ADVANCED CONTROL OF CRYSTALLIZATION PROCESSES

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Abstract: A key bottleneck in the production of pharmaceuticals and many other products is the formation of crystals from solution. 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 of recent developments in the control of crystallization processes, including activities in sensor technologies, model identification, experimental design, process simulation, robustness analysis, and optimal control.

Keywords: Biotechnology, Chemical sensors, Computer simulation, Batch control, Distributed-parameter systems, Sensors, Estimation algorithms, Robust control, Optimal control, Nonlinear systems

1. INTRODUCTION

Control of crystallization processes is critical in a number of industries, including microelectronics, food, and pharmaceuticals, which constitute a significant and growing fraction of the world economy (Adler et al., 1998; Eisenberger, 1996). For example, the microelectronics industry has an average annual growth of 20%, with sales of $200 billion in 2001. Microelectronic devices are created by a large number of steps, most of which involve either the etching or growth of crystalline material. High performance feedback control is needed to achieve the small length scales required for future microelectronic devices to provide high computational speed (National Research Council, 1992; Semiconductor Industry Association, 2001). As another example, the pharmaceuticals industry grows 10-20% annually and had sales of $150 billion in 2000. In the pharmaceutical industry, the primary bottleneck to the operation of production-scale drug manufacturing facilities is associated with difficulties in controlling the size and shape distribution of crystals produced by complex crystallization processes (Kim, 2002; Rodriguez-Hornedo and Murphy, 1999; Shekunov and York, 2000). Poor control of this crystal size distribution can completely halt the production of pharmaceuticals, certainly a serious concern for the patients needing the therapeutic benefit of the drug.

This paper provides an overview of recent advances in the control of the formation of large numbers of crystals from solution, which is a key bottleneck in the production of pharmaceuticals and many other products. 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 are the crystal purity and the crystal shape. The crystal size and shape affect the dissolution rate, which is important in most pharmaceutical applications. 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. 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 food and pharmaceutical industries, in which the crystals will be consumed.

Figure 1 shows the variability in crystal shape that can occur at a single position and time instance in a pharmaceutical crystallizer. This particular drug, paracetamol (also known as acetaminophen), can have three different crystal morphologies when grown from aqueous solution (Finnie et al., 1999).

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 Myers, 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 solution concentration and the saturation concentration. Supersaturation is typically created in crystallizers by cooling, evaporation, and/or by adding a solvent for which the solute has a lower solubility.

The challenges in controlling crystallization 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, which can result in kinetic parameters that vary over time. Also, many crystals are sufficiently fragile that the crystals break after formation, or the crystals can agglomerate or have erosion or other surface effects that are difficult to characterize. 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. The very large number of crystals is most efficiently described by a distribution (e.g., see Figure 2). For the case of distribution in shape as well as overall size, there are at least three independent variables in the equations. Simulating these equations can be 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 μm) and time scale (20 μs to 200 min). The short time scales are especially relevant in impinging jet crystallizers, in which crystal nuclei are formed directly from solution under conditions of very high supersaturation.

Another challenge in crystallization is associated with sensor limitations. The states in a crystallizer include the temperature, the solution concentration, and the crystal size and shape distribution. The solution concentration must be measured very accurately to specify the nucleation and growth kinetics. 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 subsequent sections review recent efforts towards the control of crystallization processes. A description of the current status of sensor technologies is followed by a description of an approach for model identification and experimental design. Next, recent advances are discussed in the simulation, robustness analysis, and optimal control of crystallization processes.

2. SENSOR TECHNOLOGIES

Measurements of both the solution concentration and the crystal size distribution are necessary for effective identification and control.
2.1 Solution Concentration Measurement

The nucleation and growth rates are strongly dependent on the solution concentration, making its measurement necessary for estimating kinetic parameters and highly useful for feedback control. A significant advantage of attenuated total reflection (ATR) Fourier transform infrared (FTIR) spectroscopy over most other methods for solution concentration measurement is the ability to provide simultaneous measurement of multiple chemical species. The feasibility of ATR-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, 2001; Lewiner et al., 2001a; Lewiner et al., 2001b; Togkalidou et al., 2000). In ATR-FTIR spectroscopy, the infrared spectrum is characteristic of the vibrational structure of the substance in immediate contact with the ATR immersion probe. The crystal of 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.

The combination of ATR-FTIR spectroscopy with advanced chemometrics analysis can measure solution concentrations with accuracy as high as ±0.1 wt% in dense crystal slurries (Togkalidou et al., 2001b). The absorbances measured in the mid-infrared range using ATR-FTIR are usually linearly related to the solution concentration, so nonlinear chemometrics analysis such as used in near-infrared spectroscopy (Amrhein et al., 1996) is usually unnecessary. The ATR-FTIR approach has been applied to a number of complex pharmaceutical compounds in academic and industrial laboratories. This includes applications to several polymorphic crystal systems with multiple solvents and solutes at Merck (Togkalidou et al., 2002a). Figures 3 and 4 show the ATR-FTIR spectra and solubility curve for the paracetamol-water system (Fujiwara et al., 2002), which is an especially challenging system due to the relatively low solubility of paracetamol in water. The reliability and consistency of this approach are expected to result in even more applications to industrial crystallization processes in future years, both in academia and industry.

2.2 Crystal Size Distribution Measurement

To accurately model a crystallizer, it is necessary to characterize the size and shape distribution of the crystals in situ. Recently sensors have become available that can take measurements in slurries with high crystal solids density, as occurs in industrial operations.

The laser backscattering approach is based on 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 (see Figure 5). The updated version of the instrument, the Lasentec Focused Beam Reflectance Measurement (FBRM), has been applied to numerous industrial crystallizers (Togkalidou et al., 2001c; Tahti et al., 1999).

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...
Fig. 5. Schematic for FBRM probe.

Fig. 6. Chord length distribution of paracetamol crystals in water collected from Lasentec FBRM M400L.

Fig. 7. The laser beam crosses the front of the particles from the right to the left. A chord is equal to the distance across a particle. The chord measured for a particular particle depends on its orientation and position in the beam.

distribution (see Figure 6) as the laser beam emitted from the sensor randomly crosses two edges of a particle, with this distance being the chord length (see Figure 7). There have been efforts to relate the chord length distribution to the crystal size distribution, both by the Lasentec company and by some independent researchers (Ruf et al., 2000; Tadayyon and Rohani, 1998). This relationship is dependent on a large number of operating variables, whose effects are not easy to model theoretically, especially for dense crystal slurries (Monnier et al., 1996; Monnier et al., 1997). Chemometrics methods have been used to relate the chord length distribution to the crystal size distribution (Togkalidou et al., 2001a) and to other variables such as the filtration resistance (Johnson et al., 1997; Togkalidou et al., 2001c).

A weakness of the laser backscattering and related laser-based 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.

An alternative method for measuring the crystal size distribution is through periodic sampling, video microscopy, and image analysis (Puel et al., 1997; Rawlings and Patience, 1999). Sampling can be problematic in an industrial environment. A commercial instrument that has become available is the Lasentec Particle and Vision Measurement (PVM) system, in which images of crystals...
in solution are obtained using a probe inserted directly into the dense crystal slurry (see Figure 8). This video microscope can collect 10-30 images 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 (Pacek et al., 1994), not as small as obtained by laser scattering instruments. However, the quality of the images for most dense crystal slurries limits the ability of imaging software to automatically identify individual particles and quantify the characteristics of these particles (e.g., maximum axis, minimum axis, aspect ratio). An advantage of on-line video microscopy is the direct observation of the crystals, which allows 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 only some researchers using the images for quantitative prediction (Baier and Widmer, 2000). Recently, the on-line estimation of characteristics of the crystal shape distribution has been demonstrated, using a combination of the PVM, the FBRM, and robust chemometrics (Togkalidou et al., 2001a). Given the importance of crystal shape in pharmaceutical applications, and that progress becomes easier as computers continue to increase in speed, the accuracy of such predictions can be expected to improve in future years.

3. ITERATIVE MODEL IDENTIFICATION AND EXPERIMENTAL DESIGN

In the past two years, iterative model identification and experimental design has been applied to several crystallization processes, including for crystals with different rates along their growth axes (Gunawan et al., 2002). The approach is similar to approaches used for linear lumped parameter systems, except generalized to the nonlinear distributed parameter equations needed to model crystallizers (see Figure 9). A model selection step (not shown in the figure) is used to select among different model structures, which correspond to different nucleation and/or growth mechanisms.

The overall closed loop crystal product quality can be used as the objective of the experimental design (Ma and Braatz, 2002), instead of the commonly used D-optimal experimental design objective (Box et al., 1978; Miller and Rawlings, 1994), which focuses on the uncertainty in the model parameters. Experimental design variables that have been optimized between each batch experiment include the temperature profile, antisolvent addition rates, and various characteristics of the seed distribution (Chung et al., 2000). Accurate model parameters are typically obtained with as few as four batch crystallization experiments. A typical comparison between model predictions and measurements are shown in Figure 10, where the moments \( \mu_{10} \) and \( \mu_{01} \) are closely related to the average width and length of rod-like crystals in the slurry. The moments were computed by weighted normalization of the FBRM data (Tadayyon and Rohani, 1998). This approach has been applied to several pharmaceutical crystallization processes (Togkalidou et al., 2002b). It is becoming increasingly common for companies to identify models for use in scaling up crystallization processes.

4. SIMULATION

A significant roadblock to the development of identification and control strategies for crystallization processes, especially for crystals that change shape during the growth process, was a 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 (Braatz and Hasebe, 2002; Kumar and Ramkrishna, 1996a; Rawlings et al., 1993):

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

(1)

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 solution 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. The challenge in simulating these equations is that 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 \( \mu \)m) and time scale (20 \( \mu \)s to 200 min).

Several numerical techniques have been proposed for solving population balance equations (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 distribution 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 equation (1) 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., 2000b). 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, 1996a; Kumar and Ramkrishna, 1996b; Lister et al., 1995). 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).

The governing equations for most pharmaceutical crystallization processes are more than two orders of magnitude more complex than equation (1), as their shape variation requires at least one more independent variable. High resolution finite difference schemes have recently been developed that are significantly more computationally efficient than previous methods (Ma et al., 2002a). The high resolution methods are able to obtain second-order accuracy without the undesirable oscillations that can occur with naive second-order methods.

Figure 2 shows the size distribution for potassium dihydrogen phosphate crystals with two characteristic length scales and nucleation and growth kinetics identified from laboratory data. Even with the sharp distribution in Figure 2, the entire computation time was less than 10 minutes on a PC. Numerical analysis indicates that the method can allow a coarse time discretization, which is the main reason for the short computation times. High resolution algorithms have been extended to simulate the effect of nonideal mixing (Ma et al., 2002c), as occurs in most industrial crystallizers. Exploiting sparsity and using parallel computing keep the simulation times reasonable.

Computational fluid dynamics (CFD) codes are suitable for the simulation of crystallizers that are not perfectly mixed, since in this case the simulation 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 identification and control algorithms.

Monte Carlo methods are especially suitable for simulating stochastic population balance equations, especially for 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., 1999b)
4. a crystallizer with attrition, in which there is a distribution of volumetric shape factors (Lim et al., 1999a)
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 identification 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 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 (Braatz et al., 2002; Ma et al., 2002b; Togkalidou and Braatz, 2000).

5. ROBUSTNESS ANALYSIS

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. The singular value decomposition can be used to calculate perturbations in the model parameters that have a strong effect on the supersaturation profile (Matthews et al., 1996; Miller and Rawlings, 1994). Several researchers have shown that the crystal product quality can be sensitive to uncertainties in the crystallization kinetics and to the ability of a feedback controller to closely track the temperature profile in a cooling batch crystallizer (Bohlin and Rasmuson, 1992; Chianese et al., 1984; Ma et al., 1999a).

The impact of variations in model parameters and disturbances on the product quality can be quantified without exhaustive simulation of all possible process conditions (Ma et al., 1999a; Ma and Braatz, 2001). These approaches are applicable to finite-time nonlinear distributed parameter systems, whether the simulation models are stochastic or deterministic (Nagy and Braatz, 2002). 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 (Eaton and Rawlings, 1990). 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. This robustness analysis has been applied to several batch crystallizers, both in simulations and in experiments (Ma et al., 1999a; Ma and Braatz, 2002). Robustness estimates are provided with reasonable computational requirements.

6. OPTIMAL CONTROL

An open loop control problem can be formulated where the seed mass, the mean size of seed crystals, the width of the seed crystal size distribution, and the temperature profile are decision variables (Chung et al., 1999; Miller and Rawlings, 1994). Many objective functions have been studied, including 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 (Eaton and Rawlings, 1990). The optimal solution for each objective function is calculated using successive quadratic programming. A parametric analysis shows the significant importance of optimization of the seed distribution for a wide range of nucleation and growth kinetics (Chung et al., 1999). Under the presence of disturbances, 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; Ma et al., 2002b). However, the performance of this approach will be limited by the chosen measured variables and the use of open loop control.

Several optimal feedback control algorithms including model predictive control have been proposed for batch processes (Braatz and Hasebe, 2002; Eaton and Rawlings, 1990; Rawlings et al., 1993). Even more recently, feedback control algorithms are being developed to reduce the sensitivity of the product quality to model uncertainties and disturbances, while being applicable to nonlinear distributed parameter systems (Chiu and Christofides, 2000; Lee et al., 2002). One approach, which couples geometric control with bilinear matrix inequalities, allows the direct optimization of robust performance (Togkalidou and Braatz, 2000; VanAntwerp et al., 1997; VanAntwerp et al., 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 to the linear time invariant case (Morari and Zafiriou, 1989; Skogestad and Postlethwaite, 1996). Application to a crystallization process demonstrated robustness to a wide range of nonlinear and time-varying perturbations (Togkalidou and Braatz, 2000).

While most recent publications have focused on particular control algorithms, the best control
formulation is still unclear. Usually the feedback controller is designed to follow a temperature trajectory that comes from, for example, solving an open loop optimal control problem. It has been conjectured, however, that a lower sensitivity to parameter uncertainties and disturbances may result by using the solution concentration as a function of temperature as the setpoint trajectory instead (Fujiwara et al., 2002; Gutwald and Mersmann, 1990). Such a formulation, which includes time only as an implicit variable in the setpoint trajectory, can be used in formulating either open loop or closed loop optimal control design procedures. More research is needed to completely resolve whether such implicit-in-time optimal control formulations are superior to the standard formulation.

7. CONCLUSIONS

Faster computers and advances in sensor technologies and simulation and control algorithms are removing the main bottlenecks that limited progress in crystallization control in the 1970s-1980s. Model identification, experimental design, and optimal control algorithms are being increasingly applied to crystallization processes in industry, including to pharmaceuticals processes which have been resistant to systematic first-principles approaches. Further advances are expected to lead to even more utilization of these techniques to reduce time-to-market, which is key in the pharmaceutical industry, and to increase productivity, which is important in the bulk chemicals industry. Crystallization processes have all the characteristics that make an interesting control problem—partial differential equations, nonlinear dynamics, significant uncertainties, unmeasured state variables, significant disturbances, sensor noise, etc. Crystallization processes pose a rich array of control problems that are expected to keep control engineers engaged for the next decade.

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9. REFERENCES


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