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On-Line Monitoring of Particle Shape and Size Distribution in Crystallization Processes through Image Analysis

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Abstract

On-line monitoring and control of particle shape and size distribution is important in pharmaceutical and fine chemical manufacturing. In this paper, we describe a methodology for real-time estimation of particle quality variables during crystallization using inline process video-images. Our approach integrates image analysis techniques with multivariate statistical techniques to quantify particle shape and size. This information can then be used for process monitoring and control. In this work, we demonstrate applications to systems with high particle concentration.

Keywords: Particle shape and size, In-Process Video Measurement (PVM), Image analysis techniques, multivariate statistical techniques

1. Introduction

On-line monitoring and control the product quality of particle shape and size distribution is a challenge faced by the traditional pharmaceuticals and fine chemicals industries due to the process complexity, the lack of process understanding and adequate in-situ sensors. With regulatory initiatives such as

the US Food and Drug Administration's (FDA) Process Analytical Technology (PAT) program for the pharmaceutical industry and the ongoing improvement in real-time imaging hardware (exemplified by Focused Beam Reflectance Measurement, FBRM and In-Process Video Measurement, PVM, both from Lasentec) concomitant with the developments of image analysis techniques, there is a fast growing interest in the pharmaceutical and chemical industries as well as the research community to develop advanced in-line control technologies for particulate processes using such advanced imaging sensors.

A number of studies [1-7] have recently highlighted the success of implementation of such imaging sensors to gain insights into crystallization process and thereby provide extra capability for in-line process control. However, there is still a gap between the information obtained from advanced imaging sensors and the knowledge required for in-line control of crystallization process. While variables such as crystal size and shape are critical in crystallization, available in-situ sensors do not provide direct measurements of these. Information about crystal size can be indirectly obtained in the form of chord length distribution as measured by FBRM, however in numerous situations, the chord length deviates systematically and significantly from the true crystal size distribution [8-9]. In this paper, we aim to circumvent these challenges by using in-process video imaging (PVM in particular) for determining particle shape and size distribution for the purpose of process control.

2. **Methodology**

Our method combines image processing techniques from artificial intelligence with statistical multivariate image analysis techniques for real-time analysis of PVM images from a crystallization process case study [10]. Figure 1 highlights the key steps in the methodology. In our approach, Image Analysis Techniques [4] specifically image enhancement, edge detection, morphology operations, and feature extraction are employed to detect objects (crystals) of interest in in-situ images. In parallel, multi-way principal component analysis (MPCA) is also performed on the image and statistical descriptors derived for particle shape classification. Each detected object is enclosed within a minimum-area rectangle, from which morphological descriptors (eg: shape factors) are evaluated. In this paper, we describe the further development of this work particularly focusing on situations at high solids concentration where traditional image analysis techniques fail.

During a typical crystallization process, the solid crystal concentration increases as the crystals nucleate and grow. The PVM thus acquires blank images (showing only the background) at the beginning, but towards later stages in the

crystallization shows images with many overlapping crystals. The contrast of the images also varies with time. At higher solid concentration solutions the quality of the image obtained from the in-process video measurement system suffers from many factors – while there are a number of particles in the frame, the whole image appears blurred, the background is not uniform partially due to the effect of bubbles in the medium, many of the particles are not in focus due to varying distance from the lens, and crystals appear to overlap. Example of these can be seen in Figure 3a. The situation becomes even more complex in crystallization processes with polymorph transition. Next, we explain how these issues at high concentration are overcome by the proposed methods.

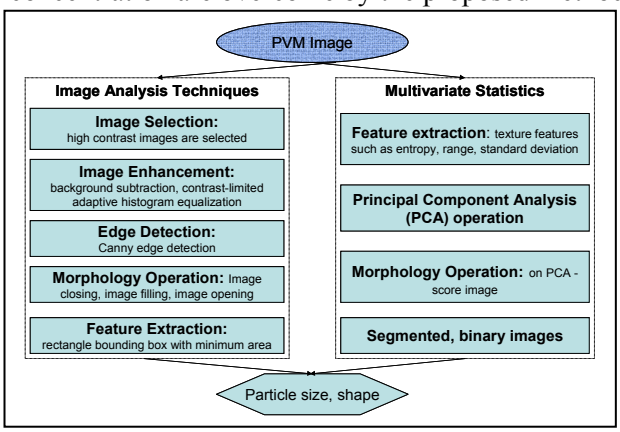

Figure 1: Proposed methodology for online image processing

2.1. Image Analysis Techniques

As detailed described in our previous work [10], the steps of Image Analysis (IA) techniques work adequately when the particle images do not have significant imperfections. Particles of different shapes including cubic NaCl particles and rod shaped Mono-Sodium Glutamate, MSG particles could be correctly recognized and classified through shape descriptors such as the aspect ratio. In this paper, we expand the domain of IA techniques to images from higher solid concentration solutions.

Image Selection The PVM is fixed in the vessel and takes images of particles as they come into the field of view. These in-process images may contain particles, but also bubbles and other aberrations caused by inadequate lighting. When the vessel contains no particles, the images may merely show the background. IA methods are fast and accurate enough for quantifying particles from images containing clear particles. But, these techniques require significantly larger computational time to search for objects from poor quality images. Therefore, while dealing with processes that are characterized by high solids concentration, the first step is to automatically select good quality images with high object to

background contrast. The intensity histogram of images containing clear particles differs substantially from those of images with aberrations. Since particles and background usually have different regions of intensity, and larger the intensity difference, the higher the contrast of particles to background, we have used the intensity range as a criteria to automatically select images with clearly identifiable particles. Only these selected images are considered in subsequent steps in order to achieve efficient computational performance.
Image Enhancement and Edge Detection The quality of selected images are further improved by background subtraction and contrast-limited adaptive histogram equalization, and the particles are highlighted by eliminating the background. Then canny edge detection is followed to find both the strong edges and weak edges of each particle, and generate a binary image containing only the edges information.
Morphology Operation and Feature Extraction According to the binary images generated by edge detection, a series of morphology operation, such as image closing, image filling and image opening, are followed to segment particles from background, and generate binary images highlighting the position and area of each particle. Feature extraction step will obtain the accurate outline of each particle from morphology binary images, and find a minimum-area rectangle bounding box to characterize particle size of length and width. Since morphology operation requires shape information of structured elements, different structured elements should be considered for different particle shapes.

2.2. Multivariate Statistical Techniques

Previously, a re-sampling of the image region within the minimum bounding rectangle was carried out to obtain an intensity-averaging matrix **X**, which captures the entire particle. **X** contains the characteristics necessary for particle classification, and MPCA was used to build a model for particles and Hotelling's T^2 statistic evaluated for particle shape classification. This technique is specifically designed for particle shape classification.

As an extension, we now seek to quantify the size (i.e. length and width) of particles directly from **X**. The main steps, as shown in Figure 2, are explained next.
Feature Extraction In this step, a number of features which differentiate particles from the background are evaluated. Various features such as Gabor features, texture features, and statistical features can be used for this purpose. In this study, three statistical texture features – entropy, range, and standard deviation, were selected. These features are all based on intensity variation within a local neighborhood of the corresponding pixel. Entropy is a statistical measure of randomness that can be used to characterize the texture of the neighbor-hood image. Mathematically, for each pixel (*i, j*) in a neighborhood, entropy $E(i,j) = -\sum_{N} \{p \cdot \log(p)\}$, where p is the histogram count of the gray-

scale intensities and the summation is over all the histogram bins. Range is defined as the difference between the maximum and minimum intensities within the neighbor-hood. It is evident that each of the selected features resulted in a matrix has the same size as the original image. When more than one feature is used (as is the case here), a multi-way image matrix is obtained. Consequently, MPCA is used to analyze the data. The first score from the MPCA analysis can be interpreted as a pseudo-image. Figure 3b shows an example of the pseudo-image which has been generated from the original image in Figure 3a.

Morphology Operations A number of morphology operations is required to further process the pseudo-image. These may include thresholding, closing, and opening. At the end of this step, a segmented binary image is obtained, an example of which is shown in Figure 3c.

Particle Quantification From the binary image in which the particles have been segmented, particles can be characterized by their bounding boxes and sizes evaluated. Figure 3d shows the particle and their bounding boxes as identified by the proposed technique.

3. **Results**

We have applied the above techniques to three sets of crystallization. Clear particles were segmented and quantified in most cases. Typical examples are shown in Figure 2. Good estimates of the particles' length and width are obtained for many of the particles, as confirmed by the human eye. However, it was noted that the estimates are not completely reliable in cases where significant particle overlap occurs. This issue is a well recognized problem and is currently the subject of our ongoing work, specifically, through the integration of multivariate statistical and image analysis methods.

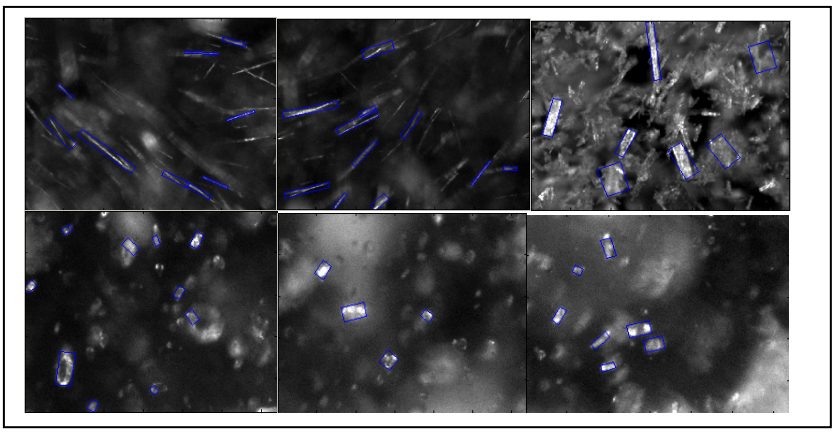

Figure 2: Primary results of image analysis techniques to process images taken from high solid concentration solutions

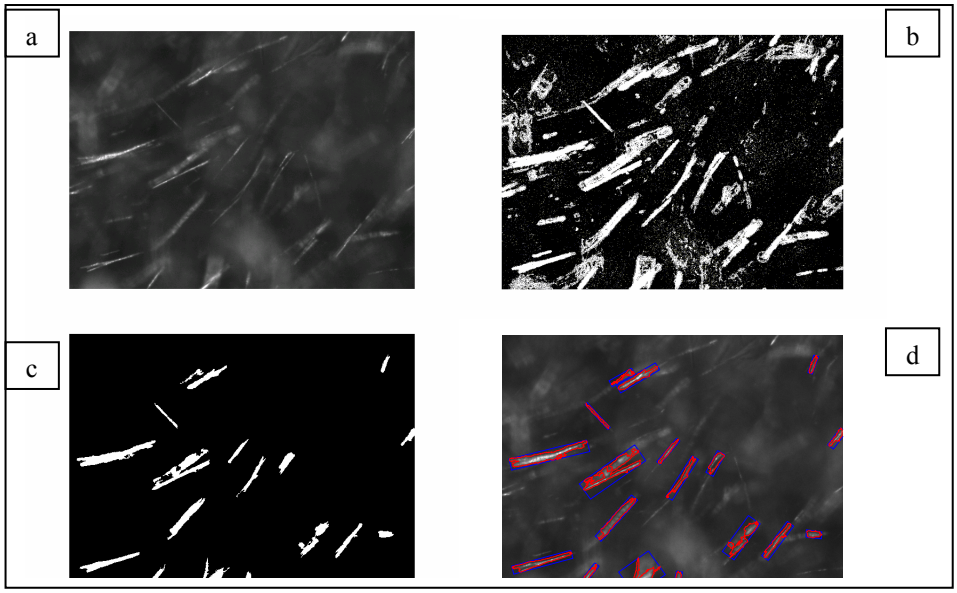

Figure 3: Results of multivariate statistical technique for selected PVM image. (a) original image. (b) pseudo image. (c) segmented binary image. (d) original image with particles' outline and bounding box embedded.

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