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Crystallization Process Modeling

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1.1

Introduction

The properties of crystalline products are not only defined by their composition and crystal structure, but also by their size and shape. The influence of these features is particularly important for downstream processing operations, such as filtration, drying, milling, granulation, blending, etc. For instance, one can surmise that thin needle-like crystals are more prone to break in an agitated dryer than compact crystals of the same material, or that the time required to separate mother liquor from crystals by cake filtration depends on how tightly crystals in the filter cake are packed, which in turn depends on the crystal size and shape.

Crystals owe their characteristic sizes and shapes to an interplay between crystal structure, thermodynamics and kinetics – in short: to some inherent properties and to the process they were manufactured in. In fact, at the level of individual crystals, it is a particle’s history, the environments and events it has encountered, that determines those features. Given the variety of possible trajectories within a process, it is no surprise that crystals also exhibit a diversity of sizes and shapes, typically described by a particle size and shape distribution (PSSD).

Simple approaches to modeling crystallization processes, e.g., a yield calculation based solely on thermodynamics, are not able to successfully describe, much less predict properties that are connected to the crystal size and shape distribution.

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Yet, as illustrated in the drying and filtration example above, this capability would be highly desirable. The remainder of this chapter is therefore focused on introducing modeling concepts for crystallization processes that allow keeping track of the properties of the liquid phase and of the solid phase, specifically the PSSD. After briefly deriving the underlying concepts in the following paragraphs, selected case studies showcasing applications of this modeling methodology are presented. Among the examples covered are polymorph transformations, crystal growth and agglomeration rate estimation, as well as examples of model-based process optimization.

1.1.1 Population Balance Equations

For the purpose of an accessible introduction to crystallization process modeling, we first assume that crystals can be described by a single characteristic length \( L \). This implies the existence of a one-dimensional particle size distribution (PSD), denoted here as \( f(L) \). Formally, \( f \) is a number density function, so that \( f(L) dL \) corresponds to the number of crystals per volume of suspension with characteristic lengths between \( L \) and \( L + dL \). The evolution of this distribution over time can be described using population balance models \([1–3]\). The corresponding equations account for changes in the number of particles within a given control element, i.e., they describe how many particles are in the control element, how many are entering it, and how many are leaving it. To illustrate this concept, we derive the population balance equation (PBE) for an idealized tubular crystallizer with constant cross-section \( A \) (cf. Figure 1.1(a)). We will then show how this model can be modified to apply also to continuous stirred tanks as well as batch crystallizers.

In the tubular crystallizer considered here, we assume that its content is perfectly mixed in radial direction, but that no mixing in axial direction occurs. Collectively, these assumptions lead to a “plug flow” behavior, however we highlight that these simplifying approximations are by no means a necessary criterion for the modeling framework, i.e., non-idealities could easily be accounted for if necessary. Regardless, here, the PSD is hence not only a function of the time \( t \), and of the internal coordinate (characteristic crystal size) \( L \), but also of the external coordinate (the position along the crystallizer axis) \( x \), that is, \( f(t, x, L) \). We consider a control element stretching from \( x \) to \( x + \Delta x \) and stretching from \( L \) to \( L + \Delta L \) (cf. Figure 1.1). In the external coordinate the control element can be visualized as a slice of the plug flow crystallizer (drawn as the green disk in Figure 1.1(a)), while the internal coordinate is not visible.
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Figure 1.1: a) Conceptual drawing of a plug flow crystallizer with control element highlighted as a slice of the reactor in green; b) drawing of the control element and fluxes into and out of it.

in this representation. Acknowledging this, the control element is redrawn in Figure 1.1(b) to visualize both internal and external coordinates. A population balance equation is obtained by accounting for all fluxes, drawn as arrows in Figure 1.1(b), and possible source or sink terms. In abstract terms, we can write for the control element:

\[
\text{Accumulation} = \text{In} - \text{Out} + \text{Birth} - \text{Death} \quad (1.1)
\]

Fluxes in \(x\)-direction represent the transport of fluid and particles along the axial coordinate of the crystallizer, while fluxes in \(L\)-direction account for crystal growth or dissolution. Nucleation, breakage or agglomeration are important examples of mechanisms that can be described using birth and death terms. For the case of a plug flow crystallizer with volumetric flow \(Q\), Eq. (1.1) can
be written as:

\[
A \Delta x \Delta L \left( [f]_{t+\Delta t} - [f]_t \right) = Q \Delta L \left( [f]_x - [f]_{x+\Delta x} \right) \Delta t \\
+ A \Delta x \left( [Gf]_L - [Gf]_{L+\Delta L} \right) \Delta t \\
+ A \Delta L \Delta x (B - D) \Delta t
\]  

(1.2)

where we have deliberately omitted the arguments of \( f \) as well as those of the growth (or dissolution) rate \( G \) for brevity’s sake. The subscripts in Eq. (1.2) indicate at which point the terms in square brackets have been evaluated. By dividing Eq. (1.2) by \( \Delta L, \Delta t, \Delta x \) and \( A \) and by letting \( \Delta L \to 0, \Delta t \to 0 \) and \( \Delta z \to 0 \), we obtain

\[
\frac{\partial f}{\partial t} + \frac{Q}{A} \frac{\partial f}{\partial x} + \frac{\partial (Gf)}{\partial L} = B - D
\]  

(1.3a)

However, the above considerations do not yet describe changes in concentration in the liquid phase, a crucial property due to its influence on the driving force for nucleation and growth. The necessary material balance for the solute yields:

\[
\frac{\partial c}{\partial t} + \frac{Q}{A} \frac{\partial c}{\partial x} = -\frac{dm_c}{dt}
\]  

(1.3b)

where \( m_c \) is the crystal mass per volume of suspension, typically given by \( m_c = k_v \rho_c \mu_3 \), where \( k_v \) is a shape factor and \( \rho_c \) is the crystal density. Here, \( \mu_3 \) is the third moment of the particle size distribution, in general defined as

\[
\mu_i = \int_0^{\infty} L^i f \, dL.
\]  

(1.4)

Eq. (1.3) forms the general description of a plug flow crystallizer with known temperature profile, both in transient phases as well as during steady state. In a similar manner, the equations describing a (well-mixed) continuously stirred
tank reactor (CSTR) with volume $V$ can be derived, yielding

$$\frac{\partial (fV)}{\partial t} + V \frac{\partial (Gf)}{\partial L} = + V(B - D) + Q_{in}f_{in} - Qf$$ \hspace{1cm} (1.5a)$$

$$\frac{d(cV)}{dt} + \frac{d(mcV)}{dt} = Q_{in}c_{in} - Qc, \hspace{1cm} (1.5b)$$

which in the case of clear input stream ($f_{in} = 0$) and at steady state reduces to the well-known mixed suspension mixed product removal (MSMPR) formulation:

$$\frac{\partial (Gf)}{\partial L} + \frac{Q}{V}f = B - D \hspace{1cm} (1.6a)$$

$$\frac{Q}{V}(c - c_{in}) = - \frac{Q}{V}mc. \hspace{1cm} (1.6b)$$

Notably, Eq. (1.6b) is not a differential, but only an algebraic equation. Finally, we consider the case of a batch crystallizer, which we find to be described by:

$$\frac{\partial f}{\partial t} + \frac{\partial (Gf)}{\partial L} = B - D \hspace{1cm} (1.7a)$$

$$\frac{dc}{dt} = - \frac{dm_c}{dt} \hspace{1cm} (1.7b)$$

In order to solve any one of Eqs. (1.3) and (1.5) to (1.7), additional information is needed. First, a set of initial and boundary conditions is required; for the case of the batch crystallizer and assuming zero-sized nuclei these can, for example, be written as:

$$f(t = 0, L) = f_0(L), \quad f(t, L = 0) = \frac{J}{G} \hspace{1cm} (1.8a)$$

$$c(t = 0) = c_0 \hspace{1cm} (1.8b)$$
where $J$ is the rate of nucleation and $f_0$ and $c_0$ are a seed distribution and the initial solute concentration, respectively. Second, we need some knowledge regarding the constitutive equations that describe the kinetics of the system, that is, we need expressions for $J$, $G$, $B$ and $D$. This requires some understanding of the underlying phenomena which is often not trivial to obtain, but has been accomplished—at least to some degree—for many of the major crystallization mechanisms [4], e.g., nucleation [5, 6], growth [7–9], agglomeration [10–13] and breakage [14, 15]. For the sake of simplicity, here, we assume that the necessary expressions are available.

1.1.2

Notes regarding Population Balance Models

Energy balances and Fluid Dynamics

The models presented in Section 1.1.1 represent useful descriptions in the case of comparably slow crystallization processes, whose temperature can be adequately controlled by some low-level feedback controller. For fast processes or those that are strongly exo- or endothermic, an additional heat balance which is coupled to the other equations is necessary for a complete model. Nevertheless, it should be noted that the assumption of perfect temperature control is often a reasonable approximation, particularly for organic compounds grown at low supersaturations, as is often the case in pharmaceutical production.

In a similar vein, the assumption of well-mixedness, be it partial (e.g., in the radial direction in Eq. (1.3)) or complete (cf. Eqs. (1.5a), (1.6a) and (1.7a)) may be violated for systems where uniform mixing is difficult (e.g., large tanks) or where crystallization occurs with very short characteristic times (e.g., precipitation). In these cases, mixing aspects need to be taken into consideration explicitly, resulting again in more complex descriptions of the process [11, 16, 17].

Solution of population balance equations

An application of the above models requires an accurate solution of the set of (integro-)partial differential equations derived above. Unfortunately, analytical solutions are only available for the simplest cases and in general numerical tools are necessary to compute model outputs. Fortunately, there exists a vast literature on the fast and efficient numerical solution of PBEs [18–21], together with various strategies to reduce the complexity of the resulting model equations making simplifying assumptions. Regarding the latter, particularly the various method of moments that have been developed deserve mention [1, 22].
Applications
The population balance models outlined in Section 1.1 represent a flexible framework to describe particulate processes and can be useful for a variety of tasks. For instance, it is possible to characterize systems whose behavior has not yet been identified by fitting parameters in population balance models to experimental data; we present examples for this application in Sections 1.2.1 to 1.2.3. Once these kinetics are known, processes can be optimized using computational studies (cf. Section 1.2.4) and become candidates for model-based control strategies, such as model predictive control. In addition, such systems can also be realistically investigated on a process design level, allowing the analysis of different flowsheets in terms of, e.g., reachable sets [23]. Finally, extensions to systems with multiple internal states (e.g., multiple characteristic sizes) are possible and represent an important new research direction, as highlighted in Section 1.3.

1.2
System Characterization and Optimization

Identifying the kinetic parameters that form part of the constitutive equations in the population balance model is vital in order to obtain a truly predictive model of a process. To some extent, this can be done through independent experiments, whose goal it is to extract information about the rate of individual mechanisms. Important examples are induction time (nucleation rate) measurements as well as growth rate studies, which may be conducted using setups that are substantially different from a standard crystallizer. However, due to the complexity of the process, it may sometimes be more meaningful to estimate kinetics from experiments that are closer to how the crystallization process would be carried out in production, thereby taking into account nonidealities that occur due to imperfect mixing, particle-particle interactions, etc. A generally applicable pathway for system identification is to run simulations and then compare the model output to experimental data (cf. route A in Figure 1.2). By defining an objective function—for example the sum of squared residuals between model predictions and experimental measurements—and embedding the process model in a higher-order optimization routine, the difference between experimental data and model outcome can be minimized through iterative adaptation of the kinetic parameters. The necessary experimental data is typically acquired by using process analytical technology (PAT) tools, which permit on-line monitoring of the continuous phase (e.g., the solution concentration through infrared spectroscopy, Raman
spectroscopy) and/or the particles (e.g., the particle size distribution or some properties of the PSD through Raman spectroscopy, focused beam reflectance measurements (FBRM), imaging probes, in-situ laser diffraction). While such data alone already helps to understand a process in greater detail, using them in the PBE modeling framework allows drawing more in-depth and more general conclusions regarding the process behavior.

Analogously to parameter estimation, one can optimize the outcome of processes whose kinetics are already known, the main difference lying in the fact that the comparison is then made by comparing the model output with some target outcome (B route in Figure 1.2) rather than the experiments, and that the decision variables are related to the operating policy instead of the kinetic parameters.

Critically, it must be noted that—due to the nature of the problem—there is generally no certainty supported by theory that any optimization (A or B in Figure 1.2) converges toward a local, much less a global optimum in reasonable time. Nevertheless, we will show in the following that, even without this guarantee, valuable results can be obtained with this approach.

1.2.1 Crystal Growth

The characterization of systems under conditions for which crystal growth plays a dominant role is probably the simplest, yet also most important application for the approach described in Section 1.2. One such example is given by Vetter et al. [7], in which the population balance model shown in Eq. (1.7) with r.h.s. zero was used to fit the growth rate of ibuprofen to measured concentration profiles in seeded batch desupersaturation experiments. By applying the estimation procedure to experiments at different concentration of a polymeric additive, the latter’s influence on the growth rate could be determined.

Likewise, Codan et al. [24] used a similar system of equations and experimental procedure to determine the growth kinetics of S-mandelic acid in the presence of its counter enantiomer within the two phase region in water, indicating the applicability of the population balance framework also for chiral systems. The growth inhibiting effect of R-mandelic acid at various concentration levels was quantified and its dependence on supersaturation demonstrated.

As for continuous crystallizers, similar strategies can be used to obtain information regarding the process kinetics. An important simplification occurs for MSMPRs: in the absence of agglomeration and breakage, the identification of
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Figure 1.2: Schematic overview of parameter estimation (A) and model-based process optimization (B). Compound data (thermodynamic/crystallographic properties, etc.), kinetic parameters and information regarding the operating parameters are generally necessary for the simulation of a crystallization process.
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both nucleation and growth rates simultaneously for a single operating condition can be done rapidly by comparing the obtained particle size distribution with the one computed from Eq. (1.6). In fact, under the above assumptions and assuming the growth rate is size-independent, that equation possesses a simple analytical solution, given by:

\[ f_{ss}(L) = \frac{J_{ss}}{G_{ss}} \exp \left( \frac{-LQ}{VG_{ss}} \right) \] (1.9)

which indicates that, ideally, nucleation and growth rates at the steady state can be computed from the y-intercept and slope of the line drawn by a plot of \( \ln(f_{ss}) \) vs. \( L \). An important discussion regarding the usefulness of such experiments is provided by Garside and Shah [25].

1.2.2 Polymorph Transformation

The modeling of solvent-mediated polymorph transformation can be achieved by extending the standard formulation in Section 1.1, which considers only one crystal species, to the case where there exist multiple solid state forms. In particular, population balance equations for all relevant species in the system need to be written and solved in parallel, taking into account the fact that the equations for the different solid forms are coupled through the concentration of the solute, which is one and the same for all of them. For the case of a well-mixed batch reactor with \( m \) different polymorphs and no source or sink terms, Eq. (1.7a) becomes

\[ \frac{\partial f_i(t, L)}{\partial t} + \frac{\partial [G_i(L, S)f_i(t, L)]}{\partial L} = 0 \quad i = 1, \ldots, m \] (1.10a)
Note that growth, dissolution and nucleation kinetics differ for different species and are typically expressed as functions of the corresponding supersaturation $S_i = c/c_i^∗$. The associated material balance, too, is rewritten to account for changes in the solution concentration due to the various polymorphs

$$\frac{dc}{dt} = -\sum_{i=1}^{m} \frac{dm_{c,i}}{dt} \quad (1.10b)$$

The system of partial and ordinary differential equations formed by Eqs. (1.10a) and (1.10b) is valid regardless of the underlying thermodynamics and can be solved in a similar way as in the case of a single species. A number of authors have reported system characterization results using this model and its variants (e.g., for continuous systems) [26, 27].

In particular, Cornel et al. [28] have investigated the solvent-mediated polymorph transformation from $\alpha$ to the monotonically stable $\beta$ L-glutamic acid, that is, a system for which $m = 2$. In particular, they performed seeded experiments and solved the above equations to fit the secondary nucleation kinetics of the $\beta$ form; nucleation rate of $\alpha$ L-glutamic acid as well as the growth and dissolution rates had been determined or estimated independently [29, 30]. The results obtained from the seeded experiments were further used to predict the behavior of the system in the unseeded case with acceptable success as illustrated in Figure 1.3. The model finally demonstrated its ability to forecast total transformation times for experiments starting from clear solutions at different supersaturation levels.

It is important to highlight the role of the two spectroscopic techniques used in that work: in situ attenuated total reflection Fourier transform infrared (ATR-FTIR) and Raman. The two PAT tools allowed insight into the main mechanisms even before the rigorous kinetics determination. Namely, the fact that the dissolution of the metastable $\alpha$ form is not the rate-determining step was established through qualitative analysis of the data alone [31].

1.2.3 Agglomeration

The characterization of systems that exhibit effects besides nucleation and growth has been performed in literature as well. Focusing on the case of agglomeration, it is convenient to first rewrite Eq. (1.7a) in the volume-based
Figure 1.3: Evolution of solid composition and liquid concentration over time for an unseeded polymorph transformation experiment. Markers indicate experimental data (composition: Raman; solute concentration: ATR-FTIR), while solid lines show model fits. Reprinted with permission from Cornel et al. [28]. Copyright 2009 American Chemical Society.
form, where the characteristic length $L$ is replaced by a characteristic volume $v = k_v L^3$. In the case of a well-mixed batch reactor this yields

$$\frac{\partial f(t, v)}{\partial t} + \frac{\partial [\Gamma(v, S)f(t, v)]}{\partial L} = B(t, v, S) - D(t, v, S)$$

where the length-based growth rate $G$ was further replaced by its volume-based equivalent, $\Gamma = 3k_v^{1/3}v^{2/3}G$. Clearly, the mass balance as well as the initial and boundary conditions previously presented in Eqs. (1.7b) and (1.8) can be easily rewritten to reflect this change in internal coordinate. If it is assumed that agglomeration is an irreversible process, that is, agglomerated particles are cemented together via a stable bridge that is strong enough to withstand all forces acting on it, the birth term can be written as (see, e.g, Ramkrishna [3] for a detailed derivation)

$$B(t, v, S) = \frac{1}{2} \int_{v'}^{v} \beta(v - v', v', S)f(t, v - v')f(t, v')dv'$$

while the death term is given by

$$D(t, v, S) = f(t, v)\int_{v'}^{\infty} \beta(v, v', S)f(t, v')dv'.$$

The newly-included kinetics are governed by the agglomeration kernel $\beta$, itself often assumed to be the product of two factors: a collision frequency $\beta_c$ and an agglomeration efficiency (or sticking probability) $\Psi$. While different derivations and expressions exist for the two factors [10, 11, 32–36], there is a general consensus that the agglomeration kernel depends on fluid viscosity, energy dissipation rate as well as supersaturation; theoretical derivations further predict a dependence of the agglomeration rate on particle size, although several authors have chosen to neglect this effect, being still able describe experiments satisfactorily [12, 37, 38].

The above model as well as variations thereof have been used to describe or characterize multiple agglomerating systems in literature [39–42]. Lindenberg
et al. [12] tested different models for $\beta_c$ and $\Psi$ together with Eqs. (1.11) to (1.13) to describe the agglomeration behavior of \( \alpha \)-glutamic acid in water under varying process conditions. The fitted model showed excellent agreement with the experimental results with respect to its prediction of the supersaturation profiles and the particle size distribution (cf. Figure 1.4). It is hence suitable for further use during process design development. The same work, in which additional computational fluid dynamics (CFD) simulations were performed to investigate shear rate variations in the stirred batch vessel (cf. Figure 1.5), further serves to demonstrate a number of key issues that play a role in the modeling of agglomeration.

First, process characterization for these systems becomes inherently more cumbersome due to the increased complexity of the process. Second, the understanding of the fluid dynamics of suspensions in stirred vessels and its role in agglomeration is still limited, particularly for the higher suspension densities and larger vessel sizes that are of industrial interest. Third, there is a difficulty to experimentally distinguish agglomeration from other processes acting on the PSD, such as growth. The reason for this is that typically only a total particle size distribution is measured, that is, a distribution that includes both agglomerates and primary particles. The problem is compounded by the fact sample preparation, such as sonication, can affect the population by breaking up otherwise stable particles.

In response to the former two issues, a trend toward reduced models, whose lower computational cost allows for faster computation of process outcomes able to be integrated in CFD software, is evident [22]. With regard to the third point, image analysis approaches have shown potential in distinguishing agglomerates from primary particles, a step that might help to obtain the higher resolution data sets necessary for experimental validation [43–47].
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Figure 1.4: Comparison of experimental (markers) and fitted modeling (solid lines) results. a) & b): effect of supersaturation; c) & d): effect of seed particle size. Reprinted with permission from Lindenberg et al. [12]. Copyright 2008 American Chemical Society.
1.2.4 Optimization

Here we shall give a brief introduction to model-based optimization in the field of crystallization, although it should be noted that several model-free approaches to optimize or control processes exist as well (e.g., [48–50]). A more comprehensive review of the current state of the art in both fields can be found elsewhere [51–53].

Schematically, model-based optimization of a (crystallization) process with respect to some generic objective, \( \Phi \), can be viewed as the following generic problem

\[
\begin{align*}
\text{minimize/} & \quad \Phi \\
\text{subject to} & \\
\text{Model equations} & \\
\text{Constraints} & \tag{1.14}
\end{align*}
\]

Figure 1.5: a) Contour plot of velocity magnitude in m/s for a stirring rate of 200 rpm; b) distribution of energy dissipation in the stirred reactor for the same stirring rate. Reprinted with permission from Lindenberg et al. [12]. Copyright 2008 American Chemical Society.
where the objective function $\Phi$ generally depends on the time (for batch systems often the end-time only), the state of the system (e.g., density function and its moments or nucleation/growth rates) and the inputs (temperature, antisolvent addition rate, etc.); as indicated also in Figure 1.2. Further, the model equations (e.g., Eqs. (1.7) and (1.8)) define the dynamics of the system, while constraints are set to make sure the solution remains within a physically and potentially economically sensible domain (feasible cooling rates, limited supersaturation, etc.).

The mathematical problem stated in Eq. (1.14) is extremely difficult due to its nonlinearity and nonconvexity, which allows for the existence of many local extrema. Consequently, there is no single pathway that guarantees successful convergence to an optimum, nor is there a simple way of demonstrating in general global optimality of an already found solution; different authors have hence used different numerical methods to optimize Eq. (1.14) with no single strategy showing clear superiority. Regardless, the optimization of crystallization processes can yield insights that are well worth the additional effort. Sheikholeslamzadeh and Rohani [54] conducted an investigation of the optimal control policy for the polymorphic transformation of L-glutamic acid based on kinetics identified using the procedure outlined in Section 1.2.2. In another study, Lindenberg et al. [55] performed multi-objective optimization to improve process time and fine fraction for the combined cooling and antisolvent crystallization of aspirin in an ethanol-water mixture. By allowing temperature and anti-solvent fraction to change simultaneously, the reachable set of possible outcomes is expected to be significantly larger [56]. Specifically, the following objective function was used:

$$\Phi = \begin{bmatrix} t_p \\ \int_0^{t_p} J dt \end{bmatrix}$$  \hspace{1cm} (1.15)

with the first element of $\Phi$ referring to the total process time and the second row referring to the number of new crystals formed during the process. The solubility, nucleation and growth kinetics were identified beforehand as function of $T$, $S$ and antisolvent concentration. In the case of multi-objective optimization, the objective function $\Phi$ is not scalar but rather a vector-valued function, whose elements are to be optimized simultaneously. This leads to a set of so-called Pareto optimal solutions, for which none of the objectives can be improved without degradation of another; an example of such a Pareto front for the
above work is shown in Figure 1.6. Focusing on one point within the Pareto set, the authors could demonstrate the superiority of the resulting cooling and antisolvent profile as compared to two alternative strategies (“cooling first” and “antisolvent first”; cf. Figure 1.7), highlighting that the overall parameter estimation and process optimization strategy was successful.

1.3 Multidimensional population balance modeling

While one-dimensional population balance models have served researchers well in the description of many systems, it is widely recognized that in many cases, the properties of the solid are not well-characterized by a single descriptor. Particularly, this is the case for systems where dynamic impurity incorporation
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a)

Figure 1.7: Different combined cooling and anti-solvent processes as investigated in Lindenberg et al. [55]; (1) anti-solvent first, (2) cooling first, (3) optimized process. (a) Process trajectories in the phase diagram, (b) particle size distribution obtained at the end of each process. The figures highlight that the non-optimized processes result in an uncontrolled supersaturation profile, which leads to undesirable particle size distributions, while the optimized process results in a unimodal particle size distribution of medium sized particles. Reprinted with permission from Lindenberg et al. [55]. Copyright 2009 American Chemical Society.

and evolving crystal shapes are observed. Indeed, in order to capture crystal shape or impurity content in particles, one requires additional internal states in the model. The resulting, generalized form of the population balance equation with $n$ internal states, e.g., for the case of a well-mixed batch reactor, is given by

$$
\frac{\partial}{\partial t} f(t, \mathbf{x}) + \sum_{i=1}^{n} \frac{\partial [G_i(\mathbf{x}, S)f(t, \mathbf{x})]}{\partial x_i} = B(t, \mathbf{x}, S) - D(t, \mathbf{x}, S). \tag{1.16}
$$

The main difference between the above equation and Eq. (1.7) is the substitution of $L$ with the more general $n \times 1$ state vector $\mathbf{x}$ and the corresponding use of
the summation operator. As in the 1D case, the mechanisms that affect the population can be modeled through $G$, $B$ and $D$, although the former has become an $n \times 1$ vector, too. In the important case where particle shape alone is of interest, the internal state vector corresponds to the vector of characteristic sizes, i.e., $\mathbf{x} = \mathbf{L}$, and $G_i = \frac{dL_i}{dt}$, typically the normal growth rate of facet $i$.

While the larger number of internal states in Eq. (1.16) grants the ability to simulate processes in greater detail, the availability of techniques to accurately measure properties such as particle shape for a statistically significant sample of particles—preferably in real-time—is limited. Furthermore, even though multidimensional population balance models have been used in multiple instances for parameter estimation and system characterization [57–59], multidimensional population balance modeling, and in particular appropriate and fast solution techniques, are an ongoing topic of research [60–65]. It is mostly for these two reasons that the use of multidimensional modeling has been very limited outside of academia, despite the fact that it represents an important research direction for the future of the application of population balances to crystallization processes.

1.4 Conclusion

Having provided the theoretical background as well as a broad outline of potential applications in this chapter, a brief discussion of the benefits and drawbacks of crystallization models together with an outlook is in order. Population balance modeling can be a powerful and versatile tool that allows a deep and quantitative understanding of crystallization processes. However, this insight typically comes at the cost of a time- and labor-intensive examination of individual systems; with guidelines for transferability of the lessons learnt being rarely investigated in detail. Similarly, issues of model distinguishability and an incomplete understanding of statistics on the side of experimenters lead to parameterized models whose predictive capabilities outside of an often narrow operating region may be unsatisfactory. All these problems are being compounded by the fact that real processes often deal with complex mixtures with significant batch-to-batch variations. Consequently, population balance models have not yet met with widespread acceptance in industry.

Nevertheless, we believe that a turning point has been reached for several reasons. First, the presence of a mathematical framework intrinsically provides a structure that facilitates systematic analysis and understanding of the process. This stands in contrast with a more qualitative understanding, which
lacks organization and is more prone to misinterpreting or completely missing important interactions. Undoubtedly, this approach brings with it a larger dependency on the know-how and experience of the person evaluating the results and varying interpretations between different experts are hence to be expected. Second, with growing availability of fast computational methods and software tools, accurate solutions to the complex set of equations presented here become more and more accessible to non-modelers. This frees up time that can be used for devising shorter and more statistically robust experimental plans. Third, once a satisfactory description of a process has been established, process models possess crucial advantages over experiments: simulations can be obtained at virtually no cost and process models can be easily integrated into higher-order hierarchies. This means that novel ideas or process designs can be tested quickly and without great financial investment, thus allowing to explore a much larger set of alternatives than can be done in a laboratory or pilot scale.

Crystallization processes are determined by the behavior of myriads of solid particles interacting with at least one fluid phase and with each other. While studies on single particles, such as studies on growth mechanisms, are necessary and important to gain fundamental insight, a single crystal does not make a crystallizer. To believe that this is sufficient for an understanding of the entire process is to fool oneself, as the variability in the history of particulates must not be neglected. Population balance modeling represents a scientific and mathematically sound pathway of dealing with these properties while providing sufficient flexibility to deal with problems of varying complexity. Thus, it remains an indispensable instrument for those seeking to further improve or develop crystallization technology.
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