

# Particle Size and Shape Control in Crystallization Processes

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## Abstract

Crystallization from solution is an industrially important unit operation due to its ability to provide high purity separations. The control of the crystal size distribution can be critically important for efficient downstream operations such as filtration and drying, and product effectiveness (e.g., bioavailability, tablet stability). This paper provides an overview on recent developments in the control of industrial crystallization processes. This includes descriptions of recent activities in the modeling, parameter estimation, state estimation, analysis, simulation, optimization, control, and design of crystallization processes.

## Keywords

Crystallization, Particulate processes, Population balance models, Distributed parameter systems, Optimization, Control, Estimation, Simulation

## Introduction

Crystallization from solution is an industrially important unit operation due to its ability to provide high purity separations. For efficient downstream operations (such as filtration and drying) and product effectiveness (e.g., bioavailability, tablet stability), the control of the crystal size distribution can be critically important. Also important is crystal purity and the crystal shape. The purity of the crystals is especially important in the food industry, where the crystals are consumed by humans. The crystal size and shape affects the dissolution rate, which is important for crystals that dissolve during final use (Winn and Doherty, 2000). In the pharmaceutical industry, the relative impact of drug benefit versus adverse side effects can depend on the dissolution rate. Control of crystal size and shape can enable the optimization of the dissolution rate to maximize the benefit while minimizing the side effects. For crystals used in photography, the size and shape uniformity is the principle concern of the customer (Miller and Rawlings, 1994). Poor control of crystal size and shape can result in unacceptably long filtration or drying times, or in extra processing steps, such as recrystallization or milling. Purity is especially important in the pharmaceutical industries, in which the crystals will be consumed.

The fundamental driving force for crystallization from solution is the difference between the chemical potential of the supersaturated solution and that of the solid crystal face (Kim and Myerson, 1996; Mullin and Sohnel, 1977). It is common to simplify this by representing the nucleation and growth kinetics in terms of the supersaturation, which is the difference between the solute concentration and the saturated solute concentration. Figure 1 is a schematic of a batch crystallizer where the supersaturation is caused by decreasing the temperature. Another method of supersaturation creation is by adding a sol-

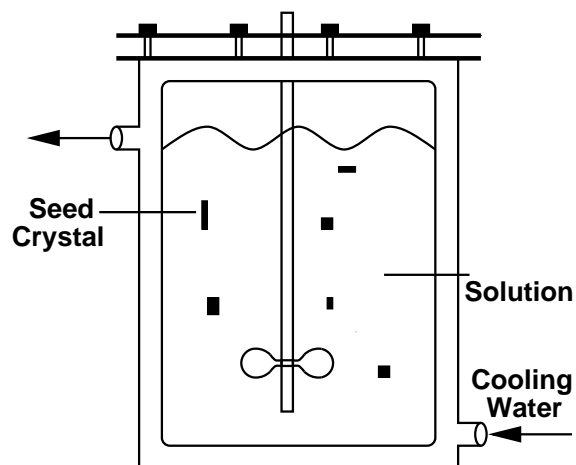


Figure 1: Schematic of a batch cooling crystallizer.

vent for which the solute has a lower solubility—this is often called *drowning out*, or *antisolvent addition*. Yet another common method of creating supersaturation is evaporation.

The challenges in crystallization processing are significant. First, there are significant uncertainties associated with their kinetics. Part of the difficulty is that the kinetic parameters can be highly sensitive to small concentrations of contaminating chemicals (Shangfeng et al., 1999), which can result in kinetic parameters that vary with time. Another significant source of uncertainty in industrial crystallizers is associated with mixing. Although crystallization models usually assume perfect mixing, this assumption is rarely true for an industrial-scale crystallizer.

Crystallization processes are highly nonlinear, and are modeled by coupled nonlinear algebraic integro-partial differential equations. For the case of distribution in shape as well as overall size, there are at least three independent variables in the equations (Ma et al., 1999). Simulating these equations can be challenging because

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the crystal size distribution can be extremely sharp in practice, and can span many orders of magnitude in crystal length scale (0.01 nm to 200  $\mu\text{m}$ ) and time scale (20  $\mu\text{s}$  to 100 min).

Another challenge in crystallization is associated with sensor limitations. The states in a crystallizer include the temperature, the solute concentration, and the crystal size and shape distribution. The solute concentration must be measured very accurately to specify the nucleation and growth kinetics. Because the kinetics are functions of the difference between two solute concentrations (one of these being the saturated solute concentration), the error in the difference is much larger than the error in a single solute concentration measurement. Obtaining an accurate measurement of the full crystal size distribution (CSD) is even more challenging. Hence it is desirable to estimate the states from the noisy measurements that are available.

The last review of efforts to control crystallization processes was published in 1993 (Rawlings et al., 1993). This paper reviews efforts towards the control of crystallization processes, focusing mostly on results since 1993. The next section describes the current status of sensor technologies for crystallization processes. This is followed by descriptions on crystallization modeling including model structure determination and parameter estimation. Activities in state estimation are reviewed. Investigations into the stability of continuous crystallization processes, and the robustness analysis of batch crystallization processes are described. The simulation techniques of method of moments, weighted residuals, discretized population balances, and Monte Carlo simulation are reviewed. On-line and off-line approaches to optimizing and controlling crystallization processes are reviewed, including a discussion of efforts to relate process design to process control. The paper concludes with some predictions on where future efforts are headed.

## Measurements

Measurements of both solute concentration and the crystal size distribution are necessary for effective estimation and control.

### Solute Concentration Measurement

The nucleation and growth rates are strongly dependent on the solute concentration, making its measurement necessary for estimating kinetic parameters, and highly useful for feedback control. One technique is to measure the refractive index (Helt and Larson, 1977; Mullin and Leci, 1972; Nyvlt et al., 1994; Sikdar and Randolph, 1976). Although this method can work when there is significant change in the refraction index with solute concentration, the method is sensitive to ambient light and air bubbles.

Another approach to obtaining solute concentration

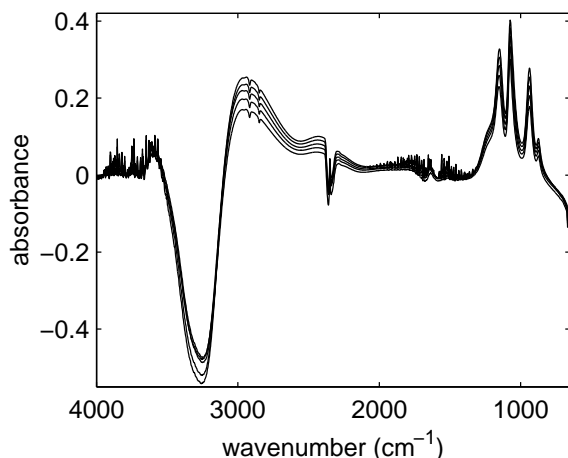
measurements is to sample the crystal slurry, filter out the crystals, and then measure the density of the liquid phase. This procedure has been demonstrated on-line for the cooling crystallization of potassium nitrate in water (Matthews III, 1997; Miller and Rawlings, 1994; Riebel et al., 1990; Redman and Rohani, 1994; Redman et al., 1997). The use of an external sampling loop can lead to operational difficulties such as clogging of the screen used to filter out the crystals, and to fluctuations in temperature in the sampling loop. This latter problem is especially important for crystals with a small metastable zone width, where a slight reduction in temperature can cause crystals to nucleate in the densitometer, leading to inaccurate solute concentration measurements.

In the crystallization of electrolytes, the solute concentration can be estimated by placing a conductivity probe in the crystal slurry (David et al., 1991; Franck et al., 1988; Garcia et al., 1999). While avoiding the operational problems associated with sampling, conductivity measurement has its own issues. It has been difficult to apply this technique to batch cooling crystallization processes, because conductivity strongly depends on temperature. Hlozny et al. (1992) and Nyvlt et al. (1994) extended the measurement technique so that temperature effect can be taken into consideration. This technique has been successfully applied to a batch cooling crystallizer (e.g., Jagadesh et al. (1996)).

An indirect method of determining the solute concentration is to use calorimetry, in which the measurements of temperature and flow rates are combined with a dynamic energy balance of the crystallizer (Fevotte and Klein, 1994, 1995, 1996). This approach has been demonstrated for the batch crystallization of adipic acid in water (Monnier et al., 1997). Solute concentration estimates determined from calorimetry can be expected to drift as the crystallization progresses.

Kuehberger and Mersmann (1997b) developed a special device for measurement of supersaturation. When the mother liquor contacts with a cold metal plate, crystals deposit on the surface. According to the amount of the solute deposited, the temperature of the metal plate rises due to the heat of crystallization. Thus, by detecting the temperature rise of the plate, the solute concentration can be estimated.

Loeffelmann and Mersmann (1999) suggested using the difference in electromagnetic properties of the crystal and solution. In this approach, a cooling plate is equipped with electrodes and the impedance between the electrodes is measured. The temperature of the plate is gradually lowered. When deposition of the crystals on the plate is detected by a change in impedance, the temperature is recorded and used to calculate the supersaturation. As an alternative to the impedance, they also suggested using attenuation ratio and phase change of electro-acoustic waves in order to detect crystal deposition.



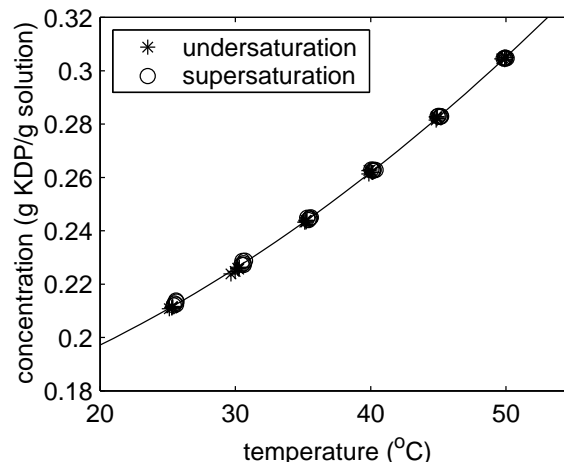
**Figure 2:** ATR-FTIR spectra for dihydrogen phosphate in water for five solute concentrations.

A limitation to the aforementioned methods for supersaturation measurement is the inability to track the concentrations of multiple dissolved species or multiple solvents.

The feasibility of attenuated total reflection (ATR) Fourier transform infrared (FTIR) spectroscopy for the in situ measurement of solution concentration in dense crystal slurries has been demonstrated (Dunuwila et al., 1994; Dunuwila and Berglund, 1997; Groen and Roberts, 1999; Lewiner et al., 1999, 2001). In ATR-FTIR spectroscopy, the infrared spectrum is characteristic of the vibrational structure of the substance in immediate contact with the ATR immersion probe (e.g., see Figure 2). A crystal in the ATR probe is selected so that the depth of penetration of the infrared energy field into the solution is smaller than the liquid phase barrier between the probe and solid crystal particles. Hence when the ATR probe is inserted into a crystal slurry, the substance in immediate contact with the probe will be the liquid solution of the slurry, with negligible interference from the solid crystals. That the crystals do not significantly affect the infrared spectra collected using the ATR probe has been verified experimentally (Dunuwila et al., 1994; Dunuwila and Berglund, 1997). The combination of ATR-FTIR with advanced chemometrics analysis can measure solute concentrations with accuracy as high as  $\pm 0.1$  wt% in dense crystal slurries (Togkalidou et al., 2000) (see Figure 3). A significant advantage of ATR-FTIR spectroscopy over most other methods for solute concentration measurement is the ability to provide simultaneous measurement of multiple chemical species.

### On-line Crystal Size Distribution Measurement

Several CSD sensors have become available. One is a Coulter Counter (Allen, 1990), which electronically counts particles as the crystal slurry passes through an



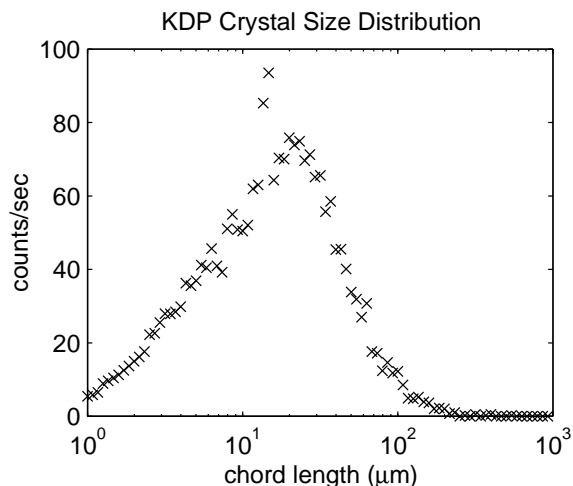
**Figure 3:** Solubility curve constructed using chemometric model and ATR-FTIR probe inserted into dense crystal slurry.

orifice. Coulter Counters have small flow orifices that are prone to clogging, especially for high density crystal slurries, and may require grounding of the fluid to reduce background noise (Rovang and Randolph, 1980).

The forward light scattering approach is to direct a laser beam through a sample cell, and collect the light scattered through the cell. These instruments, such as the Malvern or the Microtrac particle sizers, can give useful CSD measurement for slurries with low solids density (Eek, 1995; Eek and Dijkstra, 1995; Randolph et al., 1981). Information on particle shape can be determined by examining the light intensity variations (Heffels et al., 1994). This shape information can be used to correct the particle size determination using commercial laser diffraction instrumentation (Heffels et al., 1996). The CSD in dense crystal slurries can be addressed by an automatic sampling and dilution unit (Jager et al., 1987); however, it is challenging to collect a representative sample from an industrial-scale crystallizer and ensure that the temperature is constant enough so that the sample remains representative.

The transmittance, which is the fraction of light that passes through the solution, can be measured either using a light scattering instrument or a spectrophotometer. The projected area of the crystals can be computed from the transmittance. For dense crystal slurries, the transmittance is essentially zero, and no useful information is obtained. The transmittance measurement has been used for the estimation of kinetic parameters for the crystallization of naphthalene in toluene (Witkowski, 1990; Witkowski et al., 1990), potassium nitrate in water (Miller, 1993; Miller and Rawlings, 1994), and a photochemical in heptane (Matthews III, 1997; Matthews and Rawlings, 1998).

An alternative light scattering approach is based on



**Figure 4:** Chord length distribution of KDP collected from a Lasentec FBRM M400L.

inserting a probe directly in the crystallizer, focusing a laser beam forward through a window in the probe tip, and collecting the laser light scattered back to the probe. This approach can measure CSD information even for dense crystal slurries. One of the first commercial instruments of this type, the Par-Tec 100 analyzer, has been used to estimate kinetic parameters for the crystallization of adipic acid in water (Monnier et al., 1996) as well as in feedback control (Redman et al., 1997). Several publications describe applications of updated versions of the instrument, referred to as Lasentec *Focused Beam Reflectance Measurement* (FBRM) (Farrell and Tsai, 1995; Barrett and Glennon, 1999; Ma et al., 1999; Tahti et al., 1999; Togkalidou et al., 2001), which are rugged enough to be implemented on industrial crystallizers.

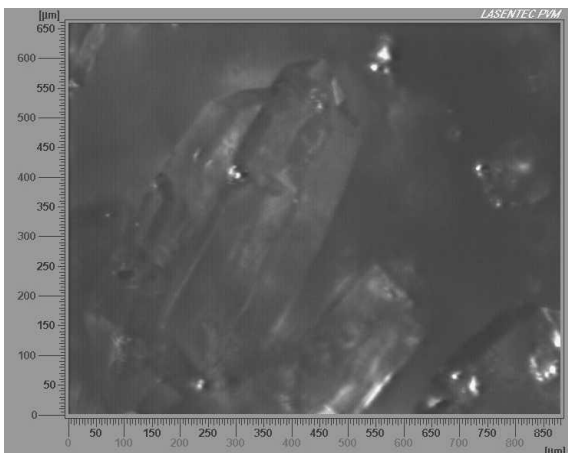
Like any laser-based method applied to a crystal slurry, a transformation is required to relate the collected laser light to the crystal size distribution. The FBRM instrument measures the chord length distribution (e.g., see Figure 4) as the laser beam emitted from the sensor randomly crosses two edges of a particle, with this distance being the chord length. There have been efforts to relate the chord length distribution to the particle size distribution, both by the Lasentec company and by some independent researchers (Becker, 2001; Clark and Turton, 1988; Han and Kim, 1993; Liu et al., 1998; Worlitschek and Mazzotti, 2000; Simmons et al., 1999; Tadayyon and Rohani, 1998). Chemometrics methods have been used to relate the chord length distribution to other variables, such as filtration resistance (Johnson et al., 1997; Togkalidou et al., 2001).

A weakness of the aforementioned CSD sensors is that the distribution of crystal shape cannot be directly determined. For example, a collection of rod-like crystals are

characterized mathematically by a two-dimensional distribution (one dimension being the length, and the other dimension being the breadth), but the light scattering instruments only provide one-dimensional distributions. It is impossible to uniquely determine a two-dimensional distribution from a one-dimensional distribution. The shape information is “averaged out” to obtain a one-dimensional distribution.

Another instrument that has become available recently is the Lasentec Particle and Vision Measurement (PVM) system, in which pictures are taken of the crystals in solution using a probe inserted directly into the dense crystal slurry (Lasentec, 1997). This video microscope can collect 10-30 pictures a second, providing two-dimensional snapshots of the crystals in real time. On-line video microscopy can image crystals as small as 5-15 microns (Lasentec, 1997; Pacek et al., 1994), not as small as obtained by laser scattering instruments. Also, the quality of the images limits the ability of imaging software to automatically identify individual particles (e.g., see Figure 5), and quantify the characteristics of these particles (e.g., maximum axis, minimum axis, aspect ratio). On-line video microscopy has the advantage that the crystals are directly observed, allowing shape information to be obtained. Also, the PVM in particular is a rugged instrument suitable for use in industrial applications. The main use of on-line video microscopy today is for qualitative troubleshooting, with some researchers working on how to use the images for quantitative prediction (Baier and Widmer, 2000; Braatz et al., 2000b). One approach is to use multiway principal component analysis, where features are tracked in the space of principal components (Bharati and MacGregor, 1998). An alternative is to take moments of the images and then to use principal components analysis to relate the image moments to characteristics of the crystals (Braatz et al., 2000b). Given the importance of crystal shape in applications, and that progress becomes easier as computers continue to increase in speed, it seems likely that quantitative predictions will become available.

An alternative approach to on-line video microscopy is to remove slurry from a sampling stream and flow it as a thin film over the focal region of an ordinary light microscope (Eek, 1995; Puel et al., 1997; Rawlings and Patience, 1999). A disadvantage of this approach is the requirement of having a sampling stream in which the crystals may not be representative of what is in the crystallizer. A strong advantage of this approach is that the contrast between crystals and background can be made much sharper, and the number of overlapping crystals can be reduced. The images are sufficiently clean that standard image analysis algorithms can be used (Rawlings and Patience, 1999).



**Figure 5:** Image of KDP crystals in solution collected from a Lasentec PVM 700L.

## Modeling

### Model Structure Determination

Derivation of optimal operation patterns or design of control system should be carried out using a model that describes the behavior of the process with sufficient accuracy. The process models can be classified into two groups: physical models, which can be obtained using first principles, and models identified from time series data. Regardless of the type of the model, the model building involves determination of the model structure and estimation of parameters appearing in the model equations. We will discuss the problems of model structure determination in the first half of this section, which is followed by a discussion of some other topics.

There are several papers that discuss methods for modeling the dynamic behavior of the crystallizer using time-series data. Bravi et al. (1995) identified a dynamic model of a continuous crystallizer using artificial neural networks. Time series data generated in a series of simulations using gPROMS were used to train the neural network so that the fines slurry density is predicted from the feed flow rate, the flow rate recirculated through the fines dissolver, and the inlet concentration. The dynamics of the input and output signals were examined to determine the sampling frequency and the number of past data points to use for prediction of the behavior of the fines slurry density.

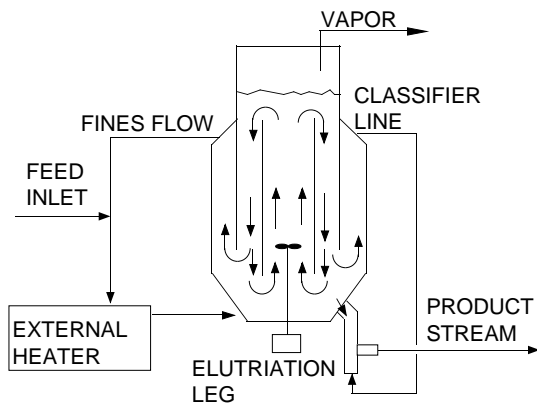
Rohani et al. (1999a) also conducted a simulation study on the modeling of the crystallizer behavior using ARX and neural network models. The identification data were generated from simulation using a model of a continuous cooling crystallizer that has been previously verified with experimental data. The fines dissolution rate, the clear liquor advance flow rate, and the crystallizer temperature were used as inputs, and out-

put variables were three variables related to crystal size distribution, the purity, and the magma density of the product stream. With the view of using the model in model predictive control (MPC), the prediction performance of each model was examined in terms of 1 step ahead and 50 step ahead predictions.

When a crystallizer is subjected to an excitation signal such as a pseudo-random binary sequence (PRBS), the state variables may deviate far from the steady state due to the strong nonlinearity of the crystallizer. Thus, in order to build a linear dynamic model around the steady state, it is advantageous to collect time series data when the process is under feedback control. Eek et al. (1996) applied closed loop identification techniques to the modeling of the continuous crystallization of ammonium sulfate. Two different closed loop identification methods, direct identification (Soderstrom and Stoica, 1989) and a two-step method (van den Hof and Schrama, 1993), were applied to build three-input three-output models that predict the fines concentration, crystal mean size, and the magma density based on the measurements of fines flow rate, product flow rate, and total heat input. Canonical observability form was the assumed model structure, and the data for identification were obtained by exciting the process using by generalized binary noise sequence (Tullken, 1991). The prediction performance of the resulting model was as good as that of first principle models.

When building ARX or neural network models, the model structure determination and parameter estimation are carried out rather simultaneously. On the other hand, when a first principle model is to be constructed, before estimating parameters it is necessary to determine the model structure suited for the description of the crystallizer dynamics. Therefore, the process of building a first principle model is more complicated than building ARX or neural network models. However, first principle models have several advantages over ARX and neural network models. In particular, the operating range of conditions where a first principle model can provide accurate predictions is wider than for ARX or neural network models. This is because the first principle model incorporates the physical properties of the crystallizer into the model. When the control system is not performing satisfactorily, the first principle model can be used to analyze the cause behind this. Also, a first principle model enables an examination of the relationship between the design and controllability of the process.

When building a physical model of a batch crystallizer, it is usually assumed that the slurry in the crystallizer is perfectly mixed and the spatial distributions of the CSD and supersaturation are negligible. In this case, when modeling a batch crystallizer, it is only necessary to identify the crystal growth rate and nucleation rate (in the absence of agglomeration, attrition, or similar phenomena). On the other hand, the dynamic behavior of



**Figure 6:** Schematic of a continuous DTB crystallizer.

an industrial continuous crystallizer is influenced by the spatial distribution of CSD and supersaturation. This is because the volume of continuous crystallizer is usually very large. It is said that the continuous crystallization is not economically advantageous over batch crystallization when the production rate is below 500 kg/hr (Wey, 1993). Figure 6 shows the schematic diagram of a continuous DTB evaporative crystallizer. A portion of fines is extracted through the settling zone around the baffle and fed to the external heater, in which the slurry is heated to dissolve crystals. This serves to reduce the total number of crystals and increases the product mean size. Only the crystals large enough to fall against the upward flow in the elutriation leg flow into the product stream. The CSD and supersaturation at each peripheral device are different from those in the crystallization vessel.

Jager et al. (1991) built a model of a continuous crystallizer in such a way that the spatial distribution of supersaturation can be taken into consideration. In their model, the crystallizer is divided into three sections. The changes in CSD and supersaturation in a lump of fluid element is calculated on the assumption that the lump circulates through the three sections in turn. They confirmed that the spatial distribution of supersaturation influences the dynamic behavior of a large scale crystallizer. The idea of circulating lump of fluid element was also applied to simulation of a batch crystallizer by Bohlin and Rasmuson (1996). They concluded that the non-ideal mixing of fluid does not have a strong influence on the performance of batch crystallizers.

Kramer et al. (1996) suggested using a compartmental approach for modeling crystallization processes. In this approach, the crystallizer vessel is divided into smaller parts, each of which is assumed to be well-mixed. Bermingham et al. (1998) presented a heuristic approach

for derivation of a compartmental model for a continuous crystallizer. The information needed in this approach can be obtained by making use of computational fluid dynamics (CFD). They suggested that the compartments should be chosen in such a way that the gradients of supersaturation and energy dissipation rate in one compartment are sufficiently small. Sotowa et al. (2000) proposed a method for deriving an expression for classification of crystals between compartments based on the behavior of particles simulated using CFD.

Kramer et al. (1999) showed an approach to the design of a large scale crystallizer using the compartmental model. First, kinetic parameters were identified by conducting an experimental study using a 22-liter crystallizer. The resulting rate expressions were incorporated into compartment models, and the performance for each of the design alternatives were compared. The comparison between the model predictions and the experimental results was presented by Neumann et al. (1999).

In an evaporative crystallizer, the external heater, which provides the energy needed to evaporate solvent, serves to reduce the number of fines by dissolution. In previous studies on the dynamics and control of continuous crystallizers, it was commonly assumed that the fines entering the external heater dissolve completely, and thus the stream recycled from the heater to the vessel does not contain any crystals. However, in practice the fines do not dissolve completely in the external heater, since the residence time of the slurry within the external heater is very short. Naito et al. (1999) built a model of an external heater by taking account of the finite dissolution rate of crystals. The model was derived using a dissolution rate equation that was identified using experimental data. They demonstrated that the behavior of the crystallizer is strongly influenced by the degree of fines dissolution in the external heater.

There are two main approaches to simulating changes in the distribution of crystal shape in a crystallizer. One way is to model shape dynamics as changes in the crystal length-to-width ratio (Matthews and Rawlings, 1998). The alternative is to model the entire  $n$ -dimensional crystal size distribution, where  $n$  is the number of independent growth faces (Togkalidou and Braatz, 2000). For example,  $n = 2$  for modeling rod-like crystals, where one dimension is the crystal length and the other is the crystal width (equal to breadth). Both methods introduce additional model parameters to be estimated.

Although various models have been used in the study of crystallizer control and operation, agglomeration is not usually taken into consideration in the population balance equation. Jagadesh et al. (1996) demonstrated that large crystals can be obtained by loading sufficiently large amount of seed crystals in batch crystallization. They argued that this is because newly born nuclei rapidly agglomerate with other crystals when the number of seed crystals is large. In order to derive an op-

timal policy for such an operation, the model must take agglomeration into consideration. However, the population balance equation with agglomeration is more challenging to analyze, and the identification of the agglomeration rate is more difficult. Recent developments in the analysis of crystallization with agglomeration should be incorporated into dynamic studies.

While many physical models are available for primary nucleation (this is nucleation directly from solution), most industrial crystallizers are seeded, with most of the nucleation occurring from particle-particle and particle-impeller collisions (this is called *secondary nucleation*). A physical model of secondary nucleation rate has been presented by Gahn and Mersmann (1997, 1999a,b). In this model, the number and distribution of secondary nuclei arising from attrition are predicted based on the frequency of crystal collision with the impeller, and the internal stress distribution at the time of each collision. This model of nucleation kinetics would represent a significant advance in crystallization modeling if the proposed model is verified by experimental data.

Progress in the computer technology has enabled the numerical simulation of slurry flow in a crystallizer with complex internal structure (see Simulation Section). CFD simulation provides hints for defining compartmental models, as well as information on particle segregation in the vessel. However, a limited number of studies have been conducted on the use of CFD results in the modeling of crystallizer behavior (Wei and Garside, 1997). More intensive effort should be conducted to enhance the progress in the modeling methodologies.

### Estimation of Kinetic Parameters

Once the model structure is specified, the modeling problem is reduced to a parameter estimation problem. In crystallization processes, the most important parameters to be estimated are those related to the kinetics of crystal growth and crystal formation/depletion. In order to build a first principle model of a crystallizer, it is necessary to express each of the rates as a function of the operating conditions and state of the slurry.

When a crystal grows, solute in the bulk is transported to the crystal surface by the concentration gradient and then it is integrated onto the crystal surface. When rate equations for surface integration and mass transfer are combined in series, a more complicated growth rate equation is obtained. It is common in the study of the operation and control of crystallizers to use the empirical power-law expression to describe the crystal growth rate:

$$G = k_g \Delta C^g \quad (1)$$

where  $G$  is the crystal growth rate,  $\Delta C$  is the supersaturation, and  $k_g$  and  $g$  are parameters that need to be estimated. When the growth rate is assumed to be

size-dependent, Equation 1 is modified:

$$G = k_g \Delta C^g G_x(x) \quad (2)$$

where  $G_x(x)$  represents variation of growth rate by the crystal size,  $x$ . When the effect of temperature on the growth rate cannot be neglected,  $k_g$  is assumed to be an Arrhenius type function of temperature.

As mentioned earlier, nucleation can be classified into two types. *Primary nucleation* takes place when the supersaturation is high. In the secondary nucleation, fine fragments of crystalline substance arise as a result of attrition or breakage of crystals which are already present in the liquor. These fragments then grow to be larger crystals. An empirical rate expression for nucleation is:

$$B_1 = k_n \Delta C^n \quad (3)$$

where  $B_1$  represents the number of primary nuclei that arise per unit time. Experimental data must be used to estimate the values of  $k_n$  and  $n$ . A commonly used rate equation for secondary nucleation is

$$B_2 = k_b M_T^j \Delta C^b \quad (4)$$

where  $B_2$  is the occurrence rate of secondary nuclei, and  $M_T$  is the magma density. In this case, three parameters ( $k_b$ ,  $j$ ,  $b$ ) need to be identified using experimental data. Again, the parameters  $k_n$  and  $k_b$  are usually assumed to be an Arrhenius type function of temperature, when the temperature effect on the nucleation rate needs to be taken into consideration.

For estimation of the values of the parameters in the crystal growth and nucleation rates, the following approach is most commonly used. When a continuous MSMPR (mixed-suspension mixed-product removal) crystallizer is at a static steady state, the relationship between the crystal size,  $x$ , and the population density of the crystal,  $n(x)$ , can be written as:

$$n(x) = n_0 \exp\left(-\frac{x}{G\tau}\right) \quad (5)$$

where  $n_0$  is the population density of nuclei, and  $\tau$  is the mean residence time. As can be seen from this equation, the population density distribution appears as a straight line on the semi-log plot. The slope and the intercept can be used to calculate the growth rate and the nucleation rate at the operating condition. When data points are collected at various operating conditions, the parameters in Equations 1, 3, and 4 can be identified. There are many other approaches to parameter identification that are based on the population balance equation. Their details can be found elsewhere (e.g., Tavare, 1995).

There have been several studies in which the parameter estimation problem is solved as an optimization problem. Dash and Rohani (1993) used Gauss-Newton method to solve the optimization problem. The parameters to be estimated are the five parameters that appear in the rate equations. The objective function was

defined as the weighted sum of squared errors of the initial solute concentration and the CSD at four instances during batch operation. Qiu and Rasmuson (1994) estimated five parameters in the growth and nucleation rate equations. In the experiments, the solute concentration was measured every five minutes by the density method, and sieve analysis data of the final crystal size distribution was recorded. The optimization algorithm employed was a combination of Gauss-Newton and quasi-Newton methods. Farrell and Tsai (1994) also measured time series data of supersaturation and final crystal size distribution, and used the prediction errors as the objective function. They applied reparametrization to avoid appearance of ill-conditioned Hessian in the optimization problem.

When estimating the parameters of a real process, it is important to assess the reliability of the estimates. Miller and Rawlings (1994) quantified the reliability of the estimates in terms of a confidence ellipsoid and in terms of confidence intervals. Using time series of solute concentration and transmittance data, it was shown that accurate nucleation and growth parameters could be obtained with as little as two batch crystallization experiments. Closely related work showed that appropriate selection of the seed distribution used in the batch experiments results in parameter estimates of higher accuracy (Chung et al., 2000).

Usually studies on the parameter estimation of crystallization processes aim at estimating parameters in the crystal growth and nucleation rate equations. However, in order to derive a model that describes the behavior of an industrial crystallizers, there are many other parameters that need to be estimated. Particularly, a model of large scale continuous crystallizers contains many parameters whose values depend on the structure and dimensions. For a 970-liter continuous crystallizer, Eek et al. (1995a) constructed a model containing fifteen parameters. Six out of fifteen parameter values were fixed using the results from preliminary experiments. The remaining nine parameter values were determined using a parameter estimation algorithm. The objective function was the prediction error of the light intensity data measured by the detector rings of the Malvern particle sizer. Since the number of parameters is large, it is important to evaluate the reliability of the estimates. In their study, the standard deviations of the estimates obtained using different experimental runs were used to assess the magnitude of the parameter uncertainties.

The advantage of constructing model based on bench scale crystallizers is that the experiments are relatively cheap. However, the slurry in an industrial scale crystallizer is not perfectly mixed. Thus, predictions based on a model constructed from bench scale experiments may not agree with the process measurements for an industrial scale crystallizer, when the model is derived by assuming perfect mixing within the crystallizer. In

building a model of an industrial process, it would be best to estimate the values of the model parameters using both process measurements (because this is based on the real process) and experimental data obtained from bench scale apparatus (since these measurements are cheap). It is desirable to establish a unified modeling methodology by exploiting various existing modeling techniques such as experimental design and CFD.

## State Estimation

The state of a crystallizer is characterized by the crystal size distribution (which can include distributions in shape, age, purity, or other variables), supersaturation, and temperature. Since the volume of a bench scale batch crystallizer is relatively small, the slurry in the vessel is usually assumed to be perfectly mixed. In this case, the state variables depend only on time. In industrial scale crystallization processes, the spatial distribution of state variables cannot be neglected in some cases. Also, even when perfect mixing can be assumed, the crystal size distribution in the crystallizer vessel is significantly different from that in the fines recirculation loop or that in the elutriation leg. Such a continuous crystallizer can be modeled by combination of several compartments in which homogeneity of the state variables can be assumed. In a real crystallization process, only a limited number of state variables can be measured on-line. If values of the unmeasured state variables are required for optimal operation or control, they must be estimated using an state estimator.

For successful state estimation by observers or Kalman filters, it is necessary to use a model that describes the process dynamics with sufficient accuracy. However, since the crystallization process is a distributed parameter system, a population balance equation cannot be directly used in state estimation, instead it is approximated by a finite order system. The moment method is one of the most commonly used model reduction techniques. When a closed set of ordinary differential equations is obtained by the moment method, a low order linear state space model can be easily obtained by linearization. The state space model can be used for designing observers and state feedback controllers (Tsuruoka and Randolph, 1987).

Hashemi and Epstein (1982) discussed the controllability and observability of a crystallizer using a moment model which took the energy balance into account. The flow rate, concentration, and temperature of the feed stream were taken as inputs, and the zeroth moment, third-order moment, solute concentration, and temperature in the vessel were used as measurable variables. The condition numbers of the controllability and observability matrices were used as a measure of the controllability and observability. It was shown that both controllability and observability improve when the crystallizer is oper-



ated at an operating condition with high supersaturation.

Chiu and Christofides (1999) presented a framework for controlling general nonlinear distributed parameter systems. In this article, they suggested using a Luenberger-type nonlinear observer for state estimation, but the systematic procedure to determine the observer gain was not clearly shown.

Eek et al. (1995b), Eek (1995), and de Wolf et al. (1989) derived a 100th order state space model by discretizing the population balance equation using finite differences. Eek et al. (1995b) and Eek (1995) calculated the steady state Kalman gain using the linearized state space model, by assuming that the laser scattering intensity data is the measurable variable. When implementing an observer to their experimental rig, a nonlinear model was used in the observer, which takes nonlinearity of the process into consideration. Estimates of the crystal size distribution were used to calculate mean size, which showed good agreement with the experimentally measured values.

An increase in the number of measurable variables facilitates state estimation. However, as mentioned in the Introduction, the number of measurable variables is limited. In particular, the measurement of the supersaturation can be challenging, though this is the key state variable that is the driving forces for crystal nucleation and growth. Thus, intensive studies have been executed to develop hardware and soft sensors to measure supersaturation (see Measurements).

## Analysis

Crystallization processes can illustrate some interesting dynamical behavior, including a high sensitivity to parameter variations. This section focuses on investigations into the analysis of dynamical behavior in continuous and batch crystallization processes.

### Analysis in Continuous Crystallization

Continuous crystallization processes can demonstrate undesirable oscillations in the crystal size distribution, even in open loop. A primary cause of the oscillations is by product being removed that has a different population density than the average population density—this is referred to as *classification*. Industrial crystallizers are often designed to remove and dissolve the smallest crystals (fines), and to preferentially remove the larger crystals as product. Both of these practices increase the tendency for the crystal size distribution to oscillate (Ishii and Randolph, 1980; Randolph, 1980; Randolph et al., 1973, 1977). Oscillations can also be caused by a high order relationship between the nucleation rate and the supersaturation (Randolph and Larson, 1988; Sherwin et al., 1967), but this is probably not the most common cause of the oscillations observed in practice (Randolph,

1980).

Most stability analyses are based on linearized stability analysis for a single continuous crystallizer, usually by determining the localized stability of the moment equations, or by calculating the spectrum of the linearized integro-differential operator (Buyevich et al., 1991a; Witkowski and Rawlings, 1987). These instabilities are characterized as Hopf bifurcations. Conditions have been derived for which a crystallization process can exhibit multiple steady states (Lakatos, 1996; Tavare, 1989; Tavare and Garside, 1985). Other investigations have studied the dynamic behavior under forced oscillations (Buyevich et al., 1991b), where it is possible to obtain more complex dynamic phenomena such as resonance horns, quasi-periodic oscillations, and chaos (Lakatos and Blicke, 1995). These studies suggest that it may be wise in practice to suppress oscillatory disturbances (for example, in the feed conditions) to limit the complexity of dynamical behavior exhibited in the crystallizer. The nonlinear dynamical behavior of a cascade of well-mixed crystallizers has also been investigated (Natalukha, 1996). Nonlinear stability analyses are supported by visualization software that produces phase portraits based on the simulation program (Epstein and Sowul, 1980; Lakatos and Blicke, 1995; Witkowski and Rawlings, 1987).

Oscillations can be reduced by manipulation of the bulk throughput rate (Lei et al., 1971) or the fines destruction flowrate (Beckman and Randolph, 1977). The main difficulty with implementing these early schemes was the lack of measurements of the crystal size distribution (Randolph, 1980). Modern instrumentation makes such schemes implementable (see Measurements section).

### Analysis in Batch Crystallization

Stability in a strict mathematical sense is not an issue in batch or semibatch crystallization processes, since the states of such a process cannot blow up in finite time. On the other hand, having consistent product quality during parameter variations or disturbances is a concern. Miller and Rawlings (1994) provided a clear analysis of the effect of model uncertainties on the product quality in batch crystallizers. Matthews et al. (1996) investigated the sensitivity of the optimal supersaturation profiles to seed loading, profile duration, and the difference in supersaturation orders for nucleation and growth. Also, the singular value decomposition was used to calculate a vector of perturbations in the model parameters that has the strongest effect on the supersaturation profile. Several researchers have shown that the quality of the product crystals is sensitive to the performance of the tracking control to the optimal temperature profile (Chianese et al., 1984; Bohlin and Rasmuson, 1992; Ma et al., 1999a).

An approach was developed that quantifies the im-

pact of such variations on the product quality without exhaustive simulation of all possible process conditions (Ma et al., 1999a; Ma and Braatz, 2001). The knowledge of the worst-case model parameters can be used to determine where experimental effort should be focused to improve model accuracy. The robustness analysis with regard to control implementation uncertainties can guide the selection of the control instrumentation, by determining where high precision sensing and actuation are required. The computation of the worst-case external disturbances determines which disturbances significantly affect the product quality and should be suppressed by redesign of the process or feedback control. The approach was applied to batch crystallization simulations, including to the multidimensional growth of crystals used in nonlinear optics applications, where the nominal parameters and uncertainties were quantified from experimental data (Ma et al., 1999a,b; Ma and Braatz, 2001). Robustness estimates were provided with reasonable computational requirements. It was found that a temperature deviation of  $\pm 0.1K$  from the optimal profile could result in substantial reductions in the product quality.

## Simulation

A significant roadblock to the development of estimation and control strategies for crystallization processes, especially for crystals that change shape during the growth process, is the lack of efficient simulation schemes for the population balance equations. Many simulation studies on crystal growth have been directed toward the solution of the population balance equation for unidirectional crystal growth:

$$\frac{\partial f}{\partial t} + \frac{\partial \{G[c(t), T(t), r]f\}}{\partial r} = h(r, t) \quad (6)$$

where  $f(r, t)$  is the crystal size distribution,  $t$  is time,  $r$  is the internal spatial coordinate (e.g., crystal size),  $c$  is the solute concentration,  $T$  is the temperature,  $G$  is the growth function, and  $h$  is the crystal creation/depletion function. This equation is augmented with associated algebraic and/or integro-differential equations to describe the energy balance, aggregation, breakage, growth, and nucleation phenomena. Simulating these equations is challenging because the crystal size distribution can be extremely sharp in practice, and can span many orders of magnitude in crystal length scale (0.01 nm to 200  $\mu\text{m}$ ) and time scale (20  $\mu\text{s}$  to 100 min).

Several numerical techniques have been proposed (Ramkrishna, 1985). The techniques can be separated into four broad categories:

1. method of moments, in which only lower order moments of the crystal size distribution are simulated, and unknown parameters of an assumed distribu-

tion are fitted to the computed moments (Hulburt and Katz, 1964)

2. weighted residuals/orthogonal collocation methods, in which the solution is approximated as linear combinations of basis functions (Singh and Ramkrishna, 1977)
3. finite difference methods/discretized population balances, in which (6) is replaced by difference schemes (Kumar and Ramkrishna, 1996a)
4. Monte Carlo simulation, in which the histories of individual particles are tracked, each exhibiting random behavior in accordance with a probabilistic model (Maisels et al., 1999; Shah et al., 1977; Song and Qiu, 1999).

The advantage of the method of moments is that only a small number of ordinary differential equations needs to be solved when the moments are closed (that is, form a finite number of equations describing the lower order moments which are not a function of the higher order moments). A weakness of the method of moments is that the moment equations are not closed for most processes, leading to an infinite number of coupled ordinary differential equations to solve. Another weakness is that, even when the moment equations are closed, the numerical errors in a fitted assumed distribution can be arbitrarily large if the assumed distribution does not accurately parameterize the true distribution. Hence a *general* numerical solution of the population balance equation cannot be developed based on the method of moments. However, the method of moments does apply to many well-mixed batch and continuous crystallizers with nucleation and growth. These assumptions can be reasonable in bench scale crystallizers such as used in teaching laboratories (Braatz et al., 2000a). The method of moments is also useful for testing the accuracy of more sophisticated numerical simulation codes.

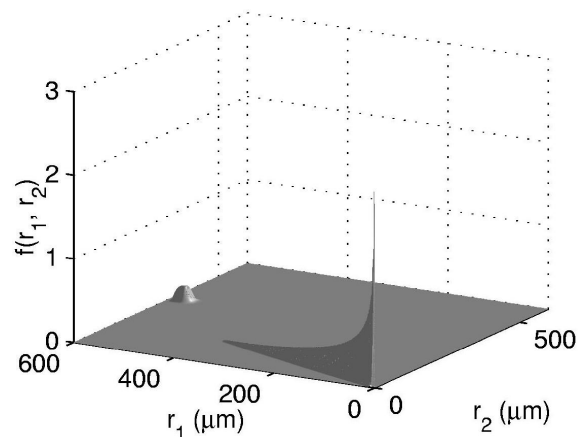
In the application of the method of weighted residuals to the population balance equation, the population density is approximated by a linear combination of user-specified time-independent basis functions with time-dependent weighting factors. The basis functions are selected so that the population density can be well approximated with only a finite number of terms. The linear combination of basis functions is substituted into the population balance equation, and ordinary differential equations for the coefficients are derived with the intent to minimize the error (or residual) in the population balance equation. The system of ordinary differential equations can be solved using any standard solver (Barton et al., 1998). A fast numerical algorithm results when only a small number of terms are needed in the expansion, which has been demonstrated for some crystallizers (Rawlings et al., 1992; Witkowski and Rawlings, 1987). The primary weakness of the method of weighted residuals is that basis functions that work well for one

type of crystallization process may not work well for another, which makes it difficult to derive a general fast algorithm for crystallization simulation using this method. This also applies to orthogonal collocation, which is essentially a class of weighted residual algorithms. Reviews of early work on the method of weighted residuals are available (Ramkrishna, 1985; Rawlings et al., 1993), including summaries of algorithms that combine orthogonal collocation with finite elements (Gelbard and Seinfeld, 1978).

Several discretizations of the population balance equation have been investigated and have been applied to various particulate systems (Gelbard et al., 1980; Hounslow, 1990; Hounslow et al., 1988; Marchal et al., 1988; Muhr et al., 1996). This includes an application to the simulation of a crystallization process in which the crystals have two characteristic growth axes, so that changes in the crystal shape distribution are simulated (Puel et al., 1997). Many of these algorithms were formulated with the intent to conserve moments of the computed population density. Different algorithms conserve different moments, and several choices of discretization points have been investigated (Batterham et al., 1981; Kumar and Ramkrishna, 1996b; Litster et al., 1995). Kumar and Ramkrishna (1996a) provide a critical review of these algorithms, including pointing out technical errors in some of the papers. Various numerical problems can occur when performing direct discretizations of the population balance equations. An approach that removes these problems is to combine the discretization with the method of characteristics (Kumar and Ramkrishna, 1997; Sotowa et al., 2000), which has been applied to particulate processes with pure growth, simultaneous aggregation and growth, and simultaneous nucleation and growth (Kumar and Ramkrishna, 1997).

High resolution finite difference schemes also avoid the numerical problems typically associated with discretizing population balance equations (Ma et al., 2001). The high resolution methods are able to obtain second-order accuracy without the undesirable oscillations that can occur with naive second-order methods. A high resolution method that exploits sparsity and efficiently manages memory resulted in a highly accurate dynamic simulation of the multidimensional crystal size distribution for a system with an extremely sharp distribution (see Figure 7), with the entire computation time in less than 10 minutes on a workstation. This was a simulation of a batch crystallizer which produced prism-like crystals with two characteristic length scales and nonlinear nucleation and growth rates. Numerical analysis indicates that the method can allow a coarse time discretization, which is one of the main reasons for the short computation times (Ma et al., 2001).

The use of computational fluid dynamics (CFD) codes is suitable for the simulation of crystallizers that are not perfectly mixed, since in this case the simulation



**Figure 7:** Population density function for rod-like crystals produced by nucleation and growth.

is best handled by solving the complete transport equations (Sha et al., 1999). CFD codes use either finite elements or finite volume methods, in which the conservation equations are applied directly to subregions to obtain numerical values for the variables of importance (Koenig, 1998). While such codes should probably be applied in the design of any industrial scale crystallizer, the computations are rather intensive for such simulations to be used for the development of estimation and control algorithms.

Monte Carlo methods are especially suitable for simulating stochastic population balance equations, and for especially complex systems (Ramkrishna, 1985). The number of papers applying Monte Carlo techniques has rapidly grown in recent years. Processes that have been simulated include:

1. a continuous crystallizer with size-dependent growth rate (Lim et al., 1998),
2. protein crystal growth (Durbin and Feher, 1991), including the case where both monomers and aggregates attach to the crystal surface (Ke et al., 1998; Strom and Bennema, 1997)
3. imperfectly mixed draft tube baffled and forced circulation crystallizers (Lim et al., 1999)
4. a crystallizer with attrition, in which there is a distribution of volumetric shape factors (Lim et al., 1999)
5. crystallizers with simultaneous growth rate dispersion and aggregation (Van Peborgh Gooch and Hounslow, 1996; Van Peborgh Gooch et al., 1996)
6. continuous crystallization of sodium chloride (Sen Gupta and Dutta, 1990b) and sucrose (Sen Gupta and Dutta, 1990a)

An advantage of Monte Carlo methods is that such code is relatively easy to write. A disadvantage of Monte Carlo methods is that they can be rather computationally expensive, which is a drawback when incorporating such models into estimation and control algorithms. Also, the main capabilities provided by Monte Carlo methods—the ability to handle nearly arbitrary stochastic phenomena and to handle extremely complex systems—may not be needed for most industrial scale crystallizers. The measurement noise is probably larger than other stochastic phenomena for most industrial scale crystallizers (Rawlings et al., 1993), in which case an adequate model can be obtained by appending additive stochastic variables to the results of a deterministic population balance equation simulation. Recent papers have shown that non-Monte Carlo simulation techniques (such as method of moments and finite differences) can be applied to more complex multidimensional crystallization processes, without requiring a significant increase in algorithm complexity (Ma et al., 1999, 2001; Togkalidou and Braatz, 2000).

## Optimal Operation

The quality of crystals is determined by various factors including mean size, crystal size and shape distribution, and purity. An optimal operation problem of a crystallizer is formulated as a problem of finding the operating conditions that optimize an objective function defined by these factors. This section focuses on such optimization problems for an existing crystallizer, and the optimal sizing problem of crystallizers will not be dealt with.

The study of optimal operating conditions for crystallizers was initiated by Ajinkya and Ray (1974). Subsequent studies on the optimal operation of crystallizers have usually focused on maximizing the crystal mean size or minimizing the coefficient of variation. The reason for this is as follows. The crystals produced in a crystallizer are separated from the mother liquor in its downstream processes in order to avoid both inclusion of mother liquor as impurities and formation of bonding between crystals. When the crystal mean size is small, a large amount of mother liquor is retained between crystals due to capillary attraction. In order to facilitate filtration and drying operation, it is desirable to produce large and mono-dispersed crystals.

Usually, formation of an excessive number of nuclei results in smaller crystals with broad distribution. Thus, it is important to operate the crystallizer in such a way that unnecessary nucleation can be minimized.

Most of the studies on the optimal operation of batch crystallizers focus on the derivation of the optimal temperature profile in batch cooling crystallization. When a batch cooling crystallizer is operated in a natural cooling mode, the slurry temperature decays just like the step response for a first order system. This means that at

the beginning of the operation, the reduction in temperature is very quick, and a large number of nuclei arise as a result of high supersaturation. On the other hand, temperature changes only slowly near the end of operation, and the nucleation rate becomes small. The first discussion on the temperature profile that increases the mean size is conducted by Mullin and Nyvlt (1971). They suggested that in order to produce large crystals, the crystallizer temperature should be changed in such a manner that the nucleation rate remains constant during the whole operation (Mullin and Nyvlt, 1971; Jones and Mullin, 1974). Rohani and Bourne (1990b) presented a simple method to calculate the temperature profile that makes nucleation rate or supersaturation constant during the operation. A method for calculating the optimal supersaturation level in batch crystallization is suggested by Mersmann (1995) and Kuehberger and Mersmann (1997a).

In the aforementioned studies, the optimal temperature trajectory has been derived on the assumption that constant nucleation rate or constant supersaturation is optimal. On the other hand, there are studies in which the temperature profile is obtained as the solution of an optimization problem using the quality of product crystals as the objective function. Jones (1974) employed the maximum principle to obtain the temperature profile that maximizes the size of the seed crystals at the final time. Chang and Epstein (1982) employed the mean size, total crystal volume, and the variance of distribution as the objective function, and the optimal temperature profile for each objective is calculated using the maximum principle.

In recent studies, the problem of deriving the optimal temperature profile is formulated as a nonlinear optimization problem, which is then solved using general purpose optimization algorithm. In Miller and Rawlings (1994), the temperature profile that maximizes the ratio of final seed mass to mass of nucleated crystals was obtained using a successive quadratic programming (SQP) code. Lang et al. (1999) used collocation on finite elements and reduced SQP to obtain the optimal temperature profile of a cooling medium that maximizes the mean size of product crystals produced by an unseeded batch crystallization.

In cooling crystallization, the temperature profile is often taken as the only optimization variable, although there are many other factors that determines the quality of the product crystals. Chianese et al. (1984) examined the impact of various parameters associated with the operation of batch crystallizers on the crystal size distribution of the product. They showed that the agitation rate, mass of seed crystals, and the distribution of seed crystals as well as temperature profile are important parameters that strongly affect the crystal size distribution of products.

There are several studies that report the influence of

the mass and size of seed crystals on the product quality. Moore (1994) argued that, to have consistent crystal product quality in batch crystallizers, the operating condition should be determined so that three- $\sigma$  variation in the initial conditions should not affect the final product qualities. In such an operation, the seed mass is at least 0.5-2.0% of the product mass, which is much greater than the seed mass employed in some conventional crystallizer operations.

Jagadesh et al. (1996) showed that when a sufficiently large amount of seed crystals is loaded, a large and monosized crystals are obtained even under natural cooling. They also presented a "seed chart" that can be used to analyze experimental data to find the seed mass above which formation of secondary nuclei becomes essentially negligible. Doki et al. (1999) experimentally verified their approach using a 600-liter pilot scale crystallizer.

Chung et al. (1999) formulated an optimal operation problem in which the seed mass, the mean size of seed crystals, the width of the seed crystal size distribution, and the temperature profile were decision variables. Three objective functions were studied: the mean size of product crystals, the ratio of standard deviation to mean size, and the ratio of nucleated crystal mass to seed crystal mass at the end of operation. The optimal solution for each objective function was calculated using SQP. A parametric analysis showed the significant importance of optimization of the seed distribution for a wide range of possible nucleation and growth kinetics.

Agitation affects the secondary nucleation rate as well as the degree of mixing. Currently, there is no general model that predicts the effects of agitation on the secondary nucleation rate and the crystal growth rate, as it depends on the dimension of the vessel and impeller. As a result, despite its strong influence on the product qualities (Chianese et al., 1984), the agitation rate was not treated as an optimization variable in almost all previous studies. It is desirable that the impact of agitation on the product quality should be modeled, so that the agitation rate can be included in the decision variables in the optimization problem.

As discussed in the Analysis section, the optimal operating condition derived from an off-line calculation may not be the true optimal profile due to the uncertainties in the model. Also, if there is an error in tracking the optimal profile, the resulting product quality becomes different from the optimal. Ge et al. (2000) focused on the problem of plant-model mismatch and errors in the initial condition, and suggested an optimization method called iterative dynamical optimization, in which the operation profile is modified from batch to batch to improve the performance. In this approach, the operation data of previous batch runs are used to derive the plant model, and then the temperature profile is updated by solving optimization problem using conjugate gradient method.

Under the presence of disturbance, modeling error, or

tracking error, the states of the crystallizer do not follow the optimal path. One way to address this problem is to incorporate robustness into the computation of the optimal path (Ma and Braatz, 2000). However, the performance of this approach will be limited by the chosen measured variables and the use of open loop optimization. Another way to address this problem is to choose another measurable variable as the controlled variable in the tracking control. As mentioned previously, the realized temperature profile has a strong influence on the quality of the product crystals. If the variation in product quality due to the modeling or tracking errors can be reduced by choosing a variable other than temperature as the controlled variable, an alternative configuration of the tracking control system should be studied. If such a variable is not directly measurable, a state estimation algorithm should also be developed.

Yet another approach is on-line optimization (Eaton and Rawlings, 1990; Rawlings et al., 1993). If the optimal profile is recomputed at regular intervals based on the state variables at each instance, the effects of various disturbances and uncertainties can be reduced. To carry out dynamic optimization using a physical model, estimates of the state variables must be known at each instance. Thus, the on-line optimization system should consist of the following subsystems (Noda et al., 2000):

1. A subsystem that estimates the current values of the state variables from past and present measurements.
2. A subsystem that derives the optimal trajectory from the current time.
3. A subsystem that controls the state variables according to the optimal path calculated by subsystem 2.
4. A subsystem that modifies the process model using the prediction and measurements.

There is a limited number of studies on the optimal operation of continuous crystallizers. This is probably due to the sustained oscillation of the crystal size distribution which can be observed in the operation of many continuous crystallization processes. Due to this phenomenon, research on the operation of continuous crystallizers have focused on development of stabilizing controllers. Recently, Hasebe et al. (1999) discussed the optimal operation of a continuous DTB crystallizer. The objective of their optimization was the maximization of the production rate of crystals which are larger than a specified size.

Under sustained oscillation, three different types of operation can be readily identified. The first type is to maintain the manipulated variables at the optimal value, while the crystal size distribution is allowed to oscillate. The second type is to periodically change the manipulated variables according to the optimal patterns. In the third type of operation, the oscillation is suppressed

using a stabilizing controller, and the crystallizer is operated at the optimal static steady state. Once a model of the crystallizer is obtained, optimal operating conditions for the first and the third types of operations can be easily obtained by solving a constrained optimization problem. However, it is difficult to derive the optimal manipulation pattern in the second type of operation. This is because the period of oscillation depends on the manipulation pattern, and the period of oscillation under optimal condition is not known before the optimization calculation. To overcome the difficulty, the manipulated variables can be defined as functions of the state variables rather than as functions of time (Hasebe et al., 1999). In their study, one cyclic period of an oscillatory variable was divided into eight phases according to the sign of the gradient and the value of the variable. It was assumed that the manipulated variable takes a unique value in each phase. With this technique, the problem of finding the optimal operation pattern is converted into a problem of finding eight optimal parameters, and the converted problem can be solved using standard optimization algorithms. The result of the optimization shows that a greater amount of large crystals can be obtained by changing the manipulated variable according to the optimal pattern, as compared with the case where the manipulated variables are maintained at the optimal values. It is extremely difficult to suppress oscillation of crystal size distribution in an industrial scale continuous crystallizer. However, the optimization result also shows that the production rate of large crystals increases dramatically, if the behavior of the crystal size distribution can be stabilized.

Sotowa et al. (1999a) demonstrated that the “ease of control” varies greatly with the operating condition. This study suggests that, when deriving the optimal operating condition for a continuous crystallizer, it is important to take controllability issues into consideration. Problems related to the interaction between the design and control are discussed in a later section.

## Control

The focus of this section is on feedback control.

Early investigations in crystallization control were directed towards the stabilization of oscillations or other fluctuations in continuous crystallizers (Beckman and Randolph, 1977; Lei et al., 1971). An experimental study showed that fluctuations in the CSD can be reduced by feedback control, by measuring the crystal size distribution in the fines stream and manipulating the fraction of fines recycled back to the crystallizer (Randolph et al., 1987). A more recent study has shown that changes in the operating condition for a crystallizer can greatly affect the ability of a conventional controller to stabilize open loop oscillations (Sotowa et al., 1999a,b).

Many industrial jacketed batch crystallizers use PI

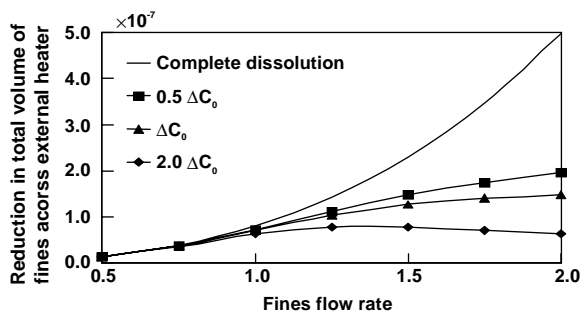
control to follow a specified temperature trajectory, with the manipulated variable being the setpoint to a lower level control loop on the flow to the jacket. When manipulating a fines dissolution rate, a self-tuning controller outperformed a PI controller for a potash alum batch crystallizer (Rohani and Bourne, 1990a). Model predictive control has been used to follow a desired temperature trajectory in a batch jacketed crystallizer, using the temperature of the incoming water to the jacket as the manipulated variable (Matthews III, 1997; Miller, 1993). The jacket water temperature was used as a setpoint to a PID slave controller that adjusted a 3-way valve that blended hot water and cold water streams. A nonlinear model predictive control algorithm was applied to an experimental crystallization apparatus with two inputs and two outputs (Eek, 1995; Eek et al., 1995b). More recently, a multivariable nonlinear model predictive controller has been applied to a KCl cooling crystallizer (Rohani et al., 1999b).

Non-MPC nonlinear feedback control algorithms have been applied to crystallization processes (Chidambaram and Malleswararao, 1990). Some recent efforts have been directed towards taking model uncertainty into account in the feedback controller design procedure. One approach is to combine an extended Luenberger-type observer with a state feedback controller designed by geometric control methods (Chiu and Christofides, 1999). Associated analysis indicates that the nonlinear controller possesses robust stability with respect to sufficiently fast stable unmodeled dynamics. Simulations indicated improved closed loop performance compared to linear PI controller. A related strategy using Lyapunov’s direct method explicitly handles time-varying uncertain variables, provided that any unmodeled dynamics are stable and sufficiently fast (Chiu and Christofides, 2000).

An alternative approach, which couples geometric control with bilinear matrix inequalities, allows the direct optimization of robust performance (Togkalidou and Braatz, 2000; Van Antwerp et al., 1997, 1999). In contrast to most approaches to robust nonlinear control, this approach introduces no conservatism during the controller synthesis procedure. Also, no prior limitations are required regarding the speed of the unmodeled dynamics; instead, engineering intuition is incorporated into weights which bound the unmodeled dynamics, similarly as to the linear time invariant case (Morari and Zafriou, 1989; Skogestad and Postlethwaite, 1996). Application to a crystallization process demonstrated robustness to a wide range of nonlinear and time-varying perturbations (Braatz et al., 2000b; Togkalidou and Braatz, 2000).

## Interaction Between Design and Control

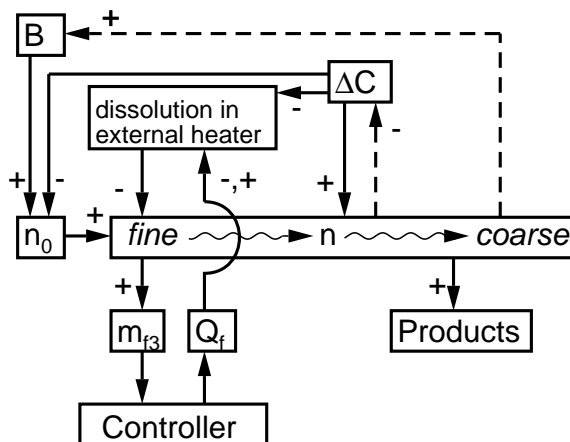
A method for designing a crystallizer with a given production rate has been studied for a long time, and summaries of the results are available (Bennet, 1993; Tavare,



**Figure 8:** Influence of supersaturation on dissolution of fines.

1995). This section does not deal with such design theories but focuses on the interaction between the design and control of crystallization processes.

Sustained oscillation is a commonly observed phenomenon in the operation of continuous crystallization processes. It is widely accepted by researchers in the field of crystallizer control that, in order to suppress the oscillation, the fines flow rate to the external heater should be manipulated in such a way that the nuclei population density or the concentration of fine crystals becomes constant. In most of the studies on the control of continuous crystallizers, the discussion on the controller performance and stability has been conducted on the assumption that the fines entering the external heater dissolve completely. However, in a real crystallization process, the fines do not always dissolve completely, because the residence time of the slurry in the external heater is very short. Naito et al. (1999) developed a model of an external heater by taking the dissolution rate of fines into consideration. Using the model, they have shown that the degree of dissolution depends on the fines flow rate, but this relationship is strongly affected by the supersaturation and the residence time in the external heater. Figure 8 shows a relationship between the fines flow rate and the reduction in total crystal volume across the external heater. When the dissolution rate is taken into consideration, the total volume of the dissolved fines is significantly smaller, as compared with that obtained with the assumption of complete dissolution of fines. Also, when the supersaturation increases from its nominal value ( $\Delta C_0$ ) by a factor of two, the amount of dissolution does not increase monotonically with increase in the fines flow rate. As a result, if the setpoint of the fines flow rate to the external heater is inappropriately determined, it is very difficult to regulate the fines concentration by the fines flow rate. By adjusting the total length and diameter of tubes in the heater, it is possible to change the residence time of the slurry in the external heater without changing the amount of heat input. Sotowa et al. (1999) demonstrated that the controller performance can be improved significantly, if



**Figure 9:** Interaction among state variables in the control system.

the external heater is designed in such a way that the residence time of the slurry is sufficiently long.

At the design stage, the controllability assessment can be easily carried out, given indices for evaluating how easily the designed crystallizer can be controlled. Hashemi and Epstein (1982) used the condition number of the controllability matrix as such an index. A controllability study for a general class of systems described by population balance equations is discussed by Semino and Ray (1995). In their study, a crystallizer was taken as an example process, and the inlet solute concentration is taken as the manipulated variable. However, their result cannot be easily applied to a real crystallizer, because their analysis was carried out on the assumption that the crystal growth rate takes a constant value regardless of the supersaturation. Mathematical treatment of the problem becomes complicated if the crystal growth rate depends on the supersaturation.

Assume that, for a continuous crystallizer, we adopt a controller that regulates the fines concentration in the vessel by manipulating the fines flow rate to the external heater. Figure 9 shows the qualitative relationship among the state variables of the control system. The crystal population density is represented by an oblong rectangle in the middle of the figure, as it is a distributed variable over the crystal size. The population density of nuclei is denoted by  $n_0$ . Two positive feedback effects, which are responsible for the sustained oscillation of crystal size distribution, can be observed in the diagram. One is the feedback effect arising from variations in the nucleation rate,  $B$ . The other is due to variations in the supersaturation,  $\Delta C$ . On the other hand, the controller adjusts the amount of fines dissolution by manipulating the fines flow rate so as to counteract the positive feedback effects. The time constants of these positive feedback loops are very long as compared with

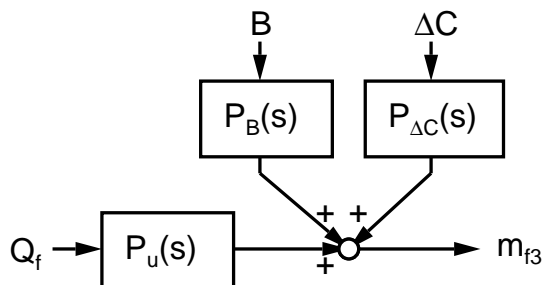


Figure 10: Block diagram of the fines subprocess.

the time constant of the controller. Thus, in order to examine the short term effects of the supersaturation, the nucleation rate, and the fines flow rate on the fines concentration, a hypothetical process is defined by removing the two broken arrows from Figure 9. In the following the hypothetical process will be referred to as the *fines subprocess* (Sotowa et al., 1999a,b).

Figure 10 shows a block diagram of a linear model that describes the behavior of the fines subprocess near the steady state. It is expected that oscillation of the crystal size distribution can be suppressed, if the fines flow rate can be manipulated in such a way that the fines concentration is kept constant regardless of the variations in supersaturation and nucleation rate. Such control action can exist only when the influence of the fines flow rate on the fines concentration is stronger than those of supersaturation and nucleation rate. Sotowa et al. (1999a,b) proposed the following indices which evaluate the relative strength of the influence of the fines flow rate on the fines concentration, as compared with those of supersaturation and nucleation rate:

$$R_{\Delta C} = \frac{P_u(0)}{P_{\Delta C}(0)} \quad (7)$$

$$R_B = \frac{P_u(0)}{P_B(0)} \quad (8)$$

Indices defined by Equations 7 and 8 are used as a measure of ease of control. When the absolute values of these indices are small, it is difficult to stabilize the crystallizer. It should be noted that these indices are only qualitative measures of the ease of control.

Once a dynamic model of the process is obtained, the steady state gains of the transfer functions in Figure 10 can be easily calculated, since the fines subprocess is a stable process. The validity of these indices as measures of the ease of control has been verified by simulation studies (Sotowa et al., 1999a,b). Hamamura et al. (2000) used these indices to study the interaction between the design and control of a continuous crystallizer. In their study, the cross sectional area of the annular settling zone and the volume of the external heater were taken as design variables. Through the study using the indices, they derived a design condition at which a great amount

of large crystals can be produced and the crystallizer can be easily controlled. This idea can be extended to a general design problem of a crystallizer. For example, when the equipment cost function is given, the design condition can be obtained as a solution of a multi-objective optimization problem which derives the relationship between the ease of control and equipment cost.

## Conclusions and Future Directions

The control of crystallization processes has been an active research area in recent years. Now is a good time to be working in this area, as advances in measurement technologies and computing power are removing the main factors that limited progress in the 1970s-1980s. Also, the need for improved control of crystallization processes has increased in recent years. Increased global competition has refocused efforts in optimizing industrial processes in general. Crystallization processes are often the least optimized in a chemical facility, and hence have the most to gain by optimization. Before a process can be optimized, however, its behavior must be understood. Also, the pharmaceuticals industry is continuing to grow faster than other segments of the process industries, and most pharmaceuticals must undergo multiple crystallization steps before arriving at the final product. This has increased the relative importance of crystallization processes within the process industries. Although not discussed in this paper, the development of some pharmaceuticals has been slowed by difficulties in crystallizing proteins for the determination of structure (which is then related to function). Process control engineers could make significant contributions in this area of crystallization.

Several trends in crystallization research can be identified. As discussed in the Measurements section, extracting accurate size shape information from in-process sensors is a very challenging theoretical problem. Substantial research is needed in this area, with proposed solutions likely to include the merging of digital imaging and laser backscattering information. The papers in the Measurements section and the book by van de Hulst (1981) form a starting point for such investigations.

Additives are additional solutes, usually at low concentrations, that can change the crystal shape. Many scientists and engineers have studied the effect of additives on crystal shape, and have proposed mechanisms for how the additives affect the crystal growth process (Dirksen and Ring, 1991). An exciting recent development is that simulation models are becoming available for predicting the effect of solvent type and additive concentrations on the crystal shape (Winn and Doherty, 2000). Industrial demand for such models ensures that this area will receive a significant amount of attention in future years. While there have been some successes, work is needed to validate the model predictions for more



crystal systems. This will likely result in improvements in the assumptions underlying the simulation algorithms, including better models for the interactions between the solute and solvent molecules. Such simulation models will enable the selection of solvents and additives to give a desired crystal shape, and may someday reduce the amount of experimental data needed to identify models for relating the manipulated variables to the shape distribution in industrial crystallizers.

It is expected that it will become increasingly common to study crystallizers in which the fluid is not perfectly mixed (the case in practice). One approach is to model the crystallizer as an interconnection of perfectly mixed crystallizers (Bohlin and Rasmuson, 1996; Kramer et al., 1996; Sha and Palosaari, 2000), as was discussed in the Modeling section. This is already easily feasible with modern computing power. Others have started to apply full-blown computational fluid dynamics codes (Sha et al., 1999; Wei and Garside, 1997). It is expected that stochastic modeling techniques will receive greater attention in future years. Significant effort is expected over the next decade to incorporate the understanding obtained by these more complex simulation codes into estimation and control algorithms.

Another trend is that advanced control algorithms are beginning to be applied to crystallization processes. Crystallization processes have all the characteristics that makes an interesting control problem—partial differential equations, nonlinear dynamics, significant uncertainties, unmeasured state variables, significant disturbances and sensor noise, etc. Crystallization is among those processes that can benefit from advanced process control. Crystallization processes pose a rich array of control problems that are expected to keep process control engineers engaged for some time.

## Acknowledgments

The first author gratefully acknowledges DuPont, Merck, and the National Center for Supercomputing Applications for support, and to Mitsuko Fujiwara, David Ma, and Timokleia Togkalidou for preparing some of the figures. The second author gratefully acknowledges the financial support by the Japan Society for the Promotion of Science under the project number JSPS-RFTF96R14301. The second author wishes to thank Dr. Ken-Ichiro Sotowa for useful discussions.

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