
Abdul Samad, Noor Asma Fazli Bin; Meisler, Kresten Troelstrup; Sin, Gürkan; Gernaey, Krist; Gani, Rafiqul

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Noor Asma Fazli Abdul Samad, Kresten Troelstrup Meisler, Gürkan Sin, Krist V. Gernaey, Rafiqul Gani

Department of Chemical and Biochemical Engineering, Søltofts Plads, Building 229, Technical University of Denmark, DK-2800, Lyngby, Denmark, rag@kt.dtu.dk

Abstract
A generic framework for systematic design of a process monitoring and control system for crystallization processes has been developed in order to obtain the desired end-product properties notably the crystal size distribution (CSD). The design framework contains a generic crystallizer modelling tool-box, a tool for design of operational policies as well as a tool for design of process monitoring and control systems. Through this framework, it is possible for a wide range of crystallization processes to generate the necessary problem-system specific model, the necessary operational policy and a Process Analytical Technology (PAT) system design including implementation of monitoring tools and control strategies in order to produce a desired product with its corresponding target properties. Application of the framework is highlighted through a case study involving the system potassium dihydrogen phosphate (KDP), for which the targeted CSD is defined and achieved in one- and two-dimensional schemes.

Keywords: Crystallization, Generic crystallization modelling, Analytical CSD estimator, Response surface method, Design of process monitoring and control system.

1. Introduction
Crystallization processes have a wide range of applications as solid-liquid separation technique in the chemical, the pharmaceutical and the food industries, due to the fact that high quality crystalline products can be obtained. The specifications of the crystal product are usually given in terms of crystal size, size distribution, shape and purity. A problem, however, in many crystallization processes is how to obtain a uniform and reproducible crystal size distribution (CSD) [1,2]. To this end, supersaturation control is often applied to drive the process within the metastable zone in order to enhance the control of the CSD. Although this approach has been shown to produce high quality crystals, the set point operating policies for the controller are usually chosen arbitrarily or by trial-and-error [2]. Therefore a systematic procedure to generate operational policies that guarantee the matching of a targeted CSD would be very useful. For such a procedure to be generic, i.e., applicable to many chemical systems, it needs to be model-based, preferably linked to a modelling framework that can generate the needed models for a wide range of systems. Furthermore, for monitoring and control purposes, an appropriate Process Analytical Technology (PAT) system ensuring that the critical process variables are identified, monitored and/or controlled within the design limits needs to be integrated as well.
In this work, a generic and systematic framework for the design and use of a process monitoring and control system to achieve the desired CSD and crystal shape for a wide range of crystallization processes is presented. This framework contains a generic multi-dimensional modelling framework [2,3] and tools for design of operational policies and for design of PAT systems [4,5]. Furthermore, for designing the operational policies, the analytical CSD estimator proposed by Aamir et al. [1] has been extended to also cover two-dimensional problems. This estimator and a response surface method are employed to generate the operational policies needed to match the desired target CSD. The application of the systematic design framework is highlighted through a potassium dihydrogen phosphate (KDP) crystallization process case study where the objective is to obtain a desired one- and two-dimensional CSD as well as crystal shape.

2. Systematic design framework for process monitoring and control system

The architecture of the generic framework for systematic design of monitoring and control systems is illustrated in Fig. 1. There are 4 main steps through which the design (operational policy together with the monitoring/control system) 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-system specific model using the generic multi-dimensional modelling framework [2,3]. The third step is concerned with the design of operational policies for the crystallizer. The objective here is to generate operational policies that guarantee that a targeted CSD is achieved. Two methods have been implemented: an analytical CSD estimator based method and a response surface method (RSM). The generated operational policies provide the supersaturation set points that need to be maintained so that the targeted CSD can be achieved. The resulting problem-system specific models and the operational policies are then ready for use in model-based design of a process monitoring and control system (PAT system) [4,5]. If the proposed PAT system design is satisfactory with respect to the desired performance then it is selected as part of the final design proposal. The final design proposal thus contains the proposed design flowsheet with the necessary monitoring tools/techniques, the model equipment data obtained from the monitoring tools for process variables (such as temperature, concentration etc.) and the graphs in 3-D to illustrate the evolution of the CSD.

3. Application of the design framework: potassium dihydrogen phosphate (KDP) crystallization case study

Application of the framework is demonstrated for KDP crystallization (adopted from [6,7]) where the objective is to design a PAT system in order to achieve the one- and two-dimensional target CSD as well as the desired crystal shape.
3.1. Problem definition (Step 1)
The desired target for the one- and two-dimensional CSD (Fig. 2) is assumed as a univariate quadratic (mean characteristic length of 60 µm and standard deviation of 2.8 µm) and a bivariate quadratic distribution [6] (mean characteristic length of 60 µm with standard deviation of 2.8 µm and mean characteristic width of 27 µm with standard deviation of 1.34 µm), respectively. The crystal shapes used for the one- and two-dimensional case are cube-shaped and tetragonal prism-shaped, respectively.

![Figure 2. Target for one- (left) and two-dimensional (right) CSD](image)

3.2. Crystallization model development (Step 2)
The problem-system specific models for the one- and two-dimensional cases are then generated using the generic multi-dimensional modelling framework [2,3] by using similar conditions and assumptions as reported in the literature [6].

3.3. Design of operational policies (Step 3)
In this section, the operational policies for the one- and two-dimensional CSD are generated using the analytical CSD estimator method and the application of the RSM.

3.3.1. Analytical CSD estimator

![Figure 3. Initial seed for the one- (left) and two-dimensional (right) CSD](image)

The initial seed distributions for the one- and two-dimensional cases (Fig. 3) are assumed as univariate and bivariate quadratic distributions [6], respectively. A common mean characteristic length (19.5 µm) and standard deviation (0.97 µm) are used for the seeded operations. The total number of crystal particles used for both initial seeds is 736 crystal particles. The analytical CSD estimator (Table 1) for size dependent growth ($\gamma_s = \gamma_w = 0$; $p_s = p_w = 1$) is used for both the one and two-dimensional case.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Analytical Expressions</th>
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</thead>
<tbody>
<tr>
<td>Final CSD</td>
<td>$f_n = f_n e^{(1/2\sigma_0^2) - (1/2\sigma_1^2)}$</td>
</tr>
<tr>
<td>Final characteristic length and width</td>
<td>$L_n = (1 + \gamma_s L_0) e^{(1/2\sigma_0^2) - 1} / \gamma_s$; $L_w = (1 + \gamma_w L_0) e^{(1/2\sigma_1^2) - 1} / \gamma_w$</td>
</tr>
</tbody>
</table>
A model-based approach is then used to optimize the supersaturation set point and the total crystallization time for one- and two-dimensional cases in order to achieve the desired target CSD, respectively. The objective is to minimize the sum of squares of the relative errors between the desired target CSD and a predicted CSD obtained through the analytical CSD estimator. The following optimal operational policy for the one-dimensional case was obtained: the supersaturation set point is 0.03 g/g and total crystallization time is 80 seconds. The optimal operation policy was found the same for the two-dimensional case.

### 3.3.2. Optimization of KDP crystallization by RSM

The RSM using a central composite design (CCD) as sampling method was used for the one-dimensional case first. A total of 9 different operating conditions were evaluated, and the response surface for the one-dimensional case was then obtained (see Fig. 4). It shows that the relative error is the lowest for a supersaturation set point of 0.03 g/g and a total crystallization time of 80 seconds. Therefore the resulting optimal operational policy to achieve the desired one-dimensional CSD with the associated target properties, is as follows: supersaturation set point = 0.03 g/g and total crystallization time = 80 seconds. A similar procedure is repeated for the two-dimensional case and the operational policy obtained is identical to the one-dimensional case.

### 3.4. Design of process monitoring and control system (Step 4)

The design of a PAT system has been implemented in the ICAS-PAT software [5] and was applied to the one- and two-dimensional KDP crystallization. As a result of the PAT design, the concentration (see Fig. 5) is well maintained at the generated operational policy (set point trajectory) until the end of operation for both the one- and two-dimensional cases in the closed-loop simulation. The narrow seed distribution (see Fig. 6(a)) for the one-dimensional case has developed into a wider CSD at the end of the crystallization due to the size dependent growth effects (see Fig. 6(b)). The cube-shape seeds have grown to a mean characteristic length of 58.9 µm with a standard deviation of 2.79 µm. Similarly, the final CSD becomes wider for the two-dimensional case (Fig. 7). The final CSD obtained shows that the tetragonal prism-shape of the seeds has been growing to reach approximately 58.54 µm mean characteristic length and 26.55 µm mean characteristic width. Meanwhile the standard deviations obtained from the two-dimensional model are 2.79 µm (length) and 1.33 µm (width), respectively. Both the one- and the two-dimensional CSD obtained are in good agreement with the predefined target CSD. The total number of crystal particles of 736 remains at the end of the operation indicating no generation of new seeds due to secondary nucleation.

![Figure 4. Response surface for one-dimensional case](image)

Figure 4. Response surface for one-dimensional case

![Figure 5. KDP concentration profiles for (a) one-dimensional and (b) two-dimensional case](image)

Figure 5. KDP concentration profiles for (a) one-dimensional and (b) two-dimensional case
3.5. Final process monitoring and control system
The final design of the PAT system for one- and two-dimensional KDP crystallization processes is then obtained. According to this design, the concentration is monitored by ATR-FTIR and the temperature is monitored by a thermocouple. The inlet water temperature is manipulated by blending hot and cold water. Meanwhile the one- and two-dimensional CSD is also monitored by using FBRM.

![Figure 6](image_url) Evolution of one-dimensional CSD (a) initial seed view (b) final seed view

4. Conclusions
The potential of the systematic framework to produce the desired one- and two-dimensional CSD as well as crystal shape has been illustrated for a KDP crystallization process. The generation of operational policies using optimization involving an analytical CSD estimator and the response surface method has been highlighted. Applying the model-based optimization using the analytical CSD estimator provides an efficient and computationally effective way to produce the optimal operational policies compared to other approaches. The results of the CSD generated with the systematic design framework have shown good agreement with the published crystallization data, indicating thereby, the power and unique features of this systematic framework.

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