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# SIMULATION AND NEW SENSOR TECHNOLOGIES FOR INDUSTRIAL CRYSTALLIZATION: A REVIEW

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A significant proportion of materials are produced in crystalline form. Many of these crystals are produced by nucleation and growth from solution. In these processes, 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., flowability, bioavailability, tablet stability). Such control has recently become possible due to new sensor technologies that can peer into the crystallization process as it occurs, and high resolution algorithms which can efficiently simulate crystallization processes. This paper provides an overview of recent advances in these areas.

## 1 Introduction

A significant proportion of materials are produced in crystalline form. Many of these crystals are produced by nucleation and growth from solution. This type of crystal production is often referred to as *industrial crystallization.*

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. The crystal purity and shape are also important. The crystal size and shape affect the dissolution rate, which is an important property of crystals for medicinal use. 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 enables 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.

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.[1,2] 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. The most common methods of supersaturation generation are cooling, evaporation, or adding a solvent for which the solute has a lower solubility.

A 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, because the kinetics are functions of the difference between the solute concentration and the saturated solute concentration—the relative error in the difference of measurements is much larger than the relative error in a single solute concentration measurement. Obtaining an accurate measurement of the full crystal size distribution (CSD) is even more challenging.

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. 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 $\mu$m) and time scale (20 $\mu$s to 100 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.

This paper reviews recent advances in sensor technologies and simulation algorithms for industrial crystallization processes.

## 2 Sensor Technologies

Measurements of both solution concentation and the crystal size distribution are necessary for understanding and controlling industrial crystallization processes.

### 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 for feedback control. Techniques for inferring the solution concentration include refractometry,[3,4,5,6] densitometry,[7,8,9,10,11] conductivity,[5,12,13,14] and calorimetry.[15] 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.[16,17,18]

The infrared spectrum is characteristic of the vibrational structure of the substance in immediate contact with the ATR immersion probe. 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 for a wide variety of systems. The combination of ATR-FTIR spectroscopy with advanced chemometrics analysis can measure solute concentrations with accuracy as high as $\pm 0.1$ wt% in dense crystal slurries.[19]

### 2.2 *On-line crystal size distribution measurement*

Numerous sensors are available for the measurement of the CSD in a slurry.[20] The most promising sensor for industrial crystallization is based on laser backscattering, as it allows CSD information to be measured by directly inserting the probe into the crystal slurry. A laser beam is focused through a window in the probe tip, and the light scattered back to the probe is collected. 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 as well as in feedback control.[11,21] Several publications describe applications of updated versions of the instrument, referred to as the Lasentec *Focused Beam Reflectance Measurement* (FBRM).[22,23]

Like any laser-based method applied to a crystal slurry, a transformation is required to relate the collected laser light to the CSD. The FBRM instrument measures the chord length distribution as the laser beam emitted from the sensor 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.[24,25,26] Chemometrics methods have been used to relate the chord length distribution to other variables, such as filtration resistance.[27]

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. 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, 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 and quantify their characteristics (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. 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. One

approach is to use multiway principal component analysis and track features in the space of principal components.[28] An alternative is to take moments of the images and use principal components analysis to relate the image moments to characteristics of the crystals.[29] 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.[30,31] 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 pictures can be made much clearer, allowing smaller particles to be seen and a reduction in overlapping crystals. The images are sufficiently clean that standard image analysis algorithms can be used.[32]

## 3 Simulation

Industrial crystallization processes are typically modeled using population balance equations. Simulating these equations is challenging because the CSD 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 100 min). The simulation techniques can be separated into four broad categories:[33]

- method of moments, in which only lower order moments of the CSD are simulated, and unknown parameters of an assumed distribution are fitted to the computed moments,[34]
- weighted residuals/orthogonal collocation methods, in which the solution is approximated as linear combinations of basis functions,[35]
- finite difference methods/discretized population balances, in which the population balance equation is replaced by difference schemes,[36]
- Monte Carlo simulation, in which the histories of individual particles are tracked, each exhibiting random behavior in accordance with a probabilistic model.[37,38,39]

This discussion will be on the latter two simulation techniques, since that is where recent advances have been made.

Several discretizations of the population balance equation have been investigated and have been applied to various particulate systems.[40,41,42] 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.[31] 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. Kumar and Ramkrishna provide a critical review of these algorithms, including pointing out technical errors in some of the papers.[36] 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, which has been applied to particulate processes with pure growth, simultaneous aggregation and growth, and simultaneous nucleation and growth.[43,44]

High resolution finite difference schemes also avoid the numerical problems typically associated with discretizing population balance equations.[45] 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 results in a highly accurate dynamic simulation of the multidimensional crystal size distribution for a system with an extremely sharp distribution (see Figure 1), with the entire computation time being 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 the main reason for the short computation times.

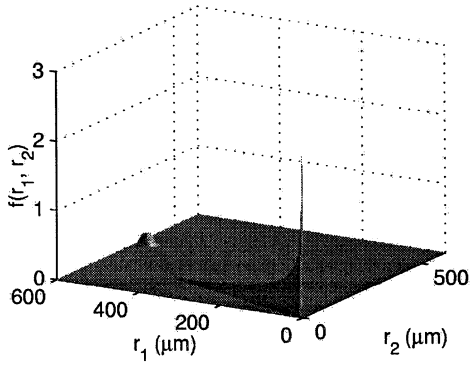


Fig. 1. Population density function for rod-like crystals produced by nucleation and growth.

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 is best handled by solving the complete transport equations.[46] 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.[47] While such codes should 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 for complex systems. The number of papers applying Monte Carlo

techniques has rapidly grown in recent years. Processes that have been simulated include:

- a continuous crystallizer with size-dependent growth rate,[48]
- protein crystal growth, including the case where both monomers and aggregates attach to the crystal surface,[49,50,51]
- imperfectly mixed draft tube baffled and forced circulation crystallizers,[52]
- a crystallizer with attrition, in which there is a distribution of volumetric shape factors,[53]
- crystallizers with simultaneous growth rate dispersion and aggregation,[54]
- continuous crystallization of sodium chloride and sucrose.[55,56]

A disadvantage of Monte Carlo methods is that they can be rather computationally expensive. 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 crystallizers. The measurement noise is probably larger than other stochastic phenomena for most industrial scale crystallizers, in which case an adequate model can be obtained by appending additive stochastic variables to the results of a deterministic population balance equation simulation.[57]

## 4 Conclusions and Future Directions

Several trends in crystallization research can be identified. As discussed in the section on sensor technologies, extracting accurate size and 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.

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.[58] 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.[59] 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, more work is needed to validate the model predictions for more crystal systems. This will likely result in improvements in the underlying 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.

The crystal slurry is not perfectly mixed in a real crystallizer. One approach to account for imperfect mixing is to model the crystallizer as an interconnection

of perfectly mixed crystallizers.[60,61,62,63] This is already easily feasible with modern computing power. Others have started to apply full-blown computational fluid dynamics codes.[46,64] Significant effort is expected over the next decade to develop more complex simulation codes to better understand and optimize industrial crystallization processes.

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