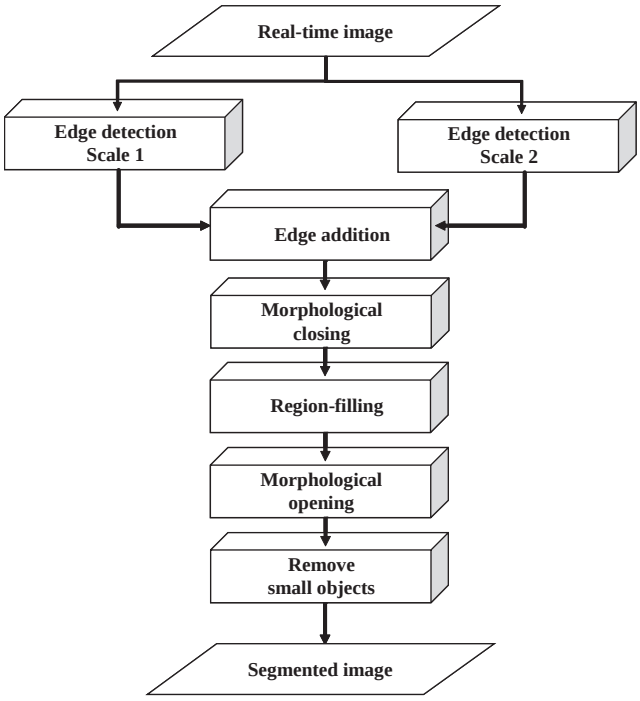


Fig. 5. Schematic of the segmentation procedure.

Polymorphism is the ability of a substance to crystallise in more than one crystal structure (Mullin, 2001), corresponding to different solid phases. It is common amongst organic compounds and may be seen as a specialised purity issue, as polymorphs reflect significantly different properties on the final product, such as dissolution rate, stability and bioavailability in the case of drugs. An indicator of polymorphic change is a significant change in crystal habit during crystallisation. (L)-glutamic acid is known to have two polymorphic forms, called α and β, when crystallising from aqueous solution (Kitamura, 1989; Kitamura and Ishizu, 2000). Each of the polymorphs exhibits a characteristic crystal habit, the α-form being prismatic and the β-form being needle shaped (Fig. 2).

3. Image analysis

Image analysis has been an active research area although only a few publications are available regarding their application to images obtained on-line from reactors. Therefore here we make a brief overview of the methods available. Detailed reviews on image segmentation techniques can be found in the literature (Freixenet et al., 2002; Pal and Pal, 1993; Gonzalez and Woods, 1992; Deklerck et al., 1993; Freixenet, 2002; Russ, 2002), with the most popular methods being thresholding (Gommes et al., 2003; Otsu, 1979), split- and-merge (Manousakas et al., 1998; Deklerck et al., 1993), region growing (Lu et al., 2003; Hojjatoleslami and Kittler, 1998), clustering (Patino and Razaz, 2001), watershed segmentation (Razaz and Hayard, 2000), snakes (Middleton and Damper, 2004; Ngoi and Jia, 1999) and edge-detection-based methods (Rajab et al., 2004; Pavlidis and Liow, 1990). Some applications of these methods have been based on a colour segmentation scheme (Onyango and Marchant, 2003; Derganc et al., 2003), but nevertheless crystals generally show a translucent and colourless appearance and therefore the segmentation is better suited in grey scale.

Many image analysis approaches for particle characterisation have been proposed in the past by several researchers (Drolon et al., 2000; Glendinning, 1999; BernardMichel et al., 1997; Thomas et al., 1995; Vallejo, 1995). Most of them however, only concentrate on the characterisation procedure itself with only a few referring to the particle segmentation from the image, usually based on threshold methods since the particle images analysed are typically acquired from off-line techniques, such as photo-microscopy, which provide images with pixel intensity profiles ideal for this type of segmentation method, i.e., images where particles exhibit a clearly different pixel intensity in relation to the background.

Recently, there have been reports on the use of on-line imaging techniques for crystallisation monitoring (Patience, 2002; Patience and Rawlings, 2001; Barrett and Glennon, 2002), as well as other industrial processes (Yu et al., 2003; Bharati et al., 2003; Chen and Wang, 2005). Chen and Wang (2005) reported a wavelet method for analysing images obtained from polymerisation reactors, and the objects are round bubbles and solid polymers. Patience (2002) reported difficulties when trying to obtain crystal shape characteristics from images taken by the Lasentec PVM probe using a commercial image analysis software. Due to the irregularity in pixel intensity and light reflection of the crystals, the software was unable to segment the crystals from the images. As a result, Patience and Rawlings (2001) developed a new imaging system by combining a stop-flow flow through cell and photo-microscopy. Since the images are taken for the static slurries in the cell after the crystals are settled down at the bottom of the cell, the image qualities are greatly improved and objects can be segmented using a threshold method.

Images of slurries with particles suspended in a solution are clearly more complex than images of pure solid particles. But 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 the edges of some particles vaguer than some others. In addition, the light effect and temporal changes of hydrodynamics within the reactor may lead to varied intensity in the background. Fig. 3 (a) shows such an example: the left part of the image has darker background than the right part, which can be more clearly seen if we plot the pixel intensity of the image, and image width and length in a three-dimensional representation (Fig. 3(b)). This can lead to difficulty in image analysis as demonstrated in Fig. 4, where a threshold method works well for an off-line image which has more uniform background

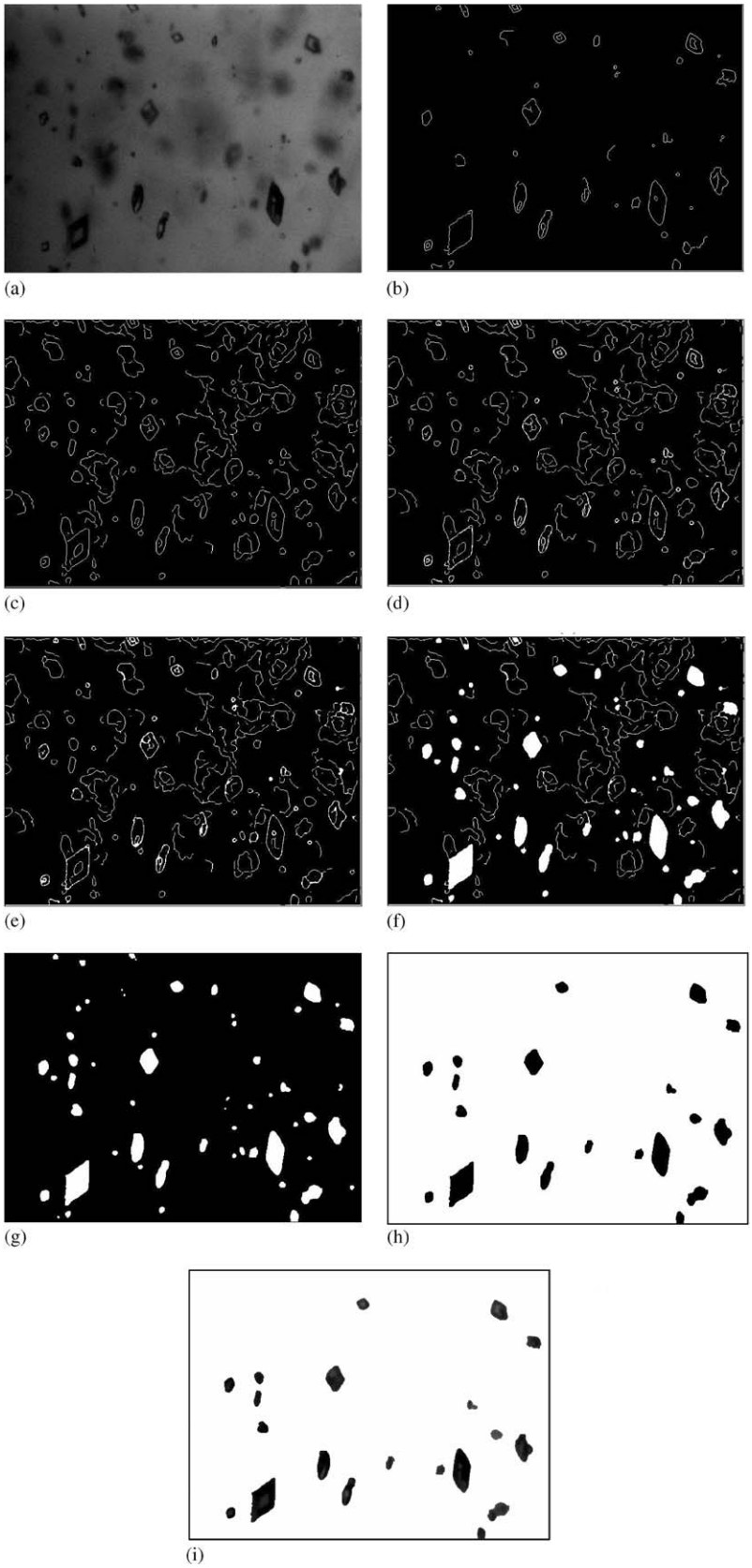


Fig. 6. The segmentation method applied on a sample in situ image with highly irregular pixel intensity. (a) Original image, (b) edges detected at the first scale, (c) edges detected at the second scale, (d) edges of first and second scales, (e) morphological closing on image (d), (f) region-filling on image (e), (g) morphological opening on image (f), (h) segmented particles after removing those with less than 200 pixels from image (g), (i) segmented particles with the original grey-scale intensity superimposed.

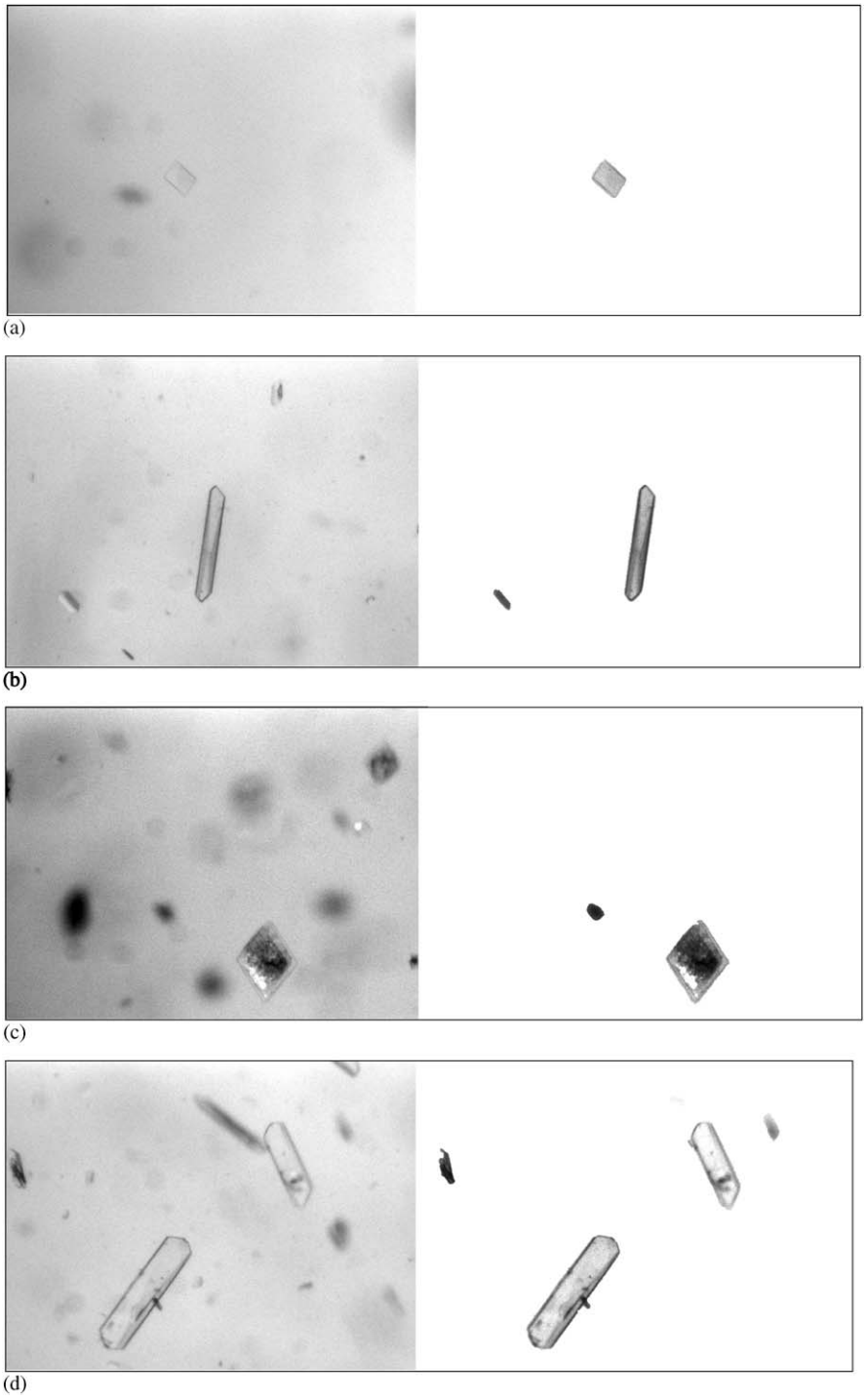


Fig. 7. The segmentation method applied on sample in situ images from the GSK system.

pixel intensity (Fig. 4(c) and (d)), but fails to the image of varied background pixel intensity (Fig. 4(a) and (b)).

The method employed in this work is depicted in Fig. 5 and was implemented using Matlab. It consists of two major steps, i.e., edge detection and image segmentation, with details of each step described below.

3.1. Multi-scale edge detection

Edge detection is an important step in image analysis that extracts small and precise edge features from a large number of pixels of an image. A major problem with direct use of available edge detection methods is that the objects of interest in an image obtained on-line can have varied

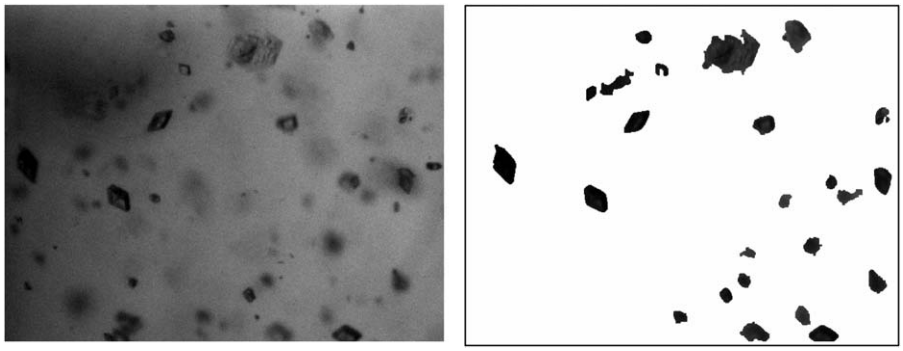


Fig. 8. The segmentation method applied on a sample in situ image with highly irregular pixel intensity.

degree of clarity and thickness for the edges. The multi-scale edge detection method is similar in principle to the "double thresholding" approach proposed by Olsson (1993). The idea is to capture the features that most definitely represent the edges at the first scale, and then at the second scale, it is to obtain a complete delineation of all edges, even accepting some noises. The edges detected at the two scales are then combined to provide the information which is used to object segmentation through morphological closing and opening operations (Russ, 2002). Multi-scale analysis is useful because what appear as edges at a particular resolution may appear as texture at a lower resolution. Information concerning an image can be obtained by extracting edges from smoothed versions of an image at various resolutions. These smoothed versions are obtained by convoluting the image with a kernel function called *filter*. Edge points correspond to inflection points of the smoothed image. These inflection points, in fact, correspond to local maxima of the absolute value of the first derivative, or equivalently, to the zero crossing of the second derivative of the smoothed image intensity function. The method of detecting edge points by using modulus maxima of the first derivative corresponds to the Canny method (Canny, 1986); employment of zero-crossing on the other hand, corresponds to a Marr–Hildreth edge detector (Marr and Hildreth, 1980). Images may contain slow variations of intensity which do not correspond to edges, sometimes due to noise, and zero-crossing methods also vanishes at these slow inflection points. Modulus of first derivative, however, is able to distinguish these changes of intensity, since slow variations correspond to local minima (Mallat and Zhong, 1992). Therefore, edge detection methods employing maxima of the first derivative, such as the Canny method, should result in a better performance.

The Canny algorithm is composed of the following steps. Firstly, the image $f(x, y)$ is smoothed by convolution with a two-dimensional Gaussian kernel function, G.

$$F = G * f(x, y), \tag{1}$$

$$G = \exp\left(-\frac{x^2 + y^2}{2\sigma^2}\right), x = 1, \ldots \mathrm{N};\ \ y = 1, \ldots \mathrm{M} \tag{2}$$

where I is the smoothed image, x and y are the coordinates of the pixel to be processed in a N×M dimensional image, and σ is the standard deviation of the Gaussian kernel. To find the points of sharp variation, which correspond to image edges, a first derivative operator is applied to the smoothed image to determine the magnitude and direction of the corresponding gradient vector. The gradient vector, $\vec{\nabla} F$, is determined by the following equation:

$$\vec{\nabla} F = \begin{bmatrix} G_x \\ G_y \end{bmatrix} = \begin{pmatrix} \dfrac{\partial F}{\partial x} \\ \dfrac{\partial F}{\partial y} \end{pmatrix}, \tag{3}$$

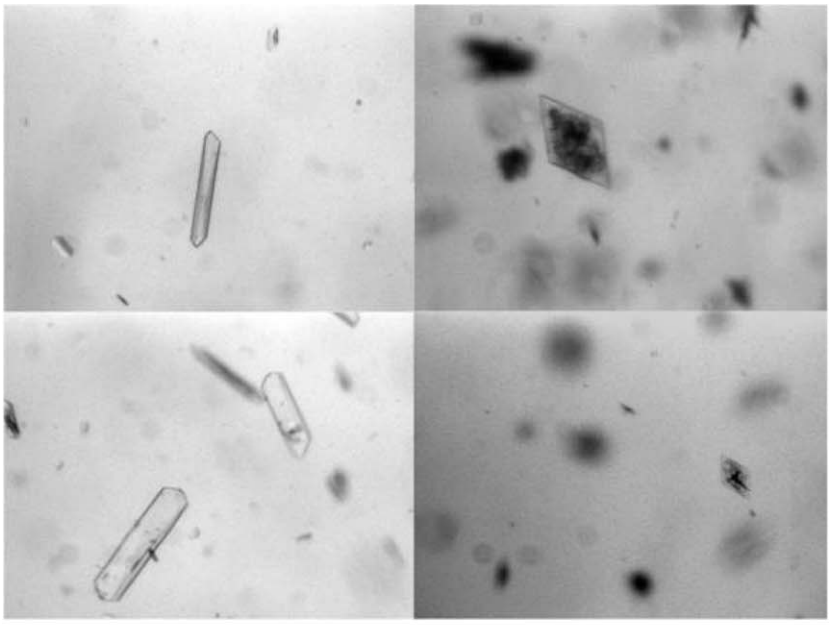
where G_x and G_y correspond to the vertical and horizontal slopes, and the modulus $|\vec{\nabla} F|$ and direction φ of the gradient are estimated by

$$|\vec{\nabla} F| = \sqrt{G_x^2 + G_y^2}, \tag{4}$$

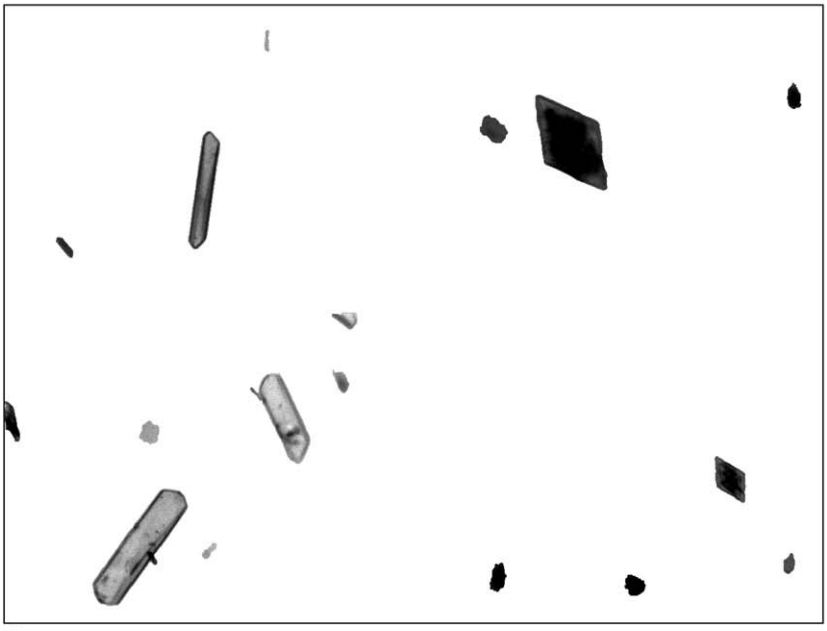
$$\varphi = \tan^{-1}\left(\frac{G_y}{G_x}\right). \tag{5}$$

When the modulus of the gradient is a local maximum at a point, (x_0, y_0), in a one-dimensional direction parallel to the direction defined by φ, the pixel (x_0, y_0) is marked as part of an edge, otherwise it is marked as background. This procedure is called non-maximal suppression. A later hysteresis threshold is used to get rid of multiple edge fragments. Two values T_1 and T_2 are used, with T_1 greater than T_2, and edges can only start from a ridge greater than the value T_1 and the tracking continues in both directions from the starting point until the edge ends or the height of the ridge falls to T_2.

The effect of the Canny operator is affected by the width of the smoothing function which corresponds to the standard deviation, σ, of the Gaussian function. Performing image convolution with a Gaussian function of different standard deviation corresponds to modifying the image scale. Increasing the width of the function, i.e., increasing the scale, reduces the sensitivity of the method to noise but finer detail information may be lost. Typically, values for standard deviation of $\sigma = 1$ and 2 provide the relevant image



(a)



(b)

Fig. 9. The segmentation method applied on a sample in situ image with highly irregular pixel intensity.

information, whereas higher values of standard deviation may not provide relevant data and the more scales are obtained the longer the analysis takes. Edges of objects detected at some particular scale may or may not be detected at a different scale, therefore the information of for example two different scales complement each other. This issue is particularly useful to complete non-closed contours obtained in a single scale.

Fig. 6(b), (c) shows the first- and second-scale analysis results of the image (a), and (d) is the combination of the two scales.

3.2. Object segmentation based on morphological operations

After edge detection, morphological closing is the next step to close the breaks in features. At this point, it is reasonable to assume that the contours of the main particles are complete, and therefore a region-filling operation is applied to fill the area covered by those edges which are closed. The rest of the lines can be easily removed by morphological opening. The procedure is demonstrated in Fig. 6(e)–(g). Finally, a procedure can be applied to remove the very small

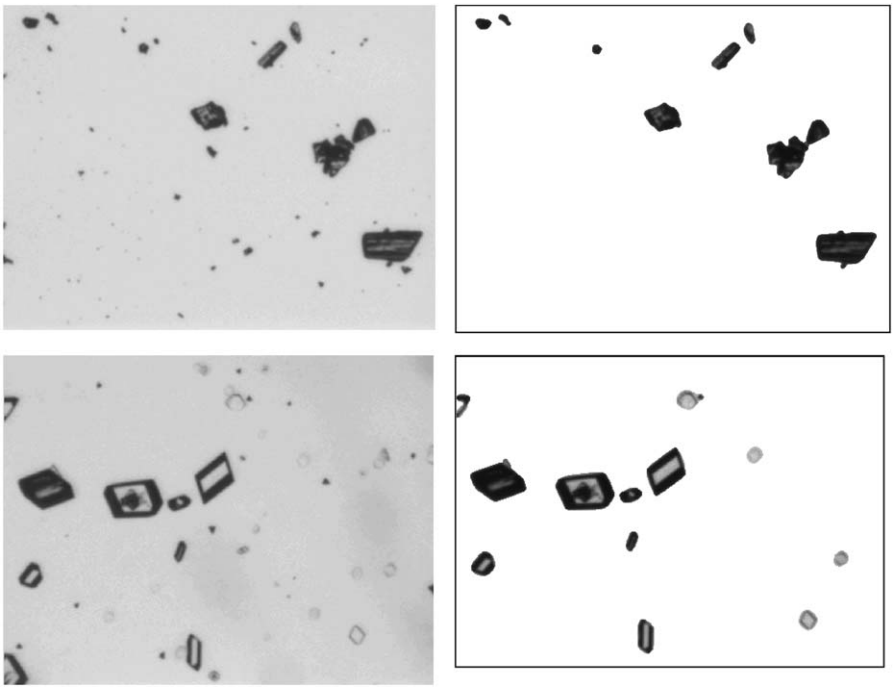


Fig. 10. The segmentation method applied on a sample off-line image from the PVS830.

particles which are not likely to provide reliable shape information. This procedure also removes some small background spots that might have been segmented during the process, and it is done by specifying a minimum number of pixels. The result is the image 6(h). Fig. 6(i) is to represent the segmented particles of (h) with the original grey-scale intensity superimposed.

For the present application, a value of 200 pixels was set to remove the small debris from the segmented images. However, this value can be specified by users. It depends on the specific application. For instance, if the particles are small, a smaller value can be used.

The processing time for a typical image of a resolution of 640×480 obtained by the GSK system is from 7 to 10 s using a PC of 2 GHz. No significant difference in processing time was observed when analysing images from the PVS830 with resolution of 756×548.

4. Results and discussion

An on-line image has been used above in the introduction of the methodology. In this section, a few more on-line images of varied crystal morphological forms are presented. In addition, to test the generalisation capability of the methodology, on-line crystallisation images taken by the PVM probe of Lasentec Inc. (Barrett, 2003; Barrett and Glennon, 2002), and off-line crystallisation slurry images taken using the PharmaVision Systems 830 of Malvern Instruments Ltd are also used in the study.

During image analysis, the parameters for the edge detector, σ, T_1 and T_2, were tuned for the first few images as to provide acceptable segmentation results, and these values were maintained constant for the analysis of the rest of the images to keep the method as independent as possible of parameters. For all the segmentation results shown in this paper, the images were analysed at two scales corresponding to values of standard deviation $\sigma = 1$ and 2, and keeping the threshold values to $T_1 = 0.2$ and $T_2 = 0.05$. Segmented objects composed by less than 200 pixels were automatically removed at the last step of the method.

Fig. 7(a)–(d) show example images obtained in-situ, corresponding to the two polymorphic forms of (L)-glutamic acid, alpha and beta forms, obtained during batch crystallisation experiments using the GSK imaging system, with their corresponding segmentation result. The processing shows that the method can extract with success the main particles present in the images and discard the very vague objects and small particles. In particular, it is worth noting that the contour of the particles are appropriately segmented, which represents an important factor for a posterior shape analysis.

Fig. 8 shows another example image with poor background pixel intensity characteristics. It is worth pointing out here that with careful tuning, the on-line imaging system can often provide better quality images than that of Fig. 8. This image is selected here in order to demonstrate that the approach is tolerant to the quality of images.

To further illustrate the capability of the proposed method, an image shown in Fig. 9(a) is artificially combined by four different in situ images containing crystals of two different

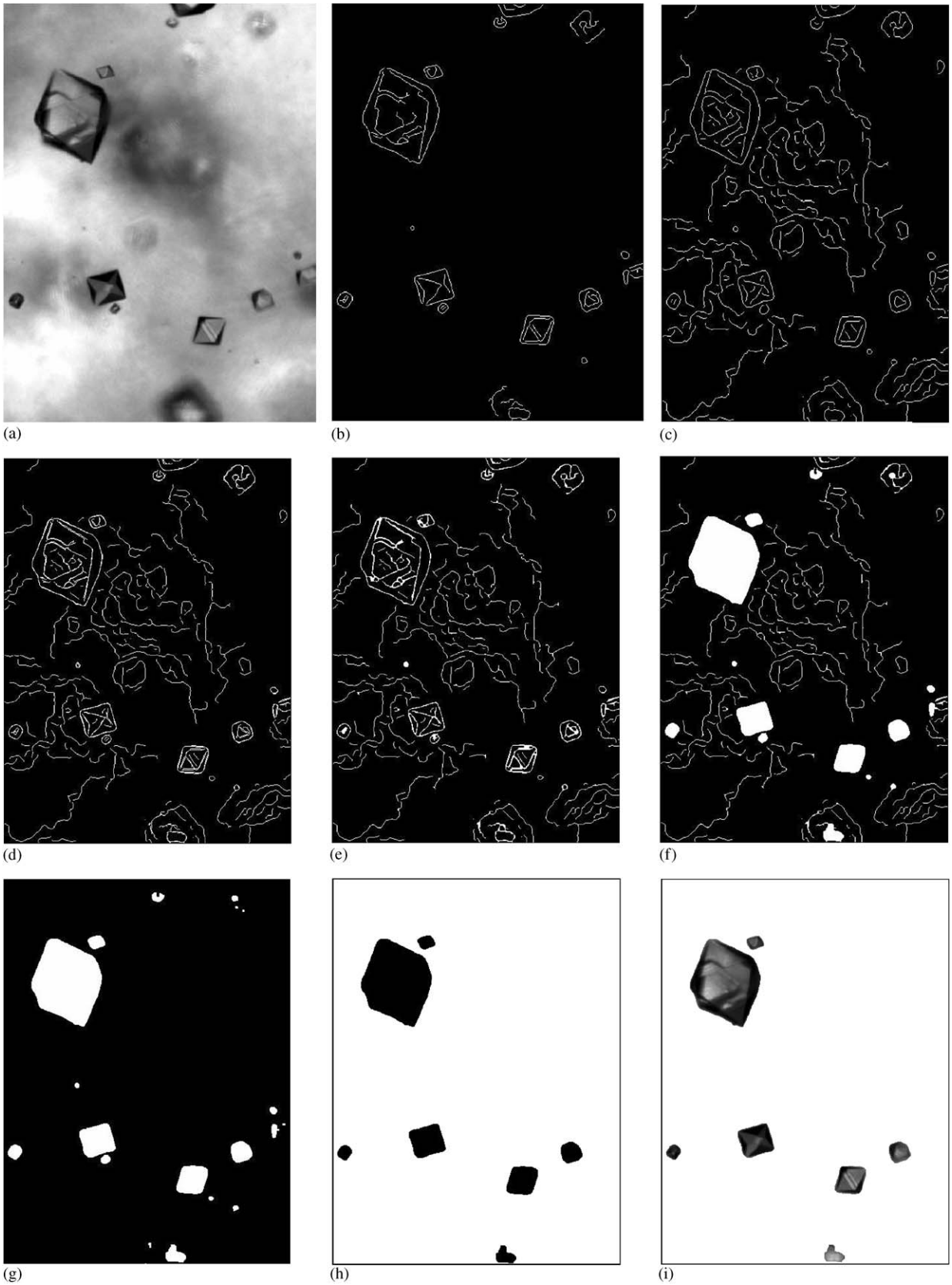


Fig. 11. The segmentation method applied on a sample in situ image from the Lasentec PVM. (a) Original image, (b) edges detected at the first scale, (c) edges detected at the second scale, (d) edges of first and second scales, (e) morphological closing on image (d), (f) region-filling on image (e), (g) morphological opening on image (f), (h) segmented particles after removing those with less than 200 pixels from image (g), (i) segmented particles with the original grey-scale intensity superimposed. Fig. 11(a) is by courtesy of Lasentec (Barrett, 2002).

polymorphic forms of (L)-glutamic acid, alpha with rhombic shape and beta with needle shape. It is also clear that the background varies significantly. The segmentation result of the whole artificial image is shown in Fig. 9(b).

The above example images are all obtained using the on-line imaging system of GlaxoSmithKline. In the following, we apply the method to images obtained using other two imaging systems.

4.1. Segmentation of images taken by PVS830

As mentioned earlier, the PVS830 system, an equipment designed for particle characterisation has been used alongside the GSK on-line imaging system for off-line image capturing. The quality of images are generally better than that of the GSK on-line system. As a result, it is expected that the image segmentation approach will have no difficulty in handling images of the PVS830. Fig. 10 shows two such images and their segmentation results, which confirmed the prediction.

4.2. Segmentation of on-line images taken by the PVM probe

The Lasentec PVM probe has been applied to crystallisation for characterising the metastable zone width and solubility curve by Barrett and Glennon (2002), for size measurement by Barrett (2003), and for shape monitoring of inorganic crystals (Patience and Rawlings, 2001). Patience (2002) described difficulties in analysing the images using a commercial image analysis software system. Lasentec PVM probe was not used in our experiment but images from literature were used in here to test the capability of generalisation of the image segmentation methodology. Fig. 11(a) shows the original image, and (b)–(d) show the edge detection at first and second scales and the combined result. Fig. 11(e)–(g) show the morphological closing, region filling and morphological opening. Fig. 11(h) is the extracted objects, and Fig. 11(i) shows the segmented particles with the original grey-scale intensity superimposed.

5. Final remarks

Compared with images obtained off-line which often have clear edges, images of crystal slurries captured on-line are much more complex. The objects can be very vague and have varied thickness of edges. In addition, the objects within a single snapshot may be in different depth, causing variation of clarity. Due to the need to use lights, and the hydrodynamics of the slurry in the reactor, the images may have varied pixel intensity. Little work has been reported in literature on analysis of such on-line images of crystal slurries. Our experience on some existing methods being unable to cope with the on-line images is consistent with that of the only reported work in literature. The methodology presented in this work proved to be able to effectively analyse on-line images obtained during the batch crystallisation of (L)-glutamic acid using the GlaxoSmithKline imaging system, some even with very poor qualities. The method is also applied to analysing images of the same chemical captured by an off-line imaging system, the PVS 830 of Malvern Instruments Ltd, and on-line images of Lasentec PVM imaging probe which were for a different compound and obtained from literature.

The future work will include investigating image analysis techniques to obtain quantitative information of the 2-D images, and developing a methodology for constructing the 3-D structure from information obtained from 2-D.

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