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Herman J. M. Kramer

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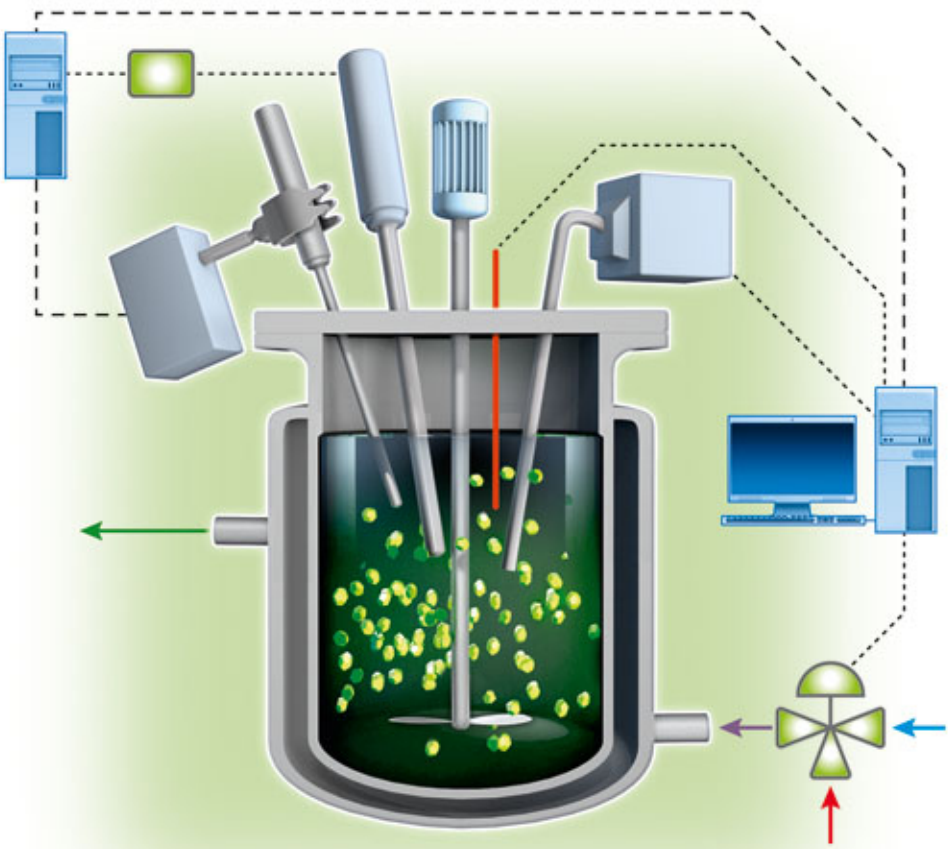
Industrial Crystallization Process Monitoring and Control



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Contents

Preface

The idea of this book was to disseminate some valuable results achieved by two European projects on monitoring and control of industrial crystallizers:

1) CRYSEN (2000–2003) on the Development of new sensors for industrial crystallization;
2) SINC-PRO (2003–2005) on Self-learning model for INtelligent predictive Control system for crystallization PROcesses. This second European project then became an international project with the partnership extended to Swiss and Japanese teams.

Most of the partners of the two projects were members of the Working Party on Crystallization (WPC) of the European Federation of Chemical Engineers, which accepts the proposal of the book and encouraged the efforts of the two editors in order to provide a new publication to the industrial crystallizer community. Then, the WPC provided a double reviewing of each books chapter by the WPC members, from academia and industry, expert in the specific subject.

Therefore, the two editors are greatly grateful to the two Chairmen of the WPC, who promoted the book writing, Joachim Ulrich and Beatrice Biscans and to the following WPC members, who with their referee's work contributed to improve the quality of the book:

Beatrice Biscans
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Matthias Raouls
Ake Rasmuson

December 2011 *Angelo Chianese and Herman J. M. Kramer*

Scope of the Book

Control of Crystallization Processes in Industrial Practice

Crystallization from a solution is a separation technique, where one of more components of the solution are separated as a solid phase. Application of a crystallization process can be aimed at the separation of a component from a multicomponent mixture, but in most cases it is focused on the production of a solid product from a liquid mixture. In both types of application, the product quality of the solid product has to meet stringent specifications, and especially for solid products manufacturers have to meet ever-increasing demands of the customers on particle properties such as particle size distribution, crystal shape, degree of agglomeration, caking behavior, and purity. Since for an economic beneficial operation a smooth separation of the produced crystals from the mother liquor is essential, additional demands on filterability and washability need to be obeyed. It is obvious that in order to achieve the increasing demands on product quality, crystallization processes have to be carefully controlled.

Crystallization from a liquid solution is the most important production and separation process in the fine chemical and food industry and one of the most important processes in the chemical process industry as a whole. Overall it is estimated that 70% of the products sold by the chemical process industry are solids. Many intermediates (e.g., adipic acid for nylon production), fine chemicals, pharmaceuticals (e.g., aspirin), biochemical, food additives, and bulk products such as fertilizers are solids obtained through crystallization.

Both market needs and governmental policies demand continuous efforts in research and development to improve existing technologies, with respect to economics, operability, and sustainability.

In order to achieve an optimal production capacity and the desired crystal properties, the process conditions during the crystallization operation should be controlled in such a way that the product specifications can be met at conditions of profitability and trouble-free production. The crystallization process variables either should be controlled by the configuration of the process/equipment or must be manipulated during operation, either to achieve a desired profile during batch operation or to compensate for process disturbances during continuous operation. In this respect three different levels of control can be identified. The first level

consists of a base layer control to keep constant the basic process variables such as the materials and enthalpy fluxes the gas–liquid level, the temperature and the pressure in the crystallizer at their design values to ensure a trouble-free reproducible production. The next level, the control of supersaturation, is more complicated as it requires a precise monitoring of the solute concentration and precise knowledge of the saturation concentration at the process conditions. The setting of this variable entails detailed knowledge of the optimal operation window for the driving force to achieve an optimal balance between the production capacity and the product quality. Finally, the control of the product quality as a whole, in most cases expressed in terms of its crystal size distribution (CSD), is the third, most difficult and worthwhile level of control and requires both an online monitoring of this product quality and detailed knowledge of the process. The advantage of supersaturation control is that in principle it allows for a so-called model-free control strategy, avoiding time-consuming development and validation of a detailed process model as is required for controlling the product quality directly.

Industrial crystallizers are seldom operated under automatic control schemes because of the lack of reliable sensors and process models. Robust and reliable sensors for *in situ* monitoring of the relevant process variables, that is, the CSD and the solute concentration, were not available for a long time and only recently some *in situ* sensors have started to be applied at industrial level. The development of process models is another obstacle for the application of feedback (FB) schemes for quality control. Due to the absence of general reliable crystallization models and problems encountered in the prediction of the effects of scale up, dedicated models have to be developed and validated for each individual case which has proven to be a very difficult and costly matter. This leads us to adopt open loop quality process control schemes where the main process variable are operated at the conditions that are supposed to lead to the desired product quality, without an automatic closed loop control of product quality. Unfortunately, the absence of an effective control system typically entails a poor quality control, which must be compensated for by additional processing such as follows:

- classification of crystalline product streams and reprocessing of under and oversized (agglomerated) products;
- exhaust air treatment for dust abatement;
- higher energy consumption in the drying process and reprocessing of the off-spec product;
- significant decrease of productivity resulting in reduced total plant throughput and impacting investment costs to reach the required capacity;
- production costs increase (about 5% of total production costs could be avoided adopting an effective control in batch processes); and
- higher environmental impact due to the required increase in use of solvent and chemicals.

Ideally industrial crystallizers are operated in such a way that the product specifications are met under conditions which permit a profitable trouble-free production of the desired crystalline material. In industrial practice however, a large number

of operational problems can be encountered which reduce the crystallizer performances, such as deposition of crystalline material on the crystallizer internals, variations in the feed composition, less effective heat transfer operations, inappropriate seeding procedures, and so on. These process disturbances will inevitably lead to production losses and/or deterioration of the product quality.

In conclusion, the problem in the quality control of industrial crystallizers is far from its solution. For this reason, much effort has to be spent on the development of new online sensors and more advanced control approaches.

Different control approaches are applied for crystallization processes belonging to pharmaceutical plants and commodities plants. In the first case, usually processes are performed in batch mode, by applying cooling or antisolvent techniques, concerning high added value products, whose quality is the first objective to be pursued. It is well known that even minor changes in crystallization process conditions and equipment, for example, supersaturation, temperature, impurity, cooling rate, or reactor hydrodynamics, can result in significant variations in the crystal and downstream powder properties, notably, polymorphic form, particle size, shape, purity, and defect structure. The market price of the active products may reach values of several thousands of Euros per kilogram, thus allowing the achievement of sophisticated instrumentations to monitor and control the product quality throughout the crystallization process.

The second area of crystallization applications concerns so-called commodities products, processed in continuous mode in huge amount with relatively poor specifications and having a small added value which does not allow high investment cost per product unity.

The development and application in recent years of expansive and sophisticated sensors are due to the increasing interest from the pharmaceutical companies in the improvement of the crystallization processes operation and their large need for research investigations at lab scale. Among these instruments are those based on attenuated total reflection (ATR)-Fourier transform infrared (FTIR) spectroscopy, *in situ* chord length distribution of crystals from laser backscattering by focus beam reflectance measurement (FBRM) probe and *in situ* online video microscope. Most of the available *in situ* sensors are robust enough to be applied in the production environment. This opened the possibility of FB control-based crystallization design and operation. The new opportunities are well described by the guideline document issued in 2004 by the U.S. Food and Drug Administration (FDA), as part of a broader initiative on current Good Manufacturing Practices (cGMP) (FDA, 2004). This document emphasized the development and use of novel technologies based on process analytical technologies (PAT) as a tool for ''twenty-first century manufacturing'' moreover, the development of tailored process control strategies was recognized as the most important way to prevent or mitigate the risk of producing poor quality products.

This new scenario provides significant potential for implementation of optimal and adaptive control methodologies with real economic benefits associated with better product quality (Nagy, Fujiwara, and Braatz, 2008; Woo, Tan, and Braatz, 2011).

A quite different situation holds for the crystallization processes included in commodities plants. In fact, in this case the productivity and the CSD are the main issues. In order to achieve these two objectives, the use of traditional online sensors with improvement performances, such as turbidimeters and refractometers, is welcome. Only seldom new sophisticated and expensive instruments such as the FBRM sensor are adopted and most of the quality product assessments in terms of the CSD are carried out off-line by taking samples and making use of sieve analysis, laser diffraction instruments, or an optical microscope. More attention is devoted to the manipulation of specific variables to maintain the crystallizer under control, even if in a nonautomatic way. In this respect the fines removal, the agitation by an impeller, and the amount of added seed crystals are the most used manipulating variables. However, to make use of various features to control the product quality in modern continuous crystallizers, such as draft tube baffled (DTB) crystallizers, simultaneous manipulation of different process inputs is needed. The full exploitation of these crystallizers therefore requires the application of multivariable control techniques, especially when different aspects of the product quality have to be controlled or when the product quality needs to be preserved at different production capacities, as has been shown in several research studies (Trifkovic, Sheikhzadeh, and Rohani, 2009; Sheikhzadeh, Trifkovic, and Rohani, 2008; Seki, Amano, and Emoto, 2010; Valencia Peroni, Parisi, and Chianese, 2010).

Content of the Book

In this book the monitoring and control of industrial crystallizers is discussed. All the necessary ingredients for the development and implementation of a control strategy for batch and continuous operated crystallization processes are reported. The emphasis will be on cooling and evaporative crystallization processes, although the methodology can also be applied for other types of crystallization processes such as pH shift and antisolvent crystallization or precipitation processes. The book is written primarily for process and control engineers interested in improving the performances of their crystallization processes and for chemical and control engineering students interested in application of online sensors and control schemes to crystallization processes.

The basic philosophy followed in the book is that the availability of an *in situ* monitoring technique is essential for the successful implementation of a control strategy. The implementation, calibration, and testing of such a sensor is not straightforward and is therefore discussed in detail in this book. The control strategy is to a large extent dependent on the choice of the sensors, but it is also related to the crystallization system, the product specifications, and the available equipment. The other aspect emphasized in this book is the possibility of applying a model-based control strategy. This choice leads to flexible and cost-effective operations of continuously and batchwise operated industrial crystallizers. One of the key factors for such an approach is the availability of generalized rigorous process models which are easily tunable for the specific application and which can

describe the evolution of the product quality in industrial crystallizers in a broad range of process conditions. This so-called master model, which in most cases is a complex nonlinear model, can then be used, provided that the appropriate tools are available, for optimization of the process conditions or trajectories, for a controllability analysis and after appropriate model reductions for the dynamic observer and the model predictive controller. This approach, which has successfully been developed recently, will be discussed in detail in this book. However, also more traditional single loop control strategies to improve the reproducibility and the product quality will be discussed extensively.

The first part of the book provides the reader with an overview on the state-of-the-art on instrumentation and methodologies for the online or *in situ* monitoring of relevant process variables in process environments, aiming at the online analysis and control of the crystallization process. After a first chapter where a number of different techniques for the characterization of the CSD are discussed and compared, instruments of commercial instruments, capable of determining either online or *in situ* some aspects of the CSD, are described (Chapters 2–5).

Traditional and new sensors for the measurement of nucleation and solubility points of solution are illustrated in Chapter 6. These techniques allow the determination of the metastable range width, which is the basis for the development of any crystallization process. Many measurements techniques are present in the literature, such as those based on dielectric constant (Hermanto *et al.*, 2011), calorimetric analysis (Lai *et al.*, 2011), and conductivity (Genceli, Himawan, and Witkamp, 2005), but those based on turbidity and ultrasound analysis are the most common and reliable ones, and moreover provided by relatively cheap instruments.

The online measurement of the solute concentration may be provided by a relatively cheap instrument, by an online refractometer, or by more sophisticated and expansive ones, as those based on ATR FTIR and Raman spectroscopy. These latter techniques, discussed in a recent paper of Kadam *et al.* (2010), are now currently adopted in investigation on pharmaceutical products, whereas that based on refractometry is advantageously applied in the sugar industry. All these techniques are widely reported in Chapters 7–10.

The second part covers the dynamic control of batch and continuously operated industrial crystallizers. In this part dynamic models suitable for model-based control strategies are discussed, as well as methods for parameter estimation and validation. Also the application of these models for the optimization of the process conditions is described. The basic, model free, control of batch operated crystallization processes is discussed in Chapters 11 and 12. In these Chapters particular attention is given to the control of the supersaturation profile during the batch process, based on a predefined recipe. The seeding technique is also examined and its optimal application is discussed with regard to the crystallization phenomena kinetics. This technique may have a very important role to control the initial phase of a batch process where the initial distribution of the crystals is generated or added to the crystallizer.

Advanced recipe and model based control is discussed in Chapters 13 and 14. In both process models are used to determine an optimal profile to achieve the desired process or product performances. In Chapter 13 the FB control is applied

on the basis of an off line determined recipe or profile, while in Chapter 14, closed loop implementations of the model based control strategy are illustrated using state estimators and a real time optimization of the trajectory. This latter approach allows an early detection and feedback of process disturbances. The control of continuously operated crystallization processes is treated in Chapters 15 and 16. Firstly the main manipulation technique, that is, the one based on fines removal, is presented. Then in Chapter 16, the application of a model predictive control (MPC) for continuous crystallization processes is introduced. Both single loop control strategies as well as multivariable predictive control strategies are discussed. This chapter also gives a introduction into the principles, the design, and the implementation of MPC, including the necessary state estimation, are discussed in detail and some application examples are given.

Finally, in Chapter 17 the main types of crystallizers adopted in continuous crystallization process involving commodities are described together with their P&I schemes. This contribution is given by one of the leader worldwide companies in the design and construction of industrial crystallizers. The choice of the main instruments to be adopted for industrial units and their location inside the crystallizer, together with a discussion on the control valve to be used, completes information of the crystallizer's design.

Herman J. M. Kramer
Angelo Chianese

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1
Characterization of Crystal Size Distribution

Angelo Chianese

1.1
Introduction

Crystalline population coming out from a crystallizer is characterized by its size distribution, which can be expressed in different ways. The crystal size distribution (''CSD'') may, in fact, be referred to the number of crystals, the volume or the mass of crystals with reference to a specific size range, or the cumulative values of number, volume or mass of crystals up to a fixed crystal size. The first approach refers to a density distribution, whereas the second one to a cumulative size distribution.

However, it is also useful to represent the CSD by means of a lumped parameter as an average size, the coefficient of variation, or other statistical parameters which may be adopted for the evaluation of a given commercial product.

In this section the more usual ways to represent both the whole CSD and the lumped CSD parameters are presented.

1.2
Particle Size Distribution

The particle size distribution may be referred to the density distribution or cumulative distribution. Each distribution may be expressed in number, volume, or mass of crystals.

The cumulative variable, $F(L)$, expresses number, volume, or mass of crystals per unit slurry volume between zero size and the size L, whereas the density distribution function, $f(L)$, refers to number, mass, or volume of crystals per unit slurry volume in a size range, whose average size is L.

The relationship between the cumulative size variable and the density distribution size one is as follows:

$$F(L) = \int_0^L f(L)\mathrm{d}L \tag{1.1}$$

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