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High accuracy online measurement of multidimensional particle size distributions during crystallization

Stefan Schorsch [a], David R. Ochsenbein [b], Thomas Vetter [a,1], Manfred Morari [b], Marco Mazzotti [a,*]

[a] ETH Zurich, Institute of Process Engineering, Sonneggstrasse 3, CH-8092 Zurich, Switzerland
[b] ETH Zurich, Automatic Control Laboratory, Physikstrasse 3, CH-8092 Zurich, Switzerland

AUTHOR-HIGHLIGHTS

- An image based setup for measuring *n*D particle size distributions online is shown.
- Particle classification and size calculation algorithms are introduced.
- Capabilities of the setup in terms of accuracy and time resolution are demonstrated.
- A virtual test bench is developed and used to investigate different image analysis effects.
- The setup is tested during the growth of organic crystals.

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ABSTRACT

A novel stereoscopic image acquisition setup and a procedure for measuring multidimensional particle size distributions (*n*D PSDs) during crystallization based on image analysis are presented. Images of crystals in suspension passing a flow through cell are generated by two cameras which are arranged in an orthogonal manner. Particles are conveyed to the flow through cell using a sampling loop, thus allowing for online monitoring. Automated image analysis provides contour data which can be used to classify crystals into different generic particle model classes. For each type of particle size data is calculated and stored. Finally, time resolved *n*D PSD data can be calculated. The accuracy of this novel size measurement was confirmed by comparison to measurements obtained with a Coulter Multisizer. The non-invasive nature and repeatability of experiments are shown by monitoring populations of sodium chloride and of the β polymorph of L-glutamic acid under different conditions. Finally, crystal growth of acetaminophen during cooling crystallization is shown. In addition, a virtual test bench is used to study the measurement method in silico.

1. Introduction

Crystallization processes are key steps during the production of pharmaceuticals and fine chemicals. During crystallization particle size and shape, which have a crucial impact on many downstream processing operations (Wibowo et al., 2001) and also on product functionality itself (Chow et al., 2008), are defined. Hence, product quality control, process design, or optimization can tremendously profit from data that accurately describes crystal size and shape. In many cases, a single characteristic length is only an insufficient measure for the shape of a particle, e.g., a needle like crystal needs to be described at least in two dimensions, i.e., its length and width. However, measuring multiple characteristics for whole ensembles of particles, leading to multidimensional particle size distributions (*n*D PSDs), on-line and in a quantitative manner without extensive sample preparation remains a challenge.

Singh et al. (2012) give an overview on available particle size measurement technologies. If one is interested in acquiring *n*D PSDs, in situ and ex situ imaging techniques have been shown to be powerful tools (see Schorsch et al., 2012 for an overview of different optical setups and image analysis approaches). A key problem of imaging approaches is the dependence of projections of particles on their spatial orientation. One promising way to mitigate these issues is the use of multiple view angles, i.e., stereoscopic imaging (Bujak and Bottlinger, 2008; Wang et al., 2008).

* Corresponding author. Tel.: +41 44 632 2456; fax: +41 44 632 11 41.
E-mail addresses: marco.mazzotti@ipe.mavt.ethz.ch, schostef@ipe.mavt.ethz.ch (M. Mazzotti).
[1] Current address: Department of Chemical Engineering, University of California Santa Barbara, United States.

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In earlier publications, a successful implementation based on a sapphire glass flow through cell has been demonstrated (Kempkes et al., 2010b; Schorsch et al., 2012). In that implementation part of the light beams of a flash lamp went straight through the flow cell while the other part was led through the flow cell in the orthogonal direction using two mirrors. This yielded projections of the same particles from orthogonal directions which were collected by a single camera. An algorithm restored the 3D position and size of each object via an automated image analysis protocol. After measuring a desired number of particles a quantitative *n*D PSD was calculated. As the flow cell was connected via a sampling loop to a stirred tank crystallizer, online measurements were made possible.

Notwithstanding the admirable performance of this setup, we aimed to further improve this technique to permit continuous, real-time monitoring of crystallization processes for a wider range of particle sizes, solvents and temperatures. In this work, a second generation stereoscopic imaging setup with improved design, particle flow pattern, and optics is thus described and enhancements to the image analysis routines used to extract particle size and shape data from the acquired images are presented.

Monitoring of crystallization processes via imaging is a complex task due to the nonlinear effects introduced by the measurement method itself. In order to qualitatively evaluate the performance of our image analysis procedure, a virtual test bench (VTB) is presented in which artificial images of ideal polytopic crystals are generated and analyzed. This allows to investigate the influence of important process parameters such as the suspension density and the particle size on the measurement. A similar idea has been pursued by Larsen and Rawlings (2008) who investigated the influence of suspension density on the accuracy of the measured number density PSD for simple needle-like crystals, while Borchert and Sundmacher (2012) investigated the accuracy of single particle measurements from images with a finite resolution. The VTB presented in this work is adapted for the perpendicular camera arrangement of our setup and for general, polytopic crystals. The input to the VTB is a list of particles that can be generated manually or via sampling of a distribution, which in turn can be obtained from the solution of a (morphological) population balance equation (PBE) model.

The new setup itself is described in Section 2. Section 3 explains particle models that are used in actual measurements and simulations of the VTB. The image analysis routines and the calculation of multidimensional particle size distributions are explained in Section 4. Artificial image generation for the virtual measurement simulation is shown in Section 5, where also several analysis cases are presented. In Section 6 we demonstrate the application of the new setup and analysis protocol in multiple studies. Additional characterization experiments for the new setup are reported in the supplementary material.

2. Measurement setup and image acquisition

The setup as described in Schorsch et al. (2012) was proven to be capable of measuring *n*D PSD data for different applications, showing that external flow through cells are a promising way to implement multidimensional size measurements. However, the need to improve the old setup to perform continuous measurements in a more robust manner for a broader range of process conditions arose. Requirements for the new design included chemical stability in the presence of organic solvents, a flow pattern in the cell that provides random particle orientation without the risk of causing a blockage of the sampling loop, a larger cross section of the measurement channel, improved optics with higher resolution, a larger field of view, and a homogenous illumination of the image. The existing sampling loop (though without using the dilution system for experiments presented in Schorsch et al., 2012) and the previously reported 2 L crystallizer (Kempkes et al., 2010b) have been used.

A conceptual drawing of the new setup is presented in Fig. 1. The two mirrors that used to guide the second light beam in an orthogonal direction through the cell have been replaced by a second flash lamp and a second camera. The central element of the new setup is the flow through cell itself, whose improvements are detailed in the following. A technical drawing is given in Fig. 2. Four sapphire glass windows, two with a rectangular and two with a T-shaped cross section, are glued together so as the glued surface is not exposed to the solvent stream resulting in a square channel of 2×2 mm. The glass is held by two brass blocks. The seamless transition between piping of a circular cross section with an inner diameter of 4 mm and the square profile of the channel is realized in flanges that connect via Teflon sealings to the brass holders. Six screws on each flange guarantee an even distribution of the contact pressure to safely seal the flange connection. The glass itself is strain-released by four spacers that assure a fixed minimal distance between the lower and upper holding block. Additionally, the temperature of both brass holders is controlled. The piping itself is insulated.

All optical components are mounted on an optical rail system allowing for high precision adjustments. Illumination of the channel is provided by two high intensity Hamamatsu LX7865 xenon-flash lamps. Flash light is collimated using a 50 mm lens in front of each lamp. The decay time of the flashes is very short (< 10 ns) such that motion blur is negligible. Images are recorded by two Allied Vision Technologies Pike F505B cameras that provide a 5 megapixel 8 bit grey scale resolution each and are equipped with 300 mm telecentric lenses. This combination of optics and cameras results in a resolution of 1.15 µm/pixel in our images. In order to guarantee the simultaneous acquisition of both images, an

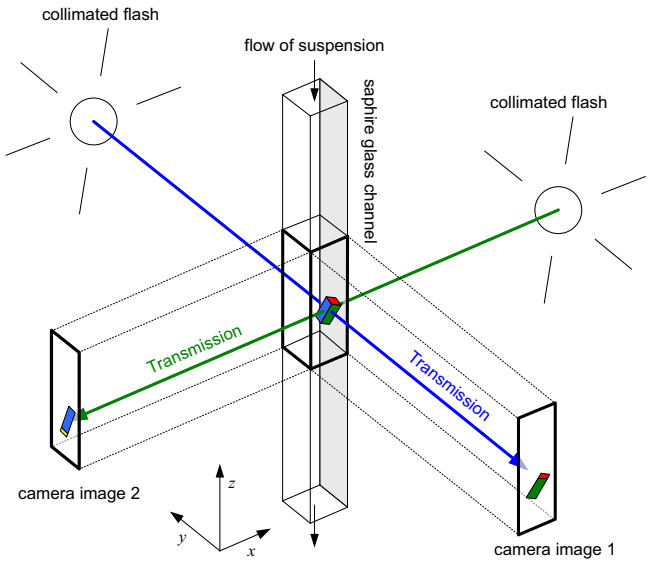

Fig. 1. Schematic drawing of the flow through cell. The light from the two xenon flashes passes straight through the cell from two orthogonal directions (blue and green rays). The particle in the cell is photographed by two cameras at the same time that are mounted perpendicular to each other as well. Vertices of particles in the cell can be assigned to Cartesian coordinates (x, y, z) whose meaning is indicated by the three arrows labeled with x, y and z, i.e., the particle projection recorded by camera 1 holds information on (x, z) data whereas camera 2 records (y, z) data. It is important to point out that in this way z coordinates of the same vertex are identical in both projections. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)