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REDUCING THE EFFECT OF INPUT UNCERTAINTIES USING MODEL PREDICTIVE CONTROL FOR CRYSTALLIZATION PROCESSES

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ABSTRACT

The objective of this study is to test the robustness of a Process Analytical Technology (PAT) system design on a potassium dichromate crystallization process in the presence of input uncertainties using uncertainty analysis. To this end a systematic framework for managing uncertainties in PAT system design is used. For uncertainty analysis the Monte Carlo technique is used and implemented on two cases namely closed-loop operation using Proportional-integral (PI) control and Model Predictive Control (MPC). The analysis performed under closed-loop condition using PI control shows that the input uncertainties in the nucleation and crystal growth parameters affect the product-process performances (e.g. crystal size distribution (CSD)). Analysis of the proposed PAT system design (closed-loop using MPC controller), on the other hand, shows that the effect of the input uncertainties on the outputs (product quality) is minimized, and the target specifications are achieved, thus ensuring that the PAT system design is reliable under the considered uncertainty ranges.

Keywords: crystallization, uncertainty analysis, PAT design, model predictive control.

INTRODUCTION

The introduction of the Process Analytical Technology (PAT) guidance (FDA, 2004) has resulted in increased use of process control applications and process/product quality monitoring in general. This trend is also noticeable for crystallization processes, boosted also by the fact that high quality crystalline products can be produced. The main specifications of the crystal product are usually given in terms of crystal size distribution (CSD), shape and purity. A challenge, however, in many crystallization processes is how to obtain a uniform and reproducible CSD. Considerable efforts have been put in development of detailed models of crystallization processes in order to support the development of improved operation and control strategies. To this end, a generic systematic design of process monitoring and control (PAT) systems has been developed (Samad *et al.* 2013a). Through this framework, it is possible to first generate the necessary problem-system specific model for a wide range of crystallization processes using a generic multi-dimensional model-based framework (Samad et al, 2011), and then to perform a PAT system design (Singh *et al.* 2009).

Another challenge is that so far in model-based PAT system design, it has been assumed that the exact value of the model parameters is known, for example in the nucleation and crystal growth rate expressions (Singh *et al.* 2009; Samad *et al.* 2013a). These parameters are usually estimated from experimental data, often with considerable measurement errors which also implies a certain error on the estimated parameters. Consequently, there is a degree of uncertainty around the values of nucleation and crystal growth model parameters, which must be taken into account to design a reliable and robust PAT system.

In the crystallization process, several approaches have been taken to deal with uncertainties by incorporating robustness in the control of crystallization (Nagy and Braatz, 2003; 2004; Paengjuntuek *et al.* 2008; Nagy, 2009; Saengchan *et al.* 2011; Forgione *et al.* 2015). Nagy (2009) proposed a robust on-line model-based optimization algorithm using distributional batch nonlinear model predictive control (NMPC) which considers the nucleation parameter uncertainties in the optimization problem formulation to determine the robust operating profiles. By performing this approach, the variability in the product CSD has been significantly reduced. However the uncertainties around the crystal growth parameters are not considered in their work. Meanwhile, Forgione *et al.* (2015) used iterative identification control where the uncertain model parameters are iteratively estimated using the measured data. In the work of Saengchan *et al.* (2011), improvement of batch crystallization control on potassium sulfate crystallization given uncertain kinetic parameters has been proposed using model predictive control (MPC). Moreover, Yang *et al.* (2014) also proposed NMPC to handle the changes in process parameters.

Furthermore, the impact of parameter uncertainty and control implementation inaccuracies on the performance of optimal control trajectory are quantified in the work of Ma *et al.* (1999). These quantitative estimates are then used to decide whether more laboratory experiments are needed to provide more accurate parameter values or to define performance objectives for control loops that implement the optimal control trajectory. As a result, a robust feedback control whether using a simple PID controller or more advanced controller such as MPC is needed to deal with uncertainties and to ensure the desired crystal product is achieved. Before deciding for an appropriate approach to deal with uncertainties in crystallization process, foremost the impact of such model parameter uncertainties on the predicted system performance needs to be quantified and evaluated. Such an evaluation is useful to find out whether uncertainties considered may lead to a situation where the target specifications of the crystal product are no longer

reached. The latter situation is of course not desirable in a pharmaceutical production process. This requires expansion of model-based methods with formal uncertainty analysis in a comprehensive way.

Therefore, it is important to develop robust model-based design tools with the necessary features to detect such potential product quality related problems. In this study, the application of uncertainty analysis is highlighted using a potassium dichromate crystallization case study, where the objective is to test a PAT system design in achieving the target crystal properties under the considered input uncertainty ranges of nucleation and crystal growth model parameters.

SYSTEMATIC FRAMEWORK FOR PROCESS MONITORING AND CONTROL (PAT) SYSTEM

The architecture of the generic framework for systematic design of monitoring and control (PAT) systems is illustrated in Figure-1 (Samad *et al.* (2013b)). There are 6 main steps through which the design proposal is created to achieve the target product properties. The first step is the problem definition for the crystallization process under study where the overall objective is defined. Step 2, crystallization model development, involves the generation of a problem-chemical system specific model using the generic multi-dimensional modelling framework (Samad *et al.* 2009). The third step is concerned with the generation of the supersaturation set-point for the crystallizer. The objective here is to generate the necessary supersaturation set-point that guarantees a targeted CSD is achieved. Two methods are available: an analytical CSD estimator based method and a response surface method (RSM). In step 4, the PAT system that would be applicable for the process monitoring and control system to achieve the desired end product properties, is designed. For this purpose, the design methodology for PAT systems developed by Singh *et al.* (2009) is adopted. For step 5, the methods for performing uncertainty and sensitivity analysis have been incorporated into the PAT system design framework (Samad *et al.* 2013a).

The method (see Figure-1 (right)) contains two main steps: (i) framing of uncertainty and sensitivity analysis, and (ii) decision making. In the first step (step 5.1), the sources of uncertainties are identified, e.g. parameters in the nucleation and crystal growth rate in the crystallization process. Afterwards the uncertainty analysis using Monte Carlo simulations is carried out to test the effect of uncertainty of parameters from nucleation and crystal growth kinetic models on the predicted system performance, where the performance is quantified by variables such as the solute concentration and the CSD. Subsequently, the most significant parameters are identified through global sensitivity analysis techniques using Standardized Regression Coefficient (SRC) and Morris sampling methods. In the decision making (step 5.2), the robustness of the model-based solution is evaluated by judging on a number of criteria including the probability of failure to meet target product specifications.

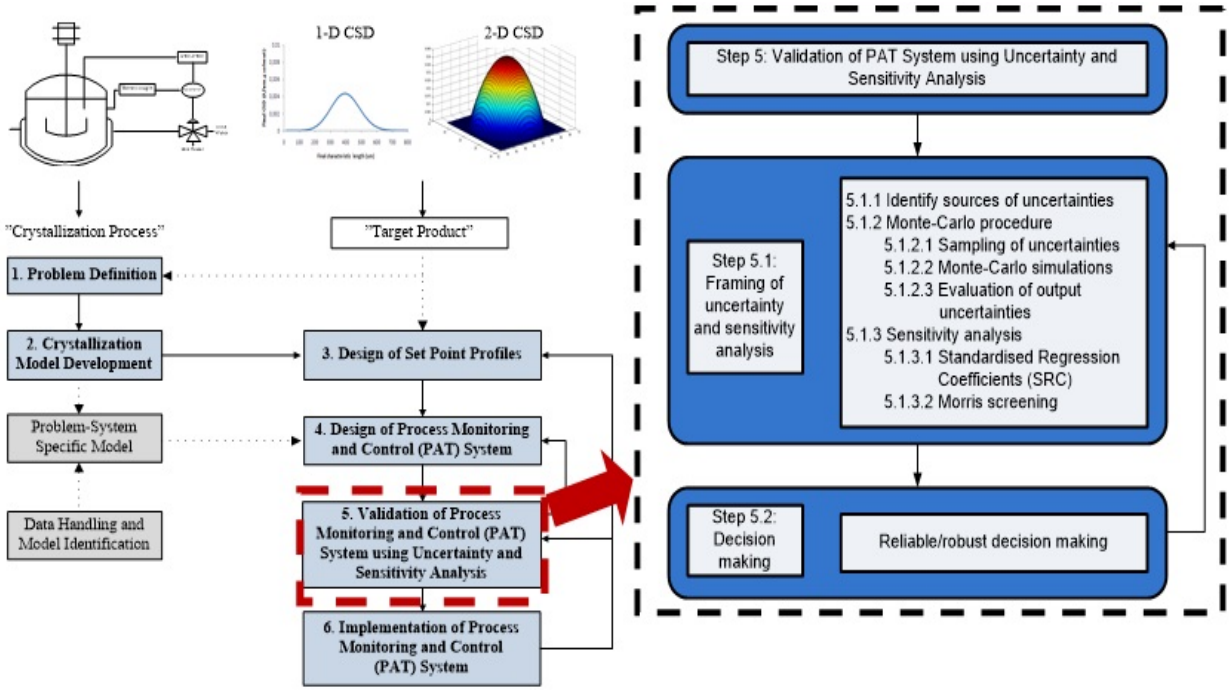

Figure-1. Incorporation of a methodology for combined uncertainty and sensitivity analysis in the framework for model-based design of product-process problems (Samad *et al.* 2013b).

If the target product specifications are not met due to the effect of the input uncertainties, then an alternative operating strategy is to be identified in order to reduce the probability of failure. One of the alternative is to propose new controller structure for example by using MPC. This new proposed controller is then implemented in the framework until an acceptable risk level is achieved.

Model Predictive Control (MPC) Algorithm

The concept of MPC is to determine a set of control moves for a time horizon minimizing an objective function subject to a dynamic process model with path and/or end point constraints (Saengchan *et al.* 2009). In this case, the objective function is set to minimize the error between the simulated CSD (f_n) and the target CSD. At each control interval, an open-loop sequence of manipulated variables is computed in such a way to optimize the future behavior of the plant. Only initial value of the control profile is applied and then the optimization procedure, based on new information (C, T, f_n), is repeated to modify a new input profile (C_{sp}) with the control and prediction horizons moving forward one sampling time step. The control strategy for MPC is shown in Figure-2. In addition, the optimization problem is solved by sequential quadratic programming (SQP) method using fmincon routine in Matlab optimization toolbox to compute a set of control moves (C_{sp}).

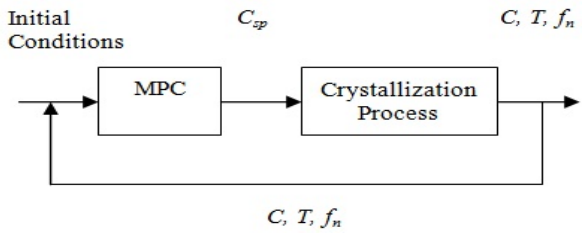

Figure-2. The MPC control strategy for this crystallization process.

Application of the Systematic Framework: Potassium Dichromate Crystallization Case Study.

Application of the framework is demonstrated for potassium dichromate crystallization (adopted from Aamir *et al.* 2010) where it will be investigated how the input uncertainties affect the target CSD and how this uncertainty can be minimized to achieve the desired target CSD.

Problem Definition (Step 1) and Crystallization Model Development (Step 2)

The objective of this study is to develop a robust PAT system design for potassium dichromate crystallization in order to achieve the target CSD in the presence of parametric uncertainties. The desired product is potassium dichromate with the following predefined qualities: target CSD assumed as a normal distribution with mean characteristic length of 490 µm and standard deviation of 52 µm. In step 2, the problem-chemical system specific model for potassium dichromate crystallization is generated using the generic modelling framework (Samad *et al.* 2009) by using similar conditions and assumptions as reported in the literature (Aamir *et al.* 2010) as shown in Table-1.

Generation of Supersaturation/Concentration Set-point (Step 3)

In this step, the set point profile that yields the desired target one-dimensional CSD is generated using model-based optimization involving the analytical CSD estimator. Firstly, the initial seed distribution (f_{n0}) for the potassium dichromate crystallization case is specified and assumed as a normal distribution by using a mean characteristic length of 156.89 µm and a standard deviation of 43.75 µm. The analytical CSD estimator for the one-dimensional and the case of size dependent growth as shown in Table-2 is used and the growth parameters for the potassium dichromate system needed in the analytical CSD estimator is obtained from Aamir *et al.* (2010). A model-based optimization approach is then used to optimize the supersaturation set-point and the total crystallization time in order to achieve the desired target CSD, respectively. The objective is to minimize the sum of squares of the relative errors between the target CSD and a predicted CSD obtained through the analytical CSD estimator. The optimal supersaturation set-point to be maintained is 1.25×10^{-4} g/g and total crystallization time is 180 minutes.

Design of PAT System (Step 4)

In this step, the closed-loop operation is considered where the PI controller is employed to maintain the supersaturation at the desired set-point obtained in Step 3. Here the closed-loop simulation results are shown in Figure-3 where the potassium dichromate concentration initially started at 0.1928 g potassium dichromate/g water and the PI controller successfully maintained the concentration at the set point once the concentration set point was reached.

In Figure-3 (left, top), approximately 0.1377 g potassium dichromate/g water remains by the end of the operation. Figure-3 (right, top) shows the temperature profiles obtained from closed-loop simulation initially at 30°C and then cooled down to 20°C in 180 minutes. Figure-3 (right, bottom) shows the final CSD (mean of 488.1 µm and a standard deviation of 51.83 µm) that has been achieved at the end of the batch crystallization. The final CSD obtained is in good agreement with the mean (490 µm) and standard deviation (52 µm) for the target CSD. Based on this closed-loop operation, it is confirmed the PI controller is efficient to maintain the super saturation at the desired trajectory. However it is important to note that in this operation, it has been assumed that there is no uncertainties presence in the crystallization. Therefore in the next section, the capability of the PI controller to handle the effect of input uncertainties will be investigated further in the next section.

Table-1. List of model equations for the potassium dichromate crystallization.

No	Equations	No	Equations
1	For $i=1$; $\frac{dN_1}{dt}+\frac{G_{x1}}{2\Delta Cl_2}N_2+\frac{G_{x1}-G_{x0}}{2\Delta Cl_1}N_1=B_{nuc}$, For $1<i<n$; $\frac{dN_i}{dt}+\frac{G_{xi}}{2\Delta Cl_{i+1}}N_{i+1}+\frac{G_{xi}-G_{xi-1}}{2\Delta Cl_i}N_i+\frac{G_{xi-1}}{2\Delta Cl_{i-1}}N_{i-1}=0,$ For $i=n$; $\frac{dN_n}{dt}+\frac{G_{xn-1}}{2\Delta Cl_n}N_n+\frac{G_{xn-1}}{2\Delta Cl_{n-1}}N_{n-1}=0,$	5	$f_n(L_{xi})=\frac{\frac{N_i}{\Delta Cl_i}+\frac{N_{i+1}}{\Delta Cl_{i+1}}}{2}$
2	$\frac{dc}{dt}=-\frac{\rho_c k_v V}{m_w}\left(\sum_{i=1} S_{xi}{}^3\frac{dN_i}{dt}\right)$	6	$S=c-c^{sat}$
3	$\rho V c_p\frac{dT}{dt}=-\Delta H_c\rho_c k_v V\left(\sum_{i=1} S_{xi}{}^3\frac{dN_i}{dt}\right)-U_1A_1(T-T_w)$	7	$B_{nuc}=k_b S^b V$
4	$\rho_w V_w c_{pw}\frac{dT_w}{dt}=\rho_w F_{win}c_{pw}(T_{win}-T_w)+U_1A_1(T-T_w)$ $+U_2A_2(T_{ex}-T_w)$	8	$G_{xi}=k_{gx}S^{gx}(1+\gamma_x L_{xi})^{p_x}$

Table-2. Generic analytical CSD estimator expressions.

Characteristics	Analytical Expressions
Final CSD	$f_{n,i}=f_{n0,i}\left[\frac{(1+\gamma_x L_{x0,i})^{1-p_x}+k_{gx}S_{sp}{}^{g_x}\gamma_x t_c(1-p_x)}{(1+\gamma_x L_{x0,i})^{1-p_x}}\right]^{\frac{p_x}{(p_x-1)}}, \quad i=1,2,\ldots,N$
Final characteristic length	$L_{x,i}=\frac{\left[(1+\gamma_x L_{x0,i})^{1-p_x}+k_{gx}S_{sp}{}^{g_x}\gamma_x t_c(1-p_x)\right]^{\frac{1}{1-p_x}}-1}{\gamma_x}, \quad i=1,2,\ldots,N$

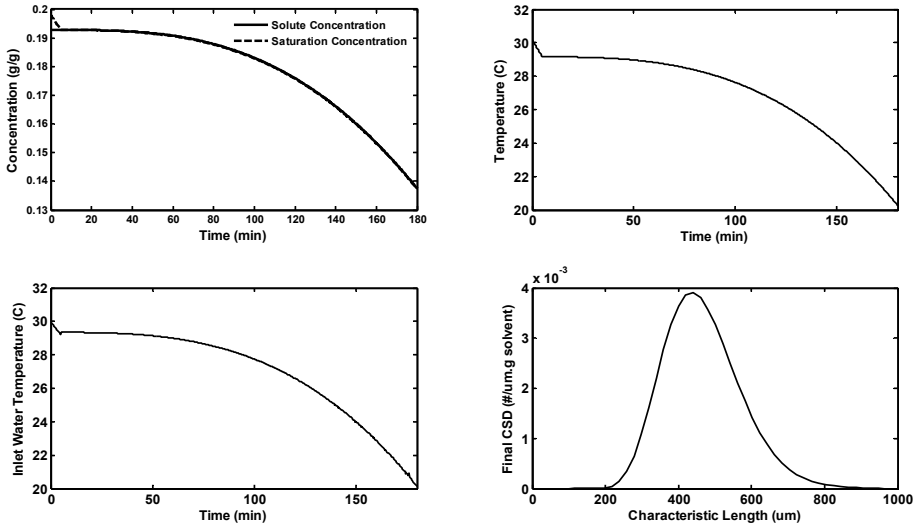

Figure-3. Closed loop simulation results for potassium dichromate concentration, temperature, inlet water temperature (manipulated variable) and final CSD.

Evaluation of Designed PAT System (Step 5)

In this study, the uncertainty analysis is performed under closed-loop operation. Notes that the sensitivity analysis is not carried out in this work due to the purpose of this work is to focus on reducing the uncertainties. The objective here is to quantify the effect of input uncertainties in nucleation and crystal growth parameters on the prediction of the crystallization process. If the input uncertainty is indeed affecting the model predictions, then the influential parameters are identified and used as an input in the closed-loop condition. In the framing scenario of uncertainty and sensitivity analysis (step 5.1), the input uncertainty has been chosen based on the 6 parameters $(k_b, b, k_{gx}, g_x, \gamma_x, p_x)$ from the nucleation and the crystal growth models (see Equations (7) and (8) in Table-1) (step 5.1.1). Table-3 shows the input uncertainty of nucleation and crystal growth parameters. The values for lower and upper bound of each parameter are calculated based on the 95% confidence interval taken from Aamir *et al.* (2010). The Monte Carlo procedure (step 5.1.2) consists of 3 sub-steps. The first sub-step is the sampling of uncertainties (step 5.1.2.1) using the Latin hypercube sampling (LHS) method to sample the uncertain parameters (Helton and Davis, 2003). In this work, 100 is selected as a suitable number of samples. Step 5.1.2.2 consists of the Monte Carlo simulations. Here the open-loop potassium dichromate model is simulated 100 times, i.e. once for each different set of model parameters. The Monte Carlo simulations have been performed in the Matlab.

The results from the Monte Carlo simulations are analyzed in the step 5.1.2.3 (evaluation of output uncertainties) by calculating typical statistics such as mean, standard deviation and relevant percentiles of model output distributions. The uncertainty is indicated by the variance of the distribution or using the percentiles, which indicates the spread of the data and the extent of uncertainties in the outputs. The larger the spread of the simulated data indicates the larger the uncertainty in that model output or the further the 10^{th} and 90^{th} percentiles away from the mean, the larger the uncertainty of the model output. Based on Figure-4, the potassium dichromate concentration (Figure-4, left, top) shows only a small variation indicating a low extent of uncertainty. This shows that the PI controller is able to counteract the effect of input uncertainty. The inlet water temperature is used as a manipulated variable in this study. Figure-4 (left, bottom) shows the inlet water temperature profile where the profile changes rather vigorously by the end of the operation in order to maintain the concentration at the set point and thus counteract the effects of the input uncertainties. Meanwhile the uncertainty is almost non-existent in the temperature profiles. The final CSD obtained as shown in Figure-4 (right, bottom) indicates that a small variation of the final CSD is achieved. In step 5.2 (decision making), it has been concluded that there is still a presence of uncertainty in the final CSD under closed-loop simulation. Therefore, in this study, the advanced control structure using MPC is proposed to further investigate the capability of MPC in reducing the effect of this input uncertainties on the CSD. Now the MPC is employed as controller and the Monte Carlo simulation in Step 5 is therefore repeated for the same framing scenario and parametric uncertainties as for the closed-loop operation using PI control. The results from the Monte Carlo simulations (using MPC) for 100 parameter samples are presented in Figure-5.

Based on Figure-5, the uncertainty of CSD data has been reduced after MPC is employed in the closed-loop condition compared to the CSD data obtained using PI control. This indicates that the MPC controller has been successfully counteract the variations of uncertain parameters and minimized the uncertainty in the CSD data compared to PI control. The data has been further analyzed using the 10^{th} and 90^{th} percentile values of the Monte Carlo simulations under both controllers as shown in Figure-6. Using PI controller, the 10^{th} and 90^{th} percentile values are little bit far away from the mean value indicating the presence of uncertainty. However, the MPC controller performance has been better and limits the uncertainty effects on a low level as indicated in Figure-6.

Table-3. Input uncertainties on nucleation and crystal growth parameters for potassium dichromate crystallization.

ID	Parameters	Units	Values	Confidence interval (95%)	Lower bound values	Upper bound values
1	Growth rate constant, k_{gx}	µm/s	9.56	±0.0832	9.4768	9.6432
2	Growth order constant, g_x	Dimensionless	0.8	±0.2411	0.5589	1.0411
3	Growth constant, γ_x	1/µm	0.0075	±0.0021	0.0054	0.0096
4	Growth constant, p_x	Dimensionless	1.24	±0.0633	1.1767	1.3033
5	Nucleation rate constant, k_b	No. of particles/µm³.s	0.038	±0.0044	0.0336	0.0424
6	Nucleation order constant, b	Dimensionless	3.4174	±0.037	3.3804	3.4544

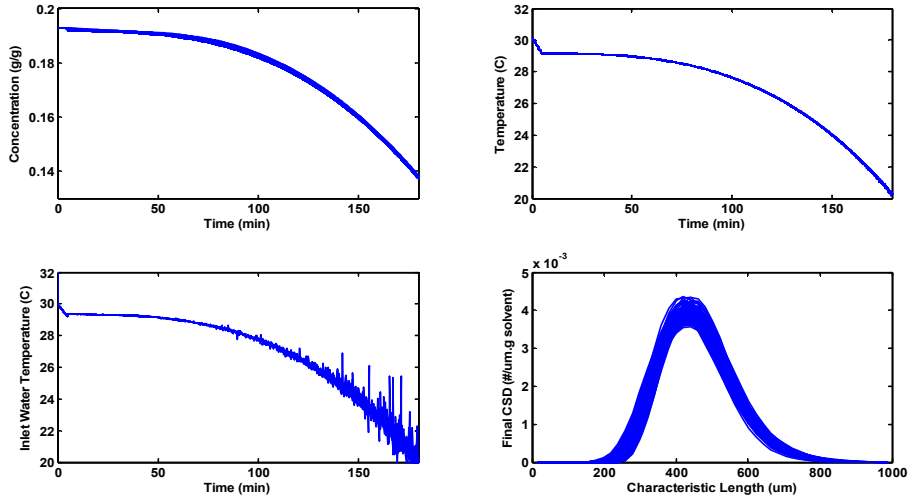

Figure-4. Closed loop simulation results for potassium dichromate concentration, temperature, inlet water temperature (manipulated variable) and final CSD obtained from the Monte Carlo simulation (in total there are 100 lines).

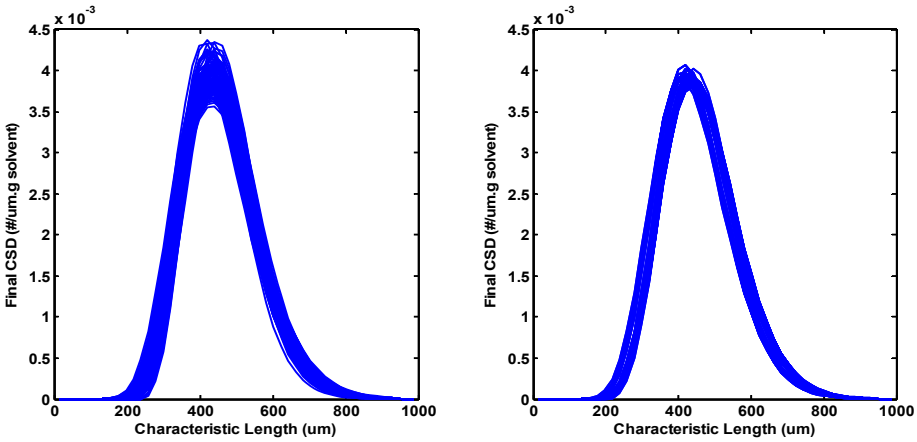

Figure-5. Comparison of CSD data based on different controllers: PI controller (left); MPC (right).

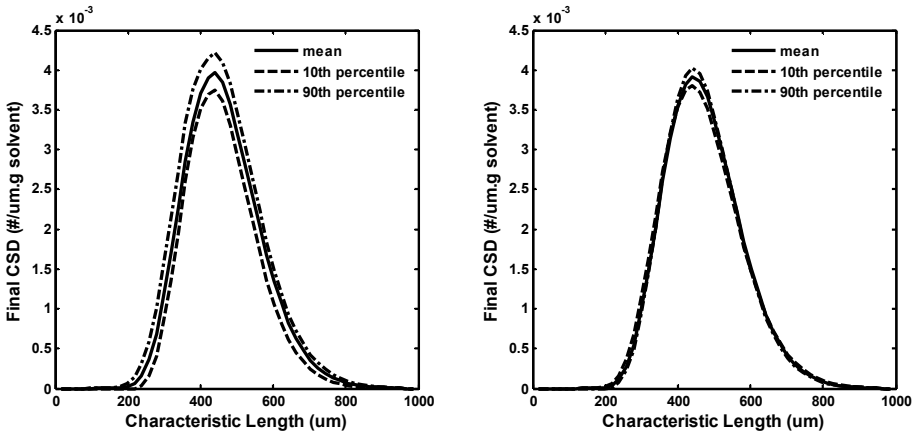

Figure-6. Representation of uncertainty using mean, 10th and 90th percentile values of the Monte Carlo simulations under different controllers: PI controller (left); MPC (right).

For the purpose of highlighting the acceptable range of desired target CSD, the target envelope for CSD is then assumed as $3.9x10^{-3} \pm 0.2x10^{-3}$ no. of particles/µm. g solvent (mean of CSD ± variance). Therefore the minimum acceptable CSD is $3.7x10^{-3}$ (lower variance) and maximum acceptable CSD is $4.1x10^{-3}$ (upper variance).

Table-4. Performance comparison between PI control, MPC and the desired target CSD.

CSD (#/µm. g solvent)	Target	Controllers	
		PI	MPC
Lower Variance	$3.7x10^{-3}$	$3.6x10^{-3}$	$3.8x10^{-3}$
Mean	$3.9x10^{-3}$	$3.9x10^{-3}$	$3.9x10^{-3}$
Upper Variance	$4.1x10^{-3}$	$4.2x10^{-3}$	$4.0x10^{-3}$

Table-4 shows the performance comparison between PI control and MPC where it can be clearly seen the CSD obtained by PI control is exceeding the target envelope for CSD. Meanwhile the CSD obtained by MPC in the range of target envelope for CSD indicating the effect of uncertainty has been greatly reduced and satisfy the acceptable range of target CSD. In addition, based on this performance, it is proven the MPC shows a robust controller compared to PI control in terms of counteract the effects of input uncertainties.

Finally, it is confirmed that the MPC controller used is capable to deal with uncertainties, indicating that a robust PAT system design has been successfully developed, and is thus ready to be implemented in step 6. However, so far the designed PAT system has been implemented only in a simulation and was shown to achieve the target crystal product. In order to have a practical application, the simulation results need to be supported by results from laboratory experiments. However, this is beyond the scope of this contribution but will be subject of future work.

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CONCLUSIONS

The methodology for performing uncertainty analysis of PAT systems of crystallization processes is successfully applied to the potassium dichromate crystallization process. The analysis is performed in the frame of the model-based design of a PAT system for closed-loop scenarios. In closed-loop using PI controller, the output uncertainty was found for the final CSD, which confirms the influence of input uncertainties on the model predictions. Subsequently the analysis for the closed-loop condition using MPC controller structure was carried out to test the reliability of the PAT system design and it was demonstrated that the PAT system using a MPC controller developed for the potassium dichromate crystallization is reliable and sufficiently robust to produce the desired CSD under a range of uncertainties.

In the future work, the uncertainty also present in the initial conditions, for example in the temperature, concentration and seed crystals. The presence of noise usually affecting the temperature and concentration profiles which significantly influences the CSD prediction. In addition the amount and size of seeds to be added to the crystallizer is determined from experimental data which contribute to some extent to the uncertainties. Therefore also, it could be interesting in the future to consider the properties of the temperature, concentration and seed crystals as an input uncertainty as well. As indicated earlier, implementation of the proposed PAT system in a real crystallization process could both be used to verify and confirm the methodology and the results obtained here.

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