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Measurement of particle size and shape by FBRM and in situ microscopy

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Abstract

In this work a model is defined allowing for a rapid calculation of chord length distributions as well as the prediction of in situ microscopy data. Both calculations are done using the same underlying algorithm. The model assumes convex polyhedral particles that are defined by their vertices only, connected by straight lines, but imposes no further restrictions on particle geometry. Due to its speed, the model can easily be used for the prediction of experimental data from in situ monitoring tools based on whole particle populations, also with non-constant shape. The model has been verified using in situ microscopy to characterize a population of disc shaped particles.

The applications of the model are focused on crystallization processes, but are not limited to these. Several relations between data measured by in situ instruments and the underlying multidimensional particle size distribution have been derived. The model is used extensively in a method that is presented allowing for the calculation of bidimensional growth rates from Focused Beam Reflectance Measurement or in situ microscopy measurements.

Keywords: Crystallization; In situ monitoring; Instrumentation; Mathematical modeling; Particle shape; Particulate processes

1. Introduction

The size and shape of particles produced in crystallization and precipitation processes is of key importance in determining not only the processability of the particle ensemble, e.g. filterability and flowability, but also its bioavailability in the case of drugs. More precisely, what counts is the particle size distribution (PSD) of the particle population, a very familiar property in particle science and technology. The evolution of the PSD during particle formation and growth processes is described by a population balance equation (PBE) (Ramkrishna, 2000). The use of one-dimensional PSDs, where all particles are assumed to have the same shape and each particle has a characteristic length L, is widespread for studies focusing on particle size and particle size distributions, typically in combination with tools that allow for the experimental characterization of the 1-D PSD. Particle growth (or dissolution) can be described in this context by defining a single growth (or dissolution) rate G as a function of solute concentration and temperature, where G is the rate of change of the characteristic length L. In the case of a 1-D PSD the shape of all particles is assumed to be identical, and is accounted for in the corresponding PBE through shape factors, e.g. the volume shape factor is defined as the ratio between the particle volume and L^3. Alternatively, one can first choose a prototypical particle shape, e.g. a generalized ellipsoid (Pons et al., 2006; Ruf et al., 2000), as well as the ratios between the characteristic lengths, i.e., the ellipsoid axis lengths, and then use a 1-D PSD to describe the particle ensemble.

If either shape is not homogeneous through the particle population, or it changes during particle growth, a one-dimensional PSD is not sufficient and at least a two-dimensional PSD, if not a multi-dimensional one, is needed. In this case, each particle is described by n characteristic lengths L_i, with $2 \leqslant i \leqslant n$, and growth is described by the corresponding n growth rates G_i. A multi-dimensional PBE is a straightforward extension of the one-dimensional PBE (Hulburt and Katz, 1964). The use of a multi-dimensional particle model has been pursued by Doherty and coworkers in a series of papers aimed at predicting the shape of crystals grown from solution (Gadewar et al., 2004; Zhang et al., 2006; Zhang and Doherty, 2004). Their approach describes the appearance or disappearance of faces during growth or dissolution, and allows for the prediction of relative growth rates of different faces based on molecular

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properties, but its application has so far been limited to modeling single particles, whereas its use in a PBE framework does not seem to be straightforward.

In most studies two-dimensional PSDs and PBEs have been used (Briesen, 2006; Ma et al., 2002; Oullion et al., 2007a,b; Puel et al., 1997, 2003a,b), the main reason being the difficulty of measuring particle size and growth in multiple directions, especially in situ during growth, as well as the computational difficulties commonly encountered in solving multi-dimensional PBEs. In the 2-D PSD case a crystal is typically described as a 3-D parallelepiped, with length L_1, height L_2 and width L_3, where one geometrical constraint is imposed to reduce the number of independent descriptors to two, e.g. by setting $L_3 = L_2$ (Briesen, 2006; Ma et al., 2002; Puel et al., 1997, 2003a,b) or by assuming that the width L_3 has the same constant value for all crystals (Oullion et al., 2007a,b).

When dealing with the measurement and characterization of the particle size and shape distributions, i.e., with the aforementioned 2-D PSD, techniques such as laser diffraction or the electrical sensing zone method are not suited. Ex situ or in situ microscopy coupled with image analysis are the techniques mostly reported in the literature (De Anda et al., 2005a–c; Larsen et al., 2006, 2007; Li et al., 2006; Puel et al., 1997; Oullion et al., 2007a, b; Puel et al., 2003a, b). Processing macroscopic images using a particle detection and measurement software yields information about the 2-D PSD, which combined with the use of the 2-D PBE to simulate the process allows estimating kinetic properties, e.g. crystal growth rates along different crystal axes. (Oullion et al., 2007a, b; Puel et al., 1997, 2003a, b). Great efforts are devoted to improving image analysis tools and algorithms and to optimizing them for the application to suspension of crystals (De Anda et al., 2005b, c; Larsen et al., 2006, 2007).

The drawbacks of ex situ particle analysis techniques have sparked a growing interest in the use of in situ monitoring tools. The focused beam reflectance measurement (FBRM) technique introduced by Lasentec and in situ microscopy, e.g. applied using a process video and measurement (PVM) microscope also commercialized by Lasentec, are in situ methods, often used to monitor the evolution of particle populations. FBRM delivers the chord length distribution (CLD) of the particle population, whereas PVM produces images of part of the particle population (those particles that can be viewed and measured by the 'artificial eye' of the instrument, i.e., the probe, namely particles that are not too small, not too large, etc.). Both are obtained by placing a probe in the crystallization vessel and are based on the sampling of a large number of 2-D projections of the 3-D particles with random orientations. It is obvious that the particles' images and the CLD are a function of the PSD of the underlying particle population, but a direct connection is not obvious, if not impossible, in the general case.

The calculation of the CLD of a population of particles with a certain PSD and constant shape, i.e., described by a 1-D PSD, as well as the back-calculation of the 1-D PSD corresponding to a measured CLD, have been the subject of a number of papers (Kail et al., 2007; Li and Wilkinson, 2005; Pons et al., 2006; Ruf et al., 2000; Vaccaro et al., 2007; Worlitschek et al., 2005). The latter, backward calculation has been shown to be an ill-posed inverse problem, whose solution requires selecting a priori a specific crystal shape. Different attempts to account for optical effects when forward calculating the CLD for a given PSD have been reported recently (Kail et al., 2007; Pons et al., 2006).

The objective of this paper is to utilize 2-D PSDs in combination with both aforementioned in situ techniques, namely microscopy and FBRM, to monitor the evolution of size and shape of crystals in a suspension during growth and to extract information about their growth kinetics. To this aim we develop an efficient model and algorithm to describe in situ measurements with both PVM and FBRM and we apply it to the estimation of bidimensional growth rates from in situ measurements. The measurement model for both FBRM and PVM is based on the same underlying algorithm which assumes convex particles with sharp edges. It does not pose any additional requirements on the particle geometry, making it more general than the models described in previous work and at the same time very computationally efficient. The model accounts for neither non-ideal optics nor camera models as others do to determine images of 2-D projections of 3-D particles (Kail et al., 2007; Li et al., 2006; Pons et al., 2006); once established, they will be incorporated in the model presented in this work. Although in principle the proposed approach could work for n-dimensional PSDs, with n larger than 2, we conjecture that the accuracy of the method will decrease with increasing n. Therefore, in this paper we focus on the theoretical foundations of the method and we confine ourselves to two-dimensional PSDs, which are anyhow those of highest practical interest.

The paper is structured as follows. First, in Section 2 we present and apply to experimental data an image analysis algorithm that allows extracting quantitative data from the PVM images, namely obtaining the two-dimensional axis length distribution (ALD). This puts the use of the PVM at the same status as that of the FBRM. In both cases a distribution (1-D in the case of FBRM, 2-D in the case of PVM) associated with the particle population is obtained from the in situ instrument, at high frequency during a growth experiment.

Secondly, in Section 3 a wire frame model is used to describe particles of any morphology, symmetric or not, with any number of sharp edges. Assuming perfect optics, we then simulate the FBRM and PVM measurement for a single such particle, and then for any ensemble of particles, thus predicting the corresponding CLD and ALD.

Then, in Section 4 we consider 3-D parallelepipeds characterized by two characteristic lengths that can vary, i.e., L_1 and L_2, a so called square cuboid, as a special case of the wire frame particles introduced in Section 3. Therefore all tools developed with reference to those particles can be applied also to the cuboids. With the cuboids we can do a number of things. First, we show how the single particle model of Section 3 can be applied to find the CLD and ALD for a population of particles. Secondly, we establish a relationship between the moments of the CLD and of the ALD and the two-dimensional PSD of the ensemble of cuboids. Then, the model presented in Section 3 is also used to address the issue of how many particles have to