



Integration of in situ imaging and chord length distribution measurements for estimation of particle size and shape

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HIGHLIGHTS

- Methods for estimating PSD from CLD and images obtained in situ are developed.
- The particle shape (aspect ratio) is estimated from images obtained in-line.
- Method 1 reduces uncertainty in the aspect ratio at which PSD is estimated from CLD.
- Method 2 decouples aspect ratio from the PSD estimation from CLD.

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ABSTRACT

Efficient processing of particulate products across various manufacturing steps requires that particles possess desired attributes such as size and shape. Controlling the particle production process to obtain required attributes will be greatly facilitated using robust algorithms providing the size and shape information of the particles from in situ measurements. However, obtaining particle size and shape information in situ during manufacturing has been a big challenge. This is because the problem of estimating particle size and shape (aspect ratio) from signals provided by in-line measuring tools is often ill posed, and therefore it calls for appropriate constraints to be imposed on the problem. One way to constrain uncertainty in estimation of particle size and shape from in-line measurements is to combine data from different measurements such as chord length distribution (CLD) and imaging. This paper presents two different methods for combining imaging and CLD data obtained with in-line tools in order to get reliable estimates of particle size distribution and aspect ratio, where the imaging data is used to constrain the search space for an aspect ratio from the CLD data.

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1. Introduction

One of key steps in the manufacture of particulate products in the pharmaceuticals and fine chemicals industry is crystallisation,

which is widely used for separation and purification of intermediates, fine chemicals and active pharmaceutical ingredients. The crystals come in different sizes and shapes. Subsequent steps in the manufacturing process, such as filtration, drying, blending and formulation of final products, require that the particle sizes and shapes lie within some desirable range. In order to provide monitoring and control of crystallisation processes it is necessary to develop techniques for estimating the shape and size

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distribution of particles in situ. There are a number of offline tools (Washington, 1992) that can be used to estimate the particle size distribution¹ (PSD) of crystals produced in a crystallisation process. However, of particular importance to the control of a crystallisation process are tools that can be used in situ. These tools should be suitable for estimating size and shape information of particles dispersed in a slurry without the need for sampling and/or dilution. Examples of such instruments are the focused beam reflectance measurement (FBRM), the three dimensional optical reflectance (3D-ORM) (Heinrich and Ulrich, 2012) and the particle vision and measurement (PVM) (Barrett and Glennon, 2002) sensors.

In-line sensors such as FBRM and 3D-ORM measure a chord length distribution (CLD)² which is related to the size and shape of the particles in a slurry. It has been a long standing challenge to be able to deduce the actual PSD and particle shape from experimental CLD data. In order to do this, an inverse problem needs to be solved. This is usually achieved by suitably discretising both CLD (which is already measured as a discrete distribution) and PSD and then constructing an appropriate transformation matrix relating these two distributions (Wynn, 2003; Li and Wilkinson, 2005; Agimelen et al., 2015). The transformation matrix depends on the choice of size bins used to discretise the two distributions and the corresponding size ranges as well as the shape of particles. The transformation matrix is usually not known in advance and needs to be estimated along with the corresponding PSD (discretised) so that the convolution of the transformation matrix with the PSD yields a CLD which agrees with the experimentally measured CLD. However, this problem is ill posed. There are a number of different transformation matrices and PSDs whose convolutions give rise to the same CLD. Hence the challenge is how to estimate a combination of transformation matrix and PSD whose convolution will agree with an experimentally measured CLD for a given slurry as well as the PSD estimated being physically reasonable and representative of the particles in the slurry.

The approach which was used in previous works (Ruf et al., 2000; Worlitschek et al., 2005; Li et al., 2014; Kail et al., 2009) when estimating the transformation matrix was to assume the same shape (quantified by a metric referred to as aspect ratio) for all the particles in the slurry, and then use a previously estimated³ range of particle sizes in the slurry to construct the transformation matrix. This approach is not suitable for monitoring a crystallisation process where nucleation and/or growth of particles is present as neither the range of particle sizes nor their aspect ratio would be known in advance. A technique which was suitable for estimating the range of particle sizes in a slurry in situ was presented in our previous work (Agimelen et al., 2015). However, like in other previous works, the transformation matrix was constructed with a single aspect ratio for all particles. This leaves open a possibility that the transformation matrix is constructed with inappropriate aspect ratio or that there is a wider range of aspect ratios present for particles of same or different sizes. It was demonstrated in our previous work (Agimelen et al., 2015) that it was still possible to calculate different CLDs that all had a very good agreement with an experimentally measured CLD even though some of the transformation matrices were constructed at aspect ratios that were far from the shape of the particles

described. However, it was also shown that as the aspect ratio deviated further from the true shape of the particles, then the corresponding PSD became increasingly noisy. This situation led to the introduction of a penalty function in order to eliminate unrealistic aspect ratios. However, when there is a wide variation of aspect ratios of the particles in the slurry, there is a need to introduce further constraints on the aspect ratio to reduce the search space and regularise the inverse problem. One way to do this is to get estimates of aspect ratio (within some reasonable bounds) using imaging, and then use this information to constrain the search for a representative aspect ratio. However, the imaging needs to be done in situ in order to develop techniques for estimation of PSD and particle shape which could be used for real time monitoring and control of particle production processes.

While it would be desirable to get good estimates of both PSD and particle aspect ratio using in situ imaging alone, this is currently not the case. The currently available in-line imaging tools (for example, the PVM used in this work) produce 2D projection images. Furthermore, the objects in the images may be partially or completely out of focus, parts of imaged object may cross the image frame or objects may overlap each other.⁴ Although advanced measurement equipment have been developed which can be used to capture 3D images of particles in a slurry and make good estimates of PSD and shape of particles, it requires sampling and dilution flow loops⁵ to allow capturing 3D images of individual particles in a flow-through cell (Eggers et al., 2008; Kempkes et al., 2010; Schorsch et al., 2012, 2014). Therefore this approach may not be generally applicable for in-line monitoring of particle manufacturing processes. Hence the current situation is that PSD cannot be estimated to a good degree of accuracy using routinely available in-line imaging tools. To overcome this challenge, we propose to combine in-line CLD measurements with imaging data to provide more reliable estimates of quantitative particle attributes.

In this paper, we present two different methods for combining imaging data with CLD data for particle size and shape estimation. The first method presented here calculates an estimate of the mean aspect ratio of all the particles in the slurry and then uses this information to constrain the search space for size and shape estimation from the CLD data. In the second method, a distribution of aspect ratios for each particle size is used for the PSD estimation. The distribution of aspect ratios is based on the data from the captured images.

2. Experiment

To demonstrate the technique for estimating particle size and shape information using a combination of the CLD and imaging data, experiments were performed in slurries containing particles of different shapes. The materials and procedure are described below.

2.1. Materials

Three different samples were used for the measurements. Sample 1 consisted of polystyrene (PS) microspheres purchased from EPRUI nanoparticles and Microspheres Co. Ltd. with batch number 2012-5-7, and 0.2 g of the PS microspheres were dispersed in 100 g of isopropanol (IPA) purchased from VWR (20842.323) giving a concentration of 0.2% by weight. Sample 2 consisted of cellobiose octaacetate (COA) particles obtained from GSK. The particles were dispersed in

¹ The term particle size distribution is broadly used here to refer both to continuous analytical probability density functions for particle sizes and discretised probability histograms of the particle sizes.

² Similar to the case of PSD, the term chord length distribution is used to cover both continuous analytical functions and discretised probability histograms.

³ The approach was to estimate the range of particle sizes in a sample by techniques such as sieving, laser diffraction, microscopy or use information supplied by the manufacturer before suspending the particles.

⁴ The issue of objects overlapping each other would not be a problem if an appropriate image processing algorithm which can resolve the objects is used.

⁵ The dilution is necessary to avoid instances of overlapping particles in images.

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