Model Based Robust Batch-to-Batch Control of Particle Size and Shape in Pharmaceutical Crystallisation

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Abstract: The paper presents a novel batch-to-batch control approach for crystallization processes, which can be used for designing the shape of the crystal size distribution (CSD) and the habit of the crystals, to robustly achieve desired product properties. The method is implemented in a hierarchical structure. On the lower level a supersaturation control approach is used that drives the system in the phase diagram according to a concentration versus temperature trajectory, providing the within batch control. On the higher level a robust model-based optimization algorithm adapts the setpoint of the supersaturation controller, after each batch, using the adapted model parameters by applying a batch-to-batch moving horizon estimation (MHE) approach, to counteract the effects of changing operating conditions, and parameter uncertainties. The process is modelled using the two dimensional population balance equation (PBE), which is solved using the method of characteristics (MOC). The control approach is corroborated through simulations studies. The results illustrate the benefits of the robust iterative learning approach which is able to control both the entire CSD and the habit of the product crystals, reducing significantly the variability in the product properties after only four batches.

1. INTRODUCTION

Crystallization is one of the key unit operations in the pharmaceutical, food and fine chemicals industries. Despite the long history and widespread application of batch crystallization, there remains a disproportionate number of problems associated with its control (Braatz, 2002), mainly related the complex nonlinear dynamics with nonideal mixing, and various disturbances characteristic to these systems. The operating conditions of the crystallization process determine the physical properties of the products which are directly related to the crystal size distribution (CSD), shape or polymorphic form. These properties determine the efficiency of downstream operations, such as filtration, drying, and tablet formation, and the product effectiveness, such as bioavailability and shelf-life. With the recent change of industrial procedures from Quality-by-Testing (QbT) to Quality-by-Design (QbD) and the advent of process analytical technology (PAT) initiative, especially in the pharmaceutical industries, approaches which can be used to design desired product properties are of great interest (Fujiwara *et al.*, 2005). The classical control objectives expressed in characteristics of the size distribution (e.g. maximize average size, minimize coefficient of variation) can lead to conservative and economically inefficient designs of the crystallization systems, and they most often neglect the shape of the crystals. The paper presents a batch-to-batch iterative control (ILC) approach which can be used to directly design the shape of the crystal size distribution and the crystal habit at the same time, to robustly achieve desired product properties. The method is able for example to minimize filtration time without generating unnecessarily large crystals, or minimize breakage by controlling the aspect ratio. Since dissolution rate depends on the shape of the CSD, when the resulting crystals represent the final product (e.g. drugs for inhalers) controlling the shape of the CSD can provide novel applications in the area of drug delivery, or environmentally friendly dosage of pesticides, where particular multimodal distributions can be designed to achieve desired concentration level of the active ingredient. The crystallization system in this study is modelled via a two-dimensional population balance equation (2D-PBE) which is directly used in the optimization procedure where the objective function is expressed in terms of the shape of the entire CSD, and the aspect ratio is added as constraints. The control of crystal size and shape has been considered previously by Lee *at al.* (2002), however in their approach the authors used a computationally more demanding high resolution finite volume method to solve the 2D population balance equation, and parameter uncertainties were not considered directly in the control problem formulation. In this paper the population balance equation (PBE) is solved using a generic 2D-method of characteristics (LeVeque, 1992). Crystallization models are generally subject to significant uncertainties. A robust model based optimization approach (Nagy and Braatz, 2003) is evaluated and it is shown that taking parametric uncertainties into account in the problem formulation can lead to significant improvement in the robustness of the product quality after a few batches only. The control approach is implemented in a hierarchical

structure where on the lower level a model-free crystallization control methodology, the supersaturation controller, drives the system in the phase diagram, rather then in the time domain, providing the within batch control methodology, whereas on the higher level a robust batch-to-batch model based optimization algorithm, the adapts the setpoint of the supersaturation controller after each batch to counteract the effects of changing operating conditions and parameter uncertainties. The method adapts the uncertain kinetic parameters using the information available over the past batches, applying a moving horizon estimation (MHE) scheme (Rawlings *et al.*, 1993), which also provides the uncertainty description used in the robust optimal control problem. The optimization problem is solved using an efficient multistage approach implemented in the optimization package OptCon (Nagy *et al.*, 2004). The proposed approach is corroborated in the case of a simulated crystallization system.

2. 2D POPULATION BALANCE MODELLING OF BATCH CRYSTALLIZATION PROCESSES

Considering a single growth direction with two characteristic lengths L_1 and L_2, and a well-mixed crystallizer with growth and nucleation as the only dominating phenomena the crystal size distribution (CSD) expressed in the number density function $f_n(L_1, L_2, t)$, is given by the population balance equation (PBE) with the form

$$\frac{\partial f_n(L_1,L_2,t)}{\partial t} + \frac{\partial\{G_1(S,L_1;\theta_{g1}) f_n(L_1,L_2,t)\}}{\partial L_1} + \frac{\partial\{G_2(S,L_2;\theta_{g2}) f_n(L_1,L_2,t)\}}{\partial L_2} = B(S;\theta_b)\delta(L_1 - r_{01}, L_2 - r_{02}) \tag{1}$$

with initial condition given by the size distribution of seed, $f(L_1,L_2,0) = f_{seed}(L_{1,0},L_{2,0})$, t is time, $G_1(S,L_1;\theta_{g1})$ and $G_2(S,L_2;\theta_{g2})$ are the generic size dependent growth rates of crystal in the two characteristic directions. $B(S;\theta_b)$ is the nucleation rate, $\delta(\cdot,\cdot)$ is the two dimensional Dirac delta function, r_{01} and r_{02} are the characteristic sizes of the nucleai, $S = C - C_{sat}$ is the supersaturation, C is the solute concentration, $C_{sat}(T)$ is the saturation concentration at the temperature T, and θ_{g1}, θ_{g2} and θ_b are vectors of growth and nucleation kinetic parameters, respectively. The partial differential equation can be reduced to a system of ODEs by applying the method of characteristics (MOC). The aim of the MOC is to solve the PBE by finding characteristic planes in the $L_1 - L_2 - t$ space that reduce the PBE to a system of ODEs. The $L_1 - L_2 - t$ space is expressed in a parametric form by $L_1 = L_1(\mathcal{Z})$, $L_2 = L_2(\mathcal{Z})$ and $t = t(\mathcal{Z})$, where the parameter $\mathcal{Z}$ gives the measure of the distance along the characteristic curve. Hence, applying the chain rule with $f_n(L_1,L_2,t) = f_n(L_1(\mathcal{Z}),L_2(\mathcal{Z}),t(\mathcal{Z}))$ gives,

$$\frac{df_n}{d\mathcal{Z}} = \frac{dL_1}{d\mathcal{Z}}\frac{\partial f_n}{\partial L_1} + \frac{dL_2}{d\mathcal{Z}}\frac{\partial f_n}{\partial L_2} + \frac{dt}{d\mathcal{Z}}\frac{\partial f_n}{\partial t}. \tag{2}$$

Comparing (2) with (1) we find $\mathcal{Z} = t$ and the characteristic equations can be derived. Solving these together with the system of equations which results by applying the method of moments (MOM), we can calculate the dynamic evolution of $f_n(L_1,L_2,t)$ by the following ODEs,

$$\begin{aligned}
&\frac{d\mu_{0,0}}{dt} = B,\\
&\frac{d\mu_{i,j}}{dt} = iG_1\mu_{i-1,j} + jG_2\mu_{i,j-1},\\
&\frac{dL_1}{dt} = G_1,\\
&\frac{dL_2}{dt} = G_2,\\
&\frac{\partial f_n}{\partial t} = -f_n(L_1,L_2,t)\left(\frac{dG_1}{dL_1} + \frac{dG_2}{dL_2}\right) + B\delta(L_1 - r_{01}, L_2 - r_{02}),
\end{aligned} \tag{3}$$

where the system was solved for zeroth moment $\mu_{0,0}$, first order moments $\mu_{1,0}$ and $\mu_{0,1}$, second order moments $\mu_{1,1}$, $\mu_{2,0}$ and $\mu_{0,2}$, and third order moments $\mu_{2,1}$, $\mu_{1,2}$, $\mu_{3,0}$, $\mu_{0,3}$, defined by

$$\mu_{i,j} = \int_0^\infty \int_0^\infty L_1{}^i L_2{}^j f_n(L_1,L_2,t)\, dL_1 dL_2, \tag{4}$$

with initial conditions given by the following vector $x_0 = [\mu_{0,0}(0),\ldots,\mu_{03}(0), L_{1,0}, L_{2,0}, f_{seed}(L_{1,0},L_{2,0})]$. The solute concentration is given by

$$C(t) = C(0) - \rho_c\left(\mu_{21}(t) - \mu_{21}(0)\right), \tag{5}$$

where ρ_c is the density of crystals. In (5) it is considered that the shape of the crystal is rectangular with L_1 and L_2 being width (and depth) and length, respectively. The nucleation kinetics is given by

$$B = k_b S^b, \tag{6}$$

with nucleation parameters $\theta_b = [k_b, \ b,]$. In the case when the growth rates are independent of size and are expressed by

$$G_1 = k_{g1}S^{g1}, \ \ G_2 = k_{g2}S^{g2}, \tag{7}$$

with growth parameters $\theta_{g1} = [k_{g1}, \ g1]$ and $\theta_{g2} = [k_{g2}, \ g2]$. In the case of size independent growth $dG_1 / dL_1 = 0$ and $dG_2 / dL_2 = 0$ and the system of ODEs (3) can be solved analytically (Rusli *et al.*, 2006) and the CSD can be constructed in any time step using different initial conditions obtained by varying $L_{1,0}$ and $L_{2,0}$, the shape of the distribution can be obtained with desired resolution. Additionally the analytical solution can be simplified by the assumption of growth dominated process, and constant supersaturation, which can be considered valid for supersaturation controlled processes. The dissolution process

was modelled similarly, with expressions similar to (7), but different constants, which apply when $S < 0$.

Several approaches have been proposed for designing the operating curves for crystallization systems. Generally speaking, two main categories can be distinguished, (i) the model-based approach (Rawlings *et al.*, 1993) and (ii) the direct design (Fujiwara *et al.*, 2005). In the model-based design approach the detailed model (4) is used together with optimization techniques to determine temperature versus time trajectories, which optimize desired product properties, usually expressed as functions of the moments of the CSD. The direct design approach is based on the understanding of the basic concept of crystallization, to operate the system within the metastable zone bounded by the nucleation and solubility curves. In this technique a supersaturation setpoint profile is chosen experimentally and it is followed in the phase diagram using a supersaturation controller based on concentration measurement. The approach proposed in the paper combines the two methods in a hierarchical control algorithm, in which a model-based robust optimization determines the operating profile in the phase diagram, which is used then as the setpoint for the supersaturation controller.

3. DISTRIBUTIONAL BATCH-TO-BATCH NMPC

The main feature of the batch-to-batch control is that variations on two time-scales must be considered. As shown on Figure 1, within and between batches variations can be considered leading to an optimization problem on two time-scales. In batch process operation often within batch measurements are not available or adjustment to the operating conditions cannot be made. In these cases batch-to-batch improvement is practically easier to implement, by learning from the information obtained usually from after-batch laboratory analyses. In this framework the within batch measurements (if available) can be used for model based parameter and state estimation/adaptation, and the updated model then can be used in an iterative learning control framework for the improvement of the future operating recipe (Figure 2).

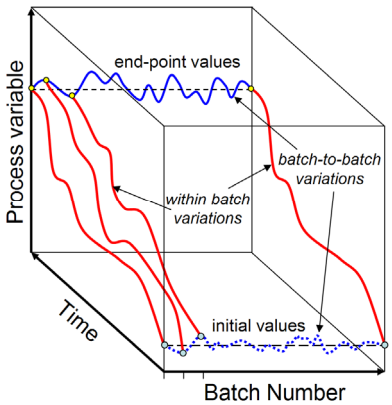

Fig. 1. Schematic representation of the dynamic two-time scale variations in batch control.

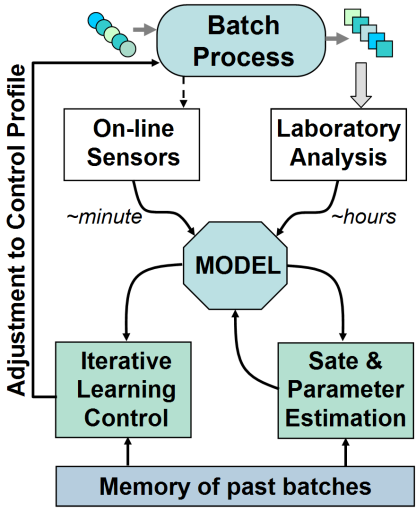

Fig. 2. Structure of the iterative learning control framework.

The optimal control problem for the iterative learning scheme can be formulated as the alternative application of a moving horizon estimation (MHE) and a robust optimal control problem. The MHE problem solved after each batch k is,

$$\min_{\hat{x}_{0,k},\theta_k} \sum_{i=k-1}^{k-N_b} W_i (y_i^{\text{model}}(\hat{x}_{0,k};\theta_k) - y_i^{\text{meas.}})^2 \tag{8}$$

subject to:

$$\dot{x}_i = f(x_i, u_i; \theta_k); \quad x_{0,i} = x_{0,k};\ x_i \in \mathcal{X} \tag{9}$$

$$y_i = g(x_i, u_i; \theta_k);\ i = k-1, \ldots, k-N_b \tag{10}$$

where N_b is the number of past batches used in the estimation and W_i is a weighting matrix with exponential forgetting factor over the past batches. The model output used in the parameter estimation in the case of crystallization processes can be the entire CSD or properties of the CSD (e.g. number or weight average mean size). From the parameter estimation problem estimates of the uncertainty bounds on the parameters are also calculated, which can then be used in the robust optimization problem for control. The model based optimal control problem is expressed as

$$\min_{\Delta u_k} \mathcal{H}(x_k, u_k; \theta_k) \tag{11}$$

subject to:

$$\dot{x}_k(t) = f(x_k(t), u_k(t); \theta_k); \quad x_k(t_0) = \hat{x}_{0,k} \tag{12}$$

$$y_k(t) = g(x_k(t), u_k(t); \theta_k) \tag{13}$$

$$u_k = u_{k-1} + \Delta u_k \tag{14}$$

$$h(x_k(t), u_k(t); \theta_k) \le 0, \quad t \in [t_0, t_F] \tag{15}$$

where $\mathcal{H}$ is the performance objective, t is the time, t_F is the final time at the end of prediction (end of batch), $x(t) \in \mathbb{R}^{n_x}$ is the vector of states, $u(t) \in \mathcal{U} \subset \mathbb{R}^{n_u}$ is the set of input vectors, $y(t) \in \mathbb{R}^{n_y}$ is the n_y vector of measured variables used to compute the estimated states $\hat{x}(t_k)$,

$\theta \in \Theta \subset \mathbb{R}^{n_\theta}$ is the n_θ vector of uncertain parameters, where the set Θ can be either defined by hard bounds or probabilistic, characterized by a multivariate probability density function. The function $f : \mathbb{R}^{n_x} \times \mathcal{U} \times \Theta \to \mathbb{R}^{n_x}$ is the twice continuously differentiable vector function of the dynamic equations of the system, $g : \mathbb{R}^{n_x} \times \mathcal{U} \times \Theta \to \mathbb{R}^{n_y}$ is the measurement equations function, and $h : \mathbb{R}^{n_x} \times \mathcal{U} \times \Theta \to \mathbb{R}^{c}$ is the vector of functions that describe all linear and nonlinear, time-varying or end-time algebraic constraints for the system, where *c* denotes the number of these constraints. The repeated optimization problem is solved by dividing the batch time $t \in [0, t_F]$ into *N* equally spaced time intervals Δt (stages), with discrete time steps $t_k = k\Delta t$, and $k = 0, 1, \ldots, N$ (Biegler and Rawlings, 1991). The model based control approach is implemented in the Matlab toolbox, OptCon (Nagy *et al.*, 2007), which is based on a state-of-the-art large-scale nonlinear optimization solver (HQP) (Franke *et al.*), which uses a multiple shooting algorithm (Diehl *et al.*, 2002).

Consider the case of parameter uncertainty, with $\delta\theta \in \mathbb{R}^{n_\theta}$ defined as the perturbation about the nominal parameter vector $\hat{\theta}$. The real uncertain parameter vector is then given by $\theta = \hat{\theta} + \delta\theta$. Assuming zero mean, normal measurement errors, and known covariance matrix, the set of possible parameter values is given by the hyperellipsoidal confidence region, defined as

$$\Theta(\alpha) \triangleq \{\theta : (\theta - \hat{\theta})^T \mathbf{V}_\theta^{-1} (\theta - \hat{\theta}) \le \chi^2_{n_\theta}(\alpha)\}, \qquad (16)$$

where α is the confidence level, $\chi^2_{n_\theta}(\alpha)$ is a quantile of the chi-squared distribution with n_θ degrees of freedom, and $\mathbf{V}_\theta \in \mathbb{R}^{n_\theta \times n_\theta}$ is the parameter covariance matrix. Uncertainty description (16) results most commonly from typical least-squares identification procedures from experimental data, and it is provided by the MHE estimation approach applied in this paper. The parameter covariance matrix is updated after each batch when a new set of parameters are also computed using the MHE algorithms. We denote with $\psi(x(t_f);\theta)$ the end-point property of interest. Considering the mean-variance approach the following objective function is used to account for parameter uncertainties in the NMPC:

$$\mathcal{H} = (1 - w)\mathcal{E}[\psi(x(t_f), \theta)] + w V_\psi(t_f), \qquad (17)$$

where $\mathcal{E}$ and $V_\psi \in \mathbb{R}$ is the expected value and variance, respectively, of the property at the end of the batch, and $w \in [0,1]$ is a weighting coefficient that quantifies the tradeoff between nominal and robust performance. The main advantage of this approach compared to the classical minmax optimizations is that the tradeoff between nominal and robust performance can be controlled by appropriately weighting the two objectives. Expected value and variance can be computed efficiently using a second order power series expansion,

$$\delta\psi = L\delta\theta + \frac{1}{2}\delta\theta^T \mathbf{M}\delta\theta + \ldots, \qquad (18)$$

where $L = (d\psi / d\theta)_{\hat{\theta},u} \in \mathbb{R}^{n_\theta}$, and $\mathbf{M} = (d^2\psi / d\theta^2)_{\hat{\theta},u} \in \mathbb{R}^{n_\theta \times n_\theta}$ are the first and second order sensitivities, respectively. Assuming zero mean, normally distributed parameters $\delta\theta$, deriving the expected value and variance of $\delta\psi$ based on (18) gives the analytical expressions:

$$\mathcal{E}[\delta\psi] = \frac{1}{2}\mathrm{tr}(\mathbf{M}\mathbf{V}_\theta) \qquad (19)$$

$$V_\psi = L\mathbf{V}_\theta L^T + \frac{1}{2}[\mathrm{tr}(\mathbf{M}\mathbf{V}_\theta)]^2 \qquad (20)$$

where $\mathrm{tr}(\mathbf{A})$ is the trace of matrix $\mathbf{A}$. The feasibility of the optimization under parametric uncertainty is achieved by reformulating the constraints in a probabilistic sense:

$$\mathbb{P}(h_i(x, u;\theta) \le 0) \ge \alpha_i, \qquad (21)$$

where $\mathbb{P}$ is the probability and α_i is the desired confidence level for the satisfaction of constraint i. The robust formulation of (21) can be written using the t-test in the form:

$$\mathcal{E}[h_i] + t_{\alpha/2, n_\theta}\sqrt{V_{h_i}} \le 0, \quad i = 1, \ldots, c. \qquad (22)$$

The expected value ($\mathcal{E}[h_i]$) and covariance (V_{h_i}) of the constraint h_i can be evaluated using first or second order approximations. For first order approximation $\mathcal{E}[h_i(x,u;\theta)] = h_i(x,u;\hat{\theta})$ and $V_{h_i} = L_{h_i}\mathbf{V}_\theta L_{h_i}^T$, whereas for second order approximation expressions similar to (19) and (20) can be used, with $L_{h_i} = (dh_i / d\theta)_{\hat{\theta},u} \in \mathbb{R}^{n_\theta}$, and $\mathbf{M}_{h_i} = (d^2 h_i / d\theta^2)_{\hat{\theta},u} \in \mathbb{R}^{n_\theta \times n_\theta}$. In this formulation the algorithm shows robust performance in the sense of constraint satisfaction and decreased variance of the performance index (Nagy and Braatz, 2004).

4. APPLICATION OF THE ROBUST BATCH-TO-BATCH NMPC FOR CRYSTALLIZATION PRODUCT DESIGN

For the case studies the crystallization of a pharmaceutical was considered as the model system, for which nucleation and growth kinetics were determined experimentally using image analysis using the Sympatec Qicpic equipment. It was found that a 1D-PBM was not able to describe accurately the variation of the CSD, since a time-varying volumetric shape factor was found to be necessary to capture the significant change in aspect ratio during the batch. Using the 2D-PBE the volume of the individual crystals are directly calculated hence the volumetric shape factor is not needed. Although, the 2D-PBM provides the full 2D CSD, in this paper the target distribution was given as a 1D CSD based on the equivalent spherical diameter, since this is the most commonly used characterisation mode of CSD used in practice. Additionally the *in situ* CSD measurement during the experiments was based on focused beam reflectance measurement (FBRM), which provides 1D information. The equivalent spherical diameter (r) is calculated by

$$r = \frac{6L_1^2 L_2}{\pi}. \qquad (23)$$

The 2D-PBM also allows the incorporation of the shape information in the optimization problem. Different product design problems were considered, when various objective functions expressed as desired shapes of the CSD and limits of the crystal aspect ratio ($\alpha = L_1 / L_2$) were optimized and the required temperature profiles were determined. The novel feature of the proposed approach is that the optimization is performed in the phase diagram, and a concentration trajectory for batch k is obtained as a function of temperature $C_{set,k} = f(T)$. This allows the direct application of the widely accepted supersaturation control in conjunction with the NMPC. The optimization problem can be expressed by the generic robust formulation:

$$\min_{C_{set,k}(T)} \{(1-w)\sum_i (f_n(r_i,t_f;\theta_k) - f_n^{desired}(r_i,t_f))^2 + wV[f_n(r,t_f;\theta_k)]\} \quad (24)$$

$$s.t. \quad T_{\min} \le T(t) \le T_{\max}$$
$$R_{\min} \le \frac{dT}{dt} \le R_{\max}$$
$$C(t_f) \le C_{\max} \quad (25)$$
$$\alpha_{\min} \le \alpha \le \alpha_{\max}$$

where $f_n^{desired}(r_i,t_f)$ is the desired (setpoint) CSD with a given shape at the end of the batch, $T_{\min}$, $T_{\max}$, $R_{\min}$, $R_{\max}$ are the operating constraints determined by the bounds and minimum and maximum rate changes of the temperature profiles, respectively, C is the concentration, $C_{\max}$ is the maximum concentration at the end of batch required to achieve a desired crystallization yield, and $\alpha_{\min}$ and $\alpha_{\max}$ are the minimum and maximum bounds on the aspect ration for the desired crystal shape. For most crystallization processes there are significant variations in the metastable zone width (MSZW), which is incorporated in the optimization by considering uncertainties in the nucleation parameters ($\theta_b = [k_b,\ b]$). The variations in the nucleation kinetics are usually significantly larger than the uncertainties in the growth hence this will be considered in this study. In the MHE scheme a fixed iteration approach was used and the convergence of the two nucleation parameters is shown on Figure 3. It can be seen that the MHE converges practically after 3-4 iterations, after which the robust profile is also constant. Figure 4 shows the metastable zone width in the phase diagram delimited by the solubility and nucleation curves. Because of the uncertainties in the nucleation kinetics there is a nucleation region, with a width given by the 99% confidence intervals obtained via Monte Carlo simulations. The operating profiles resulted by solving (24)-(25) for the nominal case ($w = 0$) and one robust case ($w = 0.3$) are shown in the phase diagram in Figure 4. The target CSD was monomodal with a shape biased toward larger particles to improve filtration. The robust operating profile which resulted after 4 iterations, corresponds to a trajectory, which is further away from the nucleation zone throughout the entire batch. The operating profiles are implemented using a supersaturation controller. Figure 5 shows the time-domain representation of the operating curves corresponding to Figure 4. Since the robust profile operates at lower superasaturation the cooling is slower than in the nominal case resulting in longer batch time for similar yield. The robust operating policy also indicates slower cooling and even a slight increase in the temperature during the initial part of the batch when the nuclei are generated. This is in correlation with the often used industrial practice, according to which slow cooling and moderate increase in temperature after the onset of nucleation can result in improved consistency in the final CSD. Monte Carlo simulations were performed by randomly sampling (100 samples) the uncertain parameter space θ_b and applying the nominal and robust temperature profiles. Figure 6 demonstrates that the robust operating curve leads to significantly reduced variability in the product quality compared to the nominal operating policy. The incorporation of the constraint with respect to the aspect ratio allows controlling the crystal habit (aspect ratio) and shape of the CSD at the same time. Figure 7 represents the variations during repeated batches in the product quality expressed as the aspect ratio and maximum Feret diameter. The Monte Carlo simulations show that the robust iterative learning control approach with the profile shown in Figures 4 and 5, provides a significantly lower variability in the crystal size and aspect ratio due to parameter uncertainty.

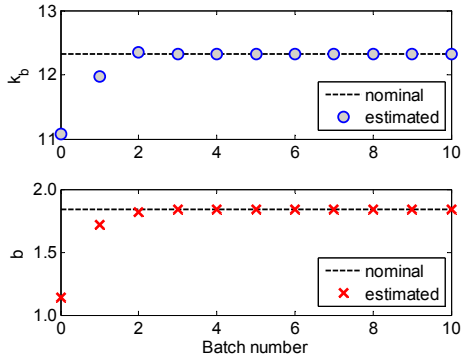

Fig. 3. Evolution of the parameters estimated by the MHE over the batches.

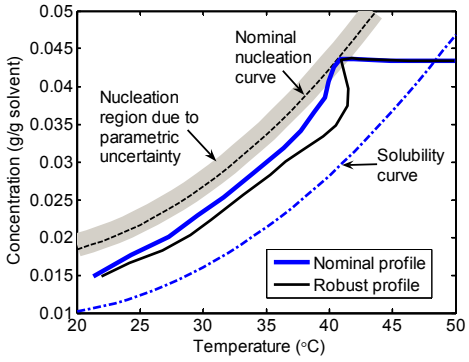

Fig. 4. Phase diagram with nominal ($w = 0$) and robust ($w = 0.3$) operating curves for monomodal target CSD.

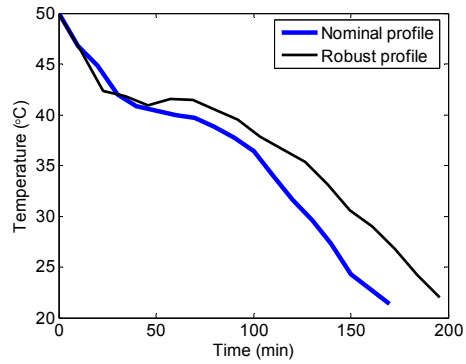

Fig. 5. Time-domain representation of the nominal and robust operating profiles corresponding to Figure 3.

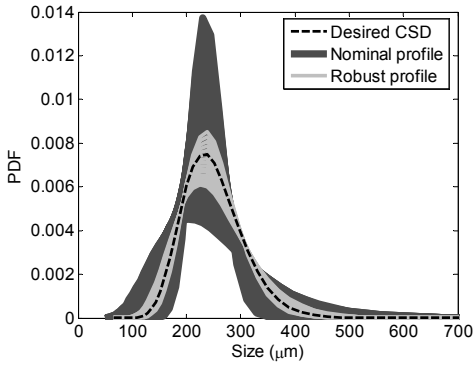

Fig. 6. Monomodal target and product CSDs resulting from Monte Carlo simulations with the uncertain nucleation parameters using the nominal and robust operating profiles.

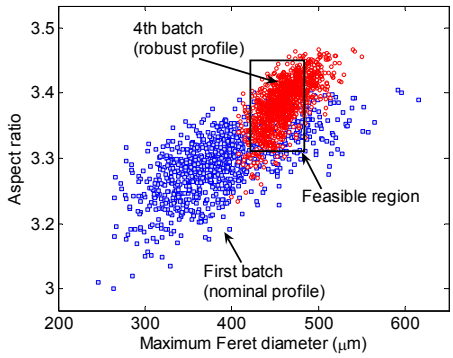

Fig. 7. Monte Carlo simulations showing the performance of the robust iterative learning control after 4 batches.

In the case of the robust ILC most of the batches provide product within the feasible region whereas the original nominal trajectory leads to a very high proportion of off-spec product, which could lead to decreased efficiency of the downstream processes or problems in formulation.

6. CONCLUSIONS

The paper presents a novel robust batch-to-batch control approach for the design of crystalline products by shaping the crystal size distribution and habit. A distributional optimization approach is used to design a robust concentration versus temperature profile, which is used as a setpoint for a lower level supersaturation controller. A two dimensional population balance model is solved using the method of characteristics, to capture the dynamic evolution of the aspect ratio which is incorporated into the robust optimization problem to control the shape of the size distribution and habit at the same time. Simulation results demonstrate the benefits of the proposed approach, which can decrease variability in size and shape of the product in a few batches.

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