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Published in:
Chemical Engineering Research and Design

Link to article, DOI:
10.1016/j.cherd.2020.08.032

Publication date:
2020

Document Version
Peer reviewed version

Link back to DTU Orbit

Citation (APA):

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Comprehensive Evaluation of a Data Driven Control Strategy: Experimental Application to a Pharmaceutical Crystallization Process

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Abstract

In this contribution, a data-driven control approach was developed and applied experimentally to a pharmaceutical batch cooling crystallization process. In this approach, a radial basis functions (RBF) network model was trained in real-time with experimental data (time varied temperature and chord length distribution) with two different input data update strategies. The control objective was to optimize the cooling profile with the aid of trained RBF to achieve the desired crystal population profile throughout the process. The robustness of the proposed control strategy was tested with 10 comprehensive experiments in the presence of several disturbances (initial supersaturation, impeller speed, water composition and seed size). The presented control strategy was able to easily handle all the case scenarios. In 8 cases, the experimental crystal population profile followed successfully the reference with less than 10 % offset. In the remaining 2 cases, the offset was 17 % that was due to the absence of the supersaturation. The proposed RBF network-driven control is a promising strategy that is easy to implement, fully-automated and relies on relatively limited data for training. Therefore, the RBF control is expected to contribute to quick process development and control, especially when there is a lack of comprehensive process understanding and historical data especially in the pharmaceutical industry.

Keywords: Pharmaceutical crystallization, data driven control, radial basis functions,

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1. Introduction

Crystallization is a key unit in the production process of high-purity pharmaceuticals and fine chemicals. However, still a major bottleneck in the pharmaceutical manufacturing remains to be establishing control over this unit operation. Control strategies and actions are mainly challenged by nonlinear and stochastic dynamics of the crystallization process. In addition to this, in the absence of any online or inline measurements, the process outcome in terms of crystal properties is difficult to be related to process inputs under the influence of such dynamics [1] [2] [3]. Fortunately, significant advances in Process Analytical Technology (PAT) tools enable the monitoring of key solution- and crystal-state properties in real-time. This enhances the understanding of the dynamics of the crystallization process and helps to correlate the relationship between the operating inputs and the critical properties of the crystal product [4] [5] [6]. Besides, the information obtained through PAT tools facilitates markedly the application of different feedback control strategies, so that some degree of control over crystal size, polymorphic form and morphology is established [7] [8] [9] [10] [11] [12] [13]. Despite the substantial progress, the control of industrial crystallization processes is assumed to be still an outstanding issue. The reasoning behind might be related to the restrictive dichotomy of the developed control strategies that fall mainly into one of two categories; model-based and model-free control [3].

Model-based approaches are mainly based on the population balance models containing nucleation, growth, agglomeration, etc and solved simultaneously with mass and energy balance equations [8] [14] [15] [16]. In the model-based control, the effects of inputs and disturbances on the system output are predicted in real-time by process model simulations. An optimization algorithm is solved in real-time to determine the optimum solution to a manipulated variable (or control signal) with respect to the pre-defined performance criterion. Therefore, the fundamental requirement of a model-based controller is a process model that is adequate with respect to complexity, accuracy and solution time [17] [18]. Among
the population balance numerical solution technique, the vast majority of model-based control literature studies employed moment-based methods and their quadrature extensions [19, 20, 21]. These methods have the main advantage of computational efficiency, while they suffer from the accuracy of the full crystal size distribution (CSD) retrieved from calculated moments [22]. On the other hand, high fidelity discretization techniques such as high-resolution finite volume methods [23, 24, 14] or method of classes [25, 26] provide a detailed CSD and state estimations. However, they suffer from the computational burden for real-time optimization that requires some efficient implementation techniques to increase the speed of solution [27].

On the other hand, developed model-free control strategies are based on expert intuition and heuristics. Among them, supersaturation control (SSC) [6, 28, 29] and direct nucleation control (DNC) [6, 29, 30] have aroused significant interest and found numerous applications [3]. The key idea in the SSC technique is to assure a constant supersaturation by manipulating the supersaturation creating variables such as temperature or antisolvent feed rate. This requires the measurement of solute concentration in the crystallizer (e.g. using ATR-UV, ATR-FTIR [31, 32, 6]) and knowledge of solubility data corresponding to the state in the crystallizer (e.g. temperature or antisolvent concentration). The DNC technique grounds on keeping total crystal number (e.g. measured by Focused Beam Reflectance Measurement (FBRM) sensor or real-time microscopy-based image analysis [33]) constant throughout the crystallization operation by heating/cooling cycles or solvent/antisolvent cycles with in situ seed generation option. Model-free techniques are generally more straightforward for the applications, but still, the relationship between the operating variables and the crystal properties is heuristic in nature and generally indirect [3]. e.g. the degree of (constant) supersaturation has a direct influence on the nucleation or growth rate, which in return (indirectly) affects the CSD. A recent contribution to model-free control approaches aimed to produce a desired crystal average size by controlling crystal mass per count ratio called spatially-guided action trajectory endpoint control [34].

A third category that does not fit into the dichotomy of established crystallization control
strategies can be attributed to data-driven (based on process data) control approaches. Data-driven approaches have proven to be useful especially for complex processes that are troublesome and costly to develop a knowledge-driven model in a timely manner for the optimization and control of industrial processes. The artificial neural network (ANN) is one of the most outstanding data-driving modeling techniques. Because the complex non-linear relationship between input and output of a process can be well-approximated without prior knowledge of the process or independent of the physical meaning of the system [3, 35]. However, in the literature a very limited number of studies dealt with the data-driven control of the crystallization process. A list of these studied can be found in Table 1. In most of these studies, the ANN was treated as a predictive model employed in a model predictive controller (MPC) for setpoint tracking [17, 36, 37, 38, 39, 40] and demonstrated only in silico. The ANN models embedded in the MPC decreased the computational time required for solving the optimization algorithm (or problem) compared to the high fidelity population balance models. The ANN models in all of them were trained offline with the historical data from a high number of the batches and the performance of the control strategy was not studied in the presence of disturbances in the process. On the other hand, the ANN also facilitated the tuning of PID controller parameters [41, 42]. Optimum temperature profile with respect to specific process performance criteria was determined with the aid of ANN [43]. Apart from the ANN, principal component regression (PCR) [44] for supersaturation setpoint tracking, least-square regression for achieving target final crystal mass-count and batch time [3] and a linear time-variant state-space model with the aim of minimizing the number of fines and controlling the shape of CSD [45] were also used as data-driven models during the control of crystallization processes. Even though the idea of the neural network has been around since 1943, the number of the literature studies on the ANN applied to a variety of domains including the control have increased starting from 1990, when the problem of solving nonlinear function approximations and nonlinear classification was overcome by adopting the automated backpropagation learning algorithm and with a breakthrough in 2006 by adopting a layer-by-layer training strategy in tandem with an increase in processing.
speed [46]. Accordingly, the limited number of studies on the ANN-based control in the
crystallization can be also attributed to the grounds of i) nonlinearity challenge, ii) lack of
powerful computing, storage, communication and programming environments, and iii) lack
of data. However, these grounds have been overcome today by the foundation of the efficient
training algorithms, availability of more powerful computers and easy-to-use software, and
access to the crystallization system data through the PAT tools [46, 47]. To the best of
the authors’ knowledge, a fully-automated experimental implementation and comprehensive
assessment of the robustness under disturbances of a data-driven control strategy applied
to a crystallization process have not been reported in the literature before.

Therefore, in this work, a data-driven control strategy was presented and applied to a
pharmaceutical crystallization process. The proposed data-driven control strategy was based
on the radial basis functions network trained in real-time with limited experimental data.
A comprehensive evaluation of the proposed control approach was demonstrated through
fully automated laboratory-scale experiments in the presence of various sources of process
disturbances.
Table 1: Data-driven control literature review for the crystallization process.

<table>
<thead>
<tr>
<th>Type</th>
<th>Inputs*</th>
<th>Outputs*</th>
<th>Objective*</th>
<th>Disturbance</th>
<th>Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rohani et al., 1999 [17, 36]</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Auto-regressive exogenous (ARX) and ANN models were used as the process models in a non-linear MPC of continuous cooling crystallization of potassium chloride. The objective was to track the setpoints of three variables representing CSD, $\Delta T_f$, crystal purity, $\Delta T_s$, and production rate, $M_p$ ($w_f$ is fines dissolution rate, $T$ is crystallizer temperature and $w_{cla}$ is the clear liquor flow rate).</td>
<td>$w_f$, $T$, $w_{cla}$, $\Delta T_f$, $\Delta T_s$, $M_p$</td>
<td>Meet $\Delta T_f$, $\Delta T_s$, $M_p$</td>
<td>No</td>
<td>Simulation</td>
<td></td>
</tr>
<tr>
<td>Georgieva and Azevedo, 2006 [37, 38]</td>
<td></td>
<td></td>
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<tr>
<td>A feed forward neural network for a fed-batch sugar crystallization was used to track supersaturation setpoint by manipulating the feed flow rate in an MPC system. Additionally, a second ANN was used in a knowledge-based hybrid model (KBHM) used for the process simulation.</td>
<td>$F_{Feed}$, $S$</td>
<td>Meet $S_{Set}$</td>
<td>No</td>
<td>Simulation</td>
<td></td>
</tr>
<tr>
<td>ANN (in KBHM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Song et al., 2006 [41]</td>
<td></td>
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</tr>
<tr>
<td>A diagonal neural network (DRNN) was used to auto-adjust its weights to vary PID controller’s parameters depending on the influence of object’s parameter to the process output performance.</td>
<td>$k_P$, $k_I$, $k_D$</td>
<td>$T$ or $H_{Liq.}$</td>
<td>Meet $T_{Set}$ or $H_{Liq.,set}$</td>
<td>No</td>
<td>Simulation</td>
</tr>
<tr>
<td>Beyou et al., 2009 [42]</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>An instantaneous linearization of a neural network was utilized to automatically tune the parameters of the PID controller implemented to a C sugar cane crystallization process. The aim was to track the conductivity setpoint.</td>
<td>$F_{Feed}$</td>
<td>Conductivity</td>
<td>Meet $R_{Set}$</td>
<td>No</td>
<td>Simulation</td>
</tr>
<tr>
<td>Zhang et al., 2009 [44]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>A batch to batch iterative learning control method, which was based on using PCR models updated batch-wise, was developed to track the supersaturation setpoint during the batch crystallization of potash alum in the presence of disturbance on the overall heat transfer coefficient, $U$.</td>
<td>$T_{in}$</td>
<td>Meet $S_{Set}$</td>
<td>$U$</td>
<td>Simulation</td>
<td></td>
</tr>
<tr>
<td>Damour et al., 2010 [39]</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>A nonlinear model predictive controller was used with an ANN predictor trained with industrial historical data as internal model with the purpose of tracking the mass of crystals in the solution, $m_{Crystals}$.</td>
<td>$F_{Feed}$</td>
<td>$m_{Crystals}$</td>
<td>Meet $m_{Crystals}$</td>
<td>No</td>
<td>Simulation</td>
</tr>
<tr>
<td>Suárez et al., 2011 [40]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent Neural Network (RNN) trained with industrial historical data was used as predictive model for four control loops in a sugar crystallization process.</td>
<td>$F_{Liquor}$</td>
<td>$V_{Mannesgen}$</td>
<td>Meet $V_{Mannesgen}$</td>
<td>No</td>
<td>Simulation</td>
</tr>
<tr>
<td>RNN-MPC 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RNN-MPC 2</td>
<td></td>
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<tr>
<td>RNN-MPC 3</td>
<td></td>
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<tr>
<td>RNN-MPC 4</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 1 (Continue): Data-driven control literature review for crystallization process.

<table>
<thead>
<tr>
<th>Type</th>
<th>Inputs</th>
<th>Outputs</th>
<th>Objective</th>
<th>Dist.</th>
<th>Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Griffin et al., 2016 [3]</td>
<td>Multiple experimental data sets from several batch crystallization of the mineral darapskite were used to train a locally weighted, constrained least-square regression model. Trained model was then used to optimum supersaturation setpoint policies in order to achieve a specific target of a mass-count and a batch time.</td>
<td>Least-square regression</td>
<td>S</td>
<td>Chord and m</td>
<td>Crystal</td>
</tr>
<tr>
<td>Garg and Mhaskar, 2018 [45]</td>
<td>A linear time-invariant (LTI) state-space model was employed in a linear MPC with the objective of a) minimizing the volume of fine crystals, $V_{\text{Fines}}$, and b) controlling shape of product CSD in the batch crystallization of potassium sulphate.</td>
<td>LTI</td>
<td>T, C</td>
<td>CSD</td>
<td>Min. $V_{\text{Fines}}$ and CSD</td>
</tr>
<tr>
<td>Montes et al., 2018-2019 [48, 49]</td>
<td>In our previous work RBF driven control is developed and assessed comprehensively in silico in the presence of disturbances such as $k_b$, $k_g$, seed, solvent, water concentration.</td>
<td>RBF</td>
<td>t, T</td>
<td>$L_{\text{mean}}$</td>
<td>Track $L_{\text{Mean}}$ profile</td>
</tr>
</tbody>
</table>

This study

A data driven control strategy based on RBF network was comprehensively tested by means of fully-automated laboratory experiments in the presence of disturbances such as initial supersaturation, stirrer speed, water concentration and seed size.

<table>
<thead>
<tr>
<th>RBF</th>
<th>t, T</th>
<th>Sqrt Wt. CLD</th>
<th>Track SqrtWt. count profile</th>
<th>Yes</th>
<th>Experiment</th>
</tr>
</thead>
</table>

$\dot{w}_{\text{f}}$ is fines dissolution rate, $T$ is crystalizer temperature, $\dot{w}_{\text{cla}}$ is the clear liquor flow rate, $\Delta T_f$ is a variable representing CSD, $\Delta T_s$ is a variable representing crystal purity, $M_p$ is production rate, $F_{\text{Feed}}$ is feed flow rate, $S$ is supersaturation, $T_m$ is temperature of massecuite, $\text{Pur}_{\text{Sol}}$ is purity of solution, $v_{\text{Crys}}$ is volume fraction of crystals, $\text{AM}$ is average (in mass) crystal size, $N_{\text{Chord}}$ is chord count, $t_{\text{Batch}}$ is time batch, $T$ is temperature, $C$ is concentration, $V_{\text{Fines}}$ is volume of fine crystals, $t$ is time, $L_{\text{Mean}}$ is mean crystal size.

2. Materials and Methods

2.1. Radial Basis Functions Networks

Radial basis functions (RBF), $\phi(x)$ shown in Eq. 1 are regarded as a special class of function. Their distinctive feature is that the function’s response is symmetric and increases or decreases monotonically according to the distance of a data point, $x$ from a central point, $\mu_j$ [50, 51, 52]:

$$\phi_j(x) = \phi(||x - \mu_j||)$$  \hspace{1cm} (1)
where $\| \cdot \|$ is a vector norm and usually an Euclidean one. Possible choices of the radial basis functions, $\phi()$ are the Gaussian, thin plate spline, multi-quadratic, inverse multi-quadratic and biharmonic shown in Eq. 2 - 6 [50, 51, 52, 53, 54]:

$$
\phi(r) = \exp\left(-\frac{r^2}{2\sigma^2}\right) \quad \text{(Gaussian)} \quad (2)
$$

$$
\phi(r) = \frac{r}{\sigma^2} \log\left(\frac{r}{\sigma}\right) \quad \text{(Thin plate spline)} \quad (3)
$$

$$
\phi(r) = \sqrt{r^2 + \sigma^2} \quad \text{(Multi-quadratic)} \quad (4)
$$

$$
\phi(r) = \frac{1}{\sqrt{r^2 + \sigma^2}} \quad \text{(Inverse multi-quadratic)} \quad (5)
$$

$$
\phi(r) = r \quad \text{(Biharmonic)} \quad (6)
$$

where $\sigma$ is a scale or width parameter that controls the impact radius of each basis function and the choice of $\sigma = 1$ was used in the literature for the function approximations [55, 56]. Gaussian-like RBF monotonically decreases with the distance from a center point and their high response only in a neighborhood around the center makes them local. Besides, their finite response makes them biologically plausible. Oppositely, multiquadratic-type RBF as shown in Eq. 4 responses globally [50]. Traditionally, RBF networks have been related to radial functions in a single-hidden-layer network in addition to the input and output layer as shown in Fig. 1. Each unit in the hidden layer represents a single radial basis function, while each output unit, $\tilde{y}(x)$ is a weighted summation of the hidden units as represented in Eq. 7. The weighed connections are only the ones between the hidden layer and the output layer. This eases the training of the network and rationalizes the choice of
RBF compared to other nonlinear approximation models [50, 52, 57, 58, 59].

\[ \hat{y}(x) = \sum_{j=1}^{m} w_j \phi_j(||x - \mu_j||) + \theta(x) \]  

(7)

where \( x \) is the vector of input variables, \( \hat{y}(x) \) is the RBF approximation of the real function or response of \( y(x) \), \( m \) is the number of basis functions in the hidden layer and \( \theta \) is an optional biased term that can be incorporated as a constant polynomial term [60].

![Radial basis function network](image)

Figure 1: Radial basis function network: Each of \( n \) members of the input vector \( x \) feeds forward to \( m \) basis functions. The outputs of the basis functions are linearly combined with the weights into the network output \( y(x) \).

The unknown coefficients, \( w_j \) can be found by minimizing the residual of the sum of the squares of the deviations between the RBF approximations and the real responses expressed as in Eq. 8 [59]:

\[ R = \sum_{i=1}^{m} \left( y(x_i) - \hat{y}(x_i) \right)^2 \]  

(8)

In this work, the RBF toolbox developed by Jēkabsons (2009) [61] was used and the work presented by Jin et al. (2002) [60] was followed. The performance of the trained RBF network model's predictions was quantified by means of calculating mean absolute percentage error, MAPE as in Eq. 9 [62]:

\[ MAPE = \frac{1}{n} \sum_{i=1}^{n} \frac{|Y_i - \hat{Y}_i|}{Y_i} \cdot 100 \]  

(9)
where $n$ is number of data points, $Y_i$ is the experimental value and $\hat{Y}_i$ is the RBF-predicted value.

2.2. RBF Driven Control Strategy

The schematic diagram of the set up for the RBF driven crystallization control experiments can be seen in Fig. 2. The idea behind the RBF driven control strategy was to use RBF network trained in real-time with the online and a reference batch data (or a golden batch data) to optimize the control input of the jacket temperature setpoint. More information about the reference batch data will be given in the next section. Optimization of the jacket temperature setpoint was performed for a future time horizon with respect to a cost function under imposed constraints. The objective of the cost function was to minimize the differences between a reference state of the system and the RBF-predicted state of the system for the same future time horizon.

![Schematic representation of the set-up for the RBF driven crystallization control experiments.](image)

Herein, time varied temperature measured by a Pt100 sensor and chord length distribution (CLD) measured by a FBRM sensor (as a footprint of CSD) were regarded as two measured online data. They were used for training of the RBF network. The reference state
of the system was characterized by a CLD profile obtained from a good batch (or preferably from a golden batch) and represented as $CLD_{Ref}$:

$$CLD_{Ref} = \sum_{i=b_0}^{b_f} N_{L_i} \cdot (L_i)^c$$

(10)

where the range $b_0 - b_f$ represents the chord length range of interest, and the exponent $c$ is the weighting factor that can have the values of -1, 1, 2 or 3 for inverse, length, square or cubic weights, respectively similar to the channel weighting types for the statistic in iC FBRM software [63]. The practical implementation and the concept of the RBF driven control approach are described in this section and the details of the experimental conditions and procedures are given in the next section. After the crystallization experiment was initiated, during the first 90 minutes the process followed a pre-defined temperature trajectory. In the meantime, the temperature in the crystallizer and CLD data were recorded with a sampling frequency, 10 seconds in this case. Afterward, the RBF control was activated. Time varied temperature as input and $CLD_{Ref}$ as output were used to train the RBF network. Two different strategies were employed for the structure of the training data:

- **Growing Data Strategy (GDS):** Only online data collected during the experiment was used for the training of RBF. The size of the training data increased at each RBF training interval as more data was collected during the experiments.

- **Updated Data Strategy (UDS):** A reference (or a golden) batch data was used and this data was partially replaced at each RBF training interval with the collected online experimental data during the experiment.

The advantage of GDS is the requirement of only online experimental data. So, it can be used also in the early stages of the process development, when there is no historical data (or a reference data) available. However, at the beginning phase of the RBF control the experimental data is limited and this reduces the prediction performance of the model. In UDS the reference data (or a golden batch data) is partially updated with the online experimental data so that the current dynamics of the system are also taken into account

11
while training data is still rich. In that sense, if there is a disturbance in the process and this
disturbance impacts the process ($CLD_{Ref}$ in this case), it is considered. On the other hand,
using only a golden batch data as training data lacks information about the current dynamics
of the system, which becomes more prominent especially in the presence of disturbances.
During the experiments, we employed both GDS and UDS as follows:

- If the current system state (CLD state), which was determined based on the latest
  measurements in the experiments, was above the reference CLD state corresponding
to the same time point, the RBF was trained based on the GDS.

- If the current CLD state was equal or below the reference CLD state ($CLD_{Ref}$), the
  RBF was trained with only UDS.

This strategy can be rationalized as follows: When the current CLD state is above the
reference state ($CLF_{Ref}$), heating can easily eliminate the offset. The RBF network, even
it is trained with the limited data, is still able to take the decision of “heating” and drives
the system to the reference profile. However, if the current CLD state in the crystallizer
is below the reference CLD state, cooling will not simply bring the current CLD state up
to the reference state. Because various complicated mechanisms play a role during the
crystallization of APIs. For instance, often the crystal growth is slow and differs for each
API compound. Accordingly, when the system is cooled down, the crystal size will not
increase (crystal growth) as quickly as they decrease (crystal dissolution) upon heating up
at the same rate. When this information is not available through data to the RBF network,
RBF might increase the cooling rate to achieve the reference state, when the current state
is below the reference state. However, since cooling will not eliminate the offset in every
case, the RBF might tend to cool the system further. When the system is sub-cooled, after
a degree of sub-cooling undesired spontaneous nucleation can occur. In that sense, UDS is
more reliable, since it is enriched with data. The trained RBF model was then facilitated
to optimize the temperature set-point to be sent to the thermoregulator as a control signal
with respect to a cost function, $J$ that was formulated as follows in Eq. (11):

$$
\begin{align*}
\min J &= \left\{ \sum_{i=1}^{P} \left[ \frac{CLD_{Ref}(k+i) - CLD_{RBF}(k+i)}{CLD_{Ref}(k+i)} \right]^2 \right\} \\
\text{subject to} & \quad R_{\text{min}}(k) \leq \frac{dT(k)}{dt} \leq R_{\text{max}}(k) \\
& \quad T_{\text{min}}(k) \leq T(k) \leq T_{\text{max}}(k)
\end{align*}
$$

where $CLD_{Ref}$ and $CLD_{RBF}$ are the reference and RBF predicted CLD profile, $R$ is the heating/cooling rate and $T$ is temperature. The optimization problem in Eq. (11) was solved using `fmincon` function in MATLAB R2018b with respect to imposed constraints of $R_{\text{min}}$ is -0.5 °C/min, $R_{\text{max}}$ is 0.5 °C/min, $T_{\text{min}}$ is 5 °C and $T_{\text{max}}$ is 35 °C. The solution of the optimization problem gave the temperature setpoints, $T_{\text{set}}$, which were then sent to the thermoregulator as the control signals. The prediction horizon, $P$ for $T_{\text{set}}$ was defined as 30 minutes, which corresponds to 180 data points, while the control horizon was the first 5 minutes corresponding to 30 data points. After implementing the control actions of the first 5 minutes (30 data points), the RBF network was re-trained with the data set enlarged or updated with these new 30 data points and the optimization was re-performed. This procedure was repeated until the end time of the crystallization process. The internal PID controller in the thermoregulator regulated the cooling liquid temperature, $T_{\text{Internal}}$ in order to minimize the differences between $T_{\text{Set}}$ and crystallizer temperature, $T_{\text{Process}}$. In general process control practice, controllers are tuned with respect to an optimized closed-loop response, by assessing some integral error criterion such as integral of the absolute error (IAE), integral of the squared error (ISE) or integral of the time-weighted absolute error (ITAE) [64]. In this work, we also calculated IAE for the purpose of evaluating the performance of the internal PID controller of the thermoregulator using the following Eq. (12):

$$
IAE = \int_{0}^{\infty} |e(t)| \, dt
$$

where $e(t)$ is the error and calculated as the difference between the setpoint ($CLD_{Ref}$)
and the measurement \((CLD_{Exp.})\). On the other hand, the total cost of the change of actuator can be computed by means of a correlation to the total variation, \(TV\) using the following Eq. \(13\):

\[
TV = \sum_{i=1}^{n} | u_{i+1} - u_i |
\]  

(13)

where \(u\) is the manipulated variable (temperature) and the subscripts \(i\) and \(i+1\) represent the consecutive sampling time.

During the experiments, the temperature was measured by the temperature sensor, and the data was acquired, monitored and controlled via a graphical programming software written in LabVIEW, National Instruments. The serial communication transmission of data between the desktop computer (where MATLAB R2018b was used to train the RBF model and estimate the temperature setpoints) and the Huber thermoregulator was established through an RS232 port. The CLD measurements by FBRM, which were connected via USB to the same desktop computer, were monitored using iC FBRM software during the experiments. To access and process the FBRM data in real-time, we employed the MATLAB OPC toolbox that enabled the connection to iC OPC UA Client supplied by Mettler Toledo.

2.3. Reference batch data

The proposed RBF driven control strategy requires a reference batch (or a golden batch) data in addition to the online experiment data. The reference batch is an optimum or a golden crystallization batch that delivered a desired a solid-state attribute such a particle size distribution or chord count profile, so-called reference crystal size profile, \(CLD_{Ref}\). During all the experiments with different disturbance scenarios, the proposed control strategy, and corresponding control actions should guarantee that the reference crystal size profile is being caught and followed throughout the operation. If an established and running crystallization process already exists, a reference batch data can be easily retrieved from historical data. When this is not possible, how to obtain a reference batch data is a fundamental question and challenge at the same time. However, we can propose several ways to create a reference batch
data. To illustrate, a validated mechanistic model of a crystallization process can be used to optimize the operation profile that can be used as golden batch data. Besides, laboratory-scale experiments can be designed and performed by implementing supersaturation control or bringing process expertise with known conventional and successful operation profiles.

2.4. Experimental Procedure

2.4.1. Materials

Ibuprofen (CAS No: 15687-27-1) and ethanol 99.9 % were bought from Molekula GmbH and Univar A\S, respectively.

2.4.2. Apparatus

The crystallization experiments were performed in a 500 mL laboratory-scale crystallizer from Radleys (Reacto-Ready System) equipped with a condenser, a cooling jacket and a PTFE turbine impeller. The impeller speed was manipulated with a Hei-Torque 200 overhead stirrer. Temperature was measured with a Pt100 temperature sensor. Huber Unistat Tango was used as the thermoregulator. Chord length distribution based on Focused Beam Reflectance Measurement technique was measured with ParticleTrack G400 from Mettler Toledo. Produced seed crystals were dried over night at 40 °C in a VACUTHERM vacuum oven from Thermo Fisher Scientific. Crystal size measurements of the seeds based on image analysis were performed using Particle Analyzer (oCelloScope) equipment applying Standard Segmentation Algorithm, which was provided by the company ParticleTech ApS in Farum, Denmark. The Particle Analyzer contains a digital camera, an illumination unit and a lens that enables the rapid and high throughput generation of a sequence of 6.25°-tilted images along the horizontal plane, so that an image Z-stack (the best-focus image) is formed. Following, the best-focus image is processed based using the advanced segmentation and feature extraction algorithms developed by ParticleTech ApS. As a result, detailed 3D information of each identified particles down to 0.5 µm in size is obtained.
2.4.3. Seed preparation

Two cooling crystallization batches were performed to produce ibuprofen seeds. In the first batch, 445.0 g of the bought product was dissolved in 500 mL ethanol, which corresponds to the saturation concentration at 25 °C. The complete dissolution of ibuprofen was guaranteed by heating up the suspension until 30 °C and keeping the solution at this temperature for a half hour. Afterward, the solution was cooled down to 5 °C following two linear temperature profiles. Firstly, the solution was cooled down with a 0.6 °C/min cooling rate between 30 - 18 °C. It was followed by further cooling with 0.33 °C/min cooling rate between 18 - 5 °C. Following, the suspension was filtered under vacuum to separate the solid crystals from the solution and washed two times. To dry the crystals completely, they were kept in a vacuum oven for overnight. Finally, dry crystals were sieved using the sieve fractions of 425, 300, 180, 90, 45 μm. The amount of obtained seed material was the highest between 45–90 μm and 90–180 μm. These two fractions were used and named fraction A and C, respectively. The second batch with 200 mL ethanol volume was also prepared following a similar procedure. However, faster cooling rates were applied with the purpose of obtaining smaller crystals. Therefore, 0.8 °C/min and 0.65 °C/min cooling rates were applied for the same temperature ranges, respectively. In this batch, obtained sieve fraction of 63–125 μm, named fraction B, was used.

2.4.4. Reference batch data

To obtain a reference batch data, a controlled cooling profile, an inverse exponential decay was applied. Because this profile tends to minimize the nucleation in a seeded batch crystallization due to the creation of lower supersaturation compared to linear or natural profiles [67]. The rest of the operation parameters were selected by consulting to the published literature and the process experts so that the seed growth dominates and nucleation is minimized. Therefore, the conditions were selected as follows; i) a controlled cooling profile (an inverse exponential decay) for about 5.5 h, ii) initial supersaturation of 1.05, since ibuprofen crystallization from ethanol has a very narrow meta-stable zone [68, 69, 70], iii) seed mass of 2.5 % and iv) the smallest seed size obtained from seed sieving, since as the
seed size decreases, the surface area available for the growth of the seed crystals increases compared to the larger crystals of the same mass. Thus, the supersaturation in the solution is consumed more quickly by the growth of the seed crystals dominating over the formation of new secondary nuclei [71]. Conditions of the reference batch data (GBE) are listed in Table 2.

2.4.5. Design of crystallization experiments

Initial supersaturation ($S_0$), impeller speed ($N_{\text{Impeller}}$), water content in ethanol solvent and seed size were considered as the sources of disturbances in the crystallization control experiments. The disturbance were selected in a way to mimic industrial scenarios such as i) initial supersaturation as unmeasured disturbance, ii) impeller speed affecting the secondary nucleation kinetics to mimic the disturbances in the nucleation dynamics due to the unknown impurities or system effects, iii) water content as a disturbance coming from the upstream and iv) different seed distributions due to batch-to-batch variations [72, 73]. Using a fractional factorial design approach with two center points, 10 experiments were designed and can be seen in Table 2.

The total solvent volume in all crystallization experiments was 200 mL. Firstly, ibuprofen amount corresponding to the specified initial supersaturation in Table 2 at 30 °C was weighed and mixed with the solvent. The suspension was heated up to 35 °C and kept at this temperature for a half hour to assure complete dissolution. The solubility of ibuprofen in ethanol at 30 °C is 1.36 kg/kg. Before the experiments started, the solution was cooled down to 30 °C. After approximately 3.03 g of ibuprofen seed was added, the solution was kept at 30 °C for 10 min. with the purpose of aging. Afterward, the experiment was initiated. The crystal size distribution of the seed material based on a microscopy-based image analysis method and an example of microscopy images of the seed material can be seen in Fig. 3. To obtain the size distribution, between 3500 - 6000 seed particles were detected and processed on the several images taken. A list of the measured mean feret diameter of all the detected particles was given by the image analysis algorithm. Following, a probability distribution of the detected crystals was calculated assuming a constant crystals size class (bin width)
of 5 µm. Different seed fractions were required to be used as different disturbances in the crystallization control experiments. In the control experiments, during the first 90 minutes a predefined temperature profile was applied. This profile followed an equal-time cooling and heating trajectories. The purpose was to enrich collected data in terms of not only cooling but also heating effects on the \( CLD_{Ref} \). At the end of 90 minutes, the RBF control was activated and the RBF control strategy took over the temperature setpoint determination as mentioned in Section 2.2.

<table>
<thead>
<tr>
<th>DoE No.</th>
<th>Pattern</th>
<th>( S_0 ) [-]</th>
<th>( N_{Impeller} ) [rpm]</th>
<th>Water [%v/v]</th>
<th>Seed fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBE</td>
<td></td>
<td>1.05</td>
<td>400</td>
<td>0.0</td>
<td>A</td>
</tr>
<tr>
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<td>- - - -</td>
<td>1.00</td>
<td>400</td>
<td>0.0</td>
<td>A</td>
</tr>
<tr>
<td>02</td>
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<td>1.10</td>
<td>550</td>
<td>0.0</td>
<td>A</td>
</tr>
<tr>
<td>03</td>
<td>+ + + +</td>
<td>1.10</td>
<td>550</td>
<td>5.0</td>
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<td>04</td>
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<td>1.00</td>
<td>550</td>
<td>5.0</td>
<td>A</td>
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<tr>
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<tr>
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<td>2.5</td>
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</tr>
<tr>
<td>08</td>
<td>0 0 0 0</td>
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<td>1.00</td>
<td>550</td>
<td>0.0</td>
<td>C</td>
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</tbody>
</table>
3. Results and Discussion

3.1. Reference batch experiment

In this study, a controlled cooling profile as shown in Fig. 4 was utilized to obtain a reference batch data. The cooling profile was assured by sending temperature setpoint, $T_{Set}$, to the thermoregulator. The internal PID controller of the thermoregulator manipulated the internal coolant temperature so that the difference between the setpoint and process temperature was minimized. From Fig. 4 it can be seen clearly that the internal PID controller in the thermoregulator was able to control the temperature in the crystallizer very well. Process temperature, $T_{Process}$ followed very well the temperature setpoint. Corresponding counts of chord length trajectories can be seen in Fig. 5.
Figure 4: Controlled cooling profile was followed during the reference batch experiment. $T_{\text{Process}}$ is the temperature inside the crystallizer, $T_{\text{Set}}$ is the temperature setpoint sent to thermoregulator and $T_{\text{Internal}}$ is the temperature of the cooling liquid in the thermoregulator.

The number of crystal particles with different sizes can be correlated and characterized by the counts of chord lengths in different channels of FBRM statistics. However, the choice of threshold for the separation of fine and coarse chord length is somehow random and is subjected to arbitrary judgment [74]. In the literature, fine particles were associated with the different channels of chord length such as between 1 - 10 $\mu$m [75], 1 - 20 $\mu$m [76] or 1 - 23 $\mu$m [77], while remaining channels of chord length were regarded as medium and/or coarse particles. In this study, we divided the chord length channels into three classes as 1 - 10 $\mu$m, 10 - 500 $\mu$m and 500 - 1000 $\mu$m. The graph at the top in Fig. 5 shows the total chord counts in the defined channel ranges of the chord length. The sum of the chord counts between 10 - 500 $\mu$m followed very similar profile to the total chord count in complete range (1 - 1000 $\mu$m) that tended to differentiate towards the latest stage in the experiment (after 200 min.). This differentiation was due to the increasing number of crystals in the fine length classes (1 - 10 $\mu$m), which can be attributed to the secondary nucleation. Crystals grown above 500 $\mu$m were not detected in the crystallizer during experiments by the FBRM probe. The graph at the bottom in Fig. 5 shows sum of square-weighted (chord-length-weighted) chord counts for different chord channels calculated using the following Eq. (14) without normalization:

$$\text{Sum of square-weighted counts} = \sum_{i=N_0}^{N_f} N_{L_i} \cdot (L_i)^2$$

(14)
where $N_0$ and $N_f$ are the initial and final channels of the chord length range, $N_{L_i}$ is the measured chord count in the corresponding to the chord channel of $L_i$.

Figure 5: Chord count profiles measured by the FBRM probe during the reference batch experiment: Total chord count of different chord length classes (top) and sum of square weighted chord counts of different chord length classes (bottom).

Square weighted function has been commonly used to emphasize coarse crystals, since it is not sensitive to fine crystals [74, 78]. This can be also observed in Fig. 5 where the sum of square-weighted counts between 1 - 10 $\mu$m showed no sensitivity or change during the crystallization process. On the other hand, the sum of square-weighted counts between 10 - 500 $\mu$m increased continuously. Therefore, the profile of the sum of square-weighted counts between 10 - 500 $\mu$m was decided as a reference trajectory, $CLD_{Ref}$ (Eq. 15) that was desired to be followed during the RBF driven control experiments under the process.
disturbances.

\[ CLD_{Ref} = \sum_{i=10}^{500} N_{Li} \cdot (L_i)^2 \]  \hspace{1cm} (15)

3.2. RBF driven control experiments under disturbances

The purpose of the design of experiments in Table 2 was to test and demonstrate the robustness of the presented RBF driven control approach with respect to various disturbance scenarios. Accordingly, the same experimental procedure was followed for each experimental design (DoE No. 1 - 10 in Table 2) and only listed known disturbances were introduced to the system. The comparison between open-loop and closed-loop control of ibuprofen crystallization was performed in our previous study both via model simulations and experimentally [49].

Firstly, the performance of RBF predictions with respect to utilized basis functions shown previously in Eq. 2 - 6 was tested by means of mean absolute percentage error, MAPE (Eq. 9). To this end, after the optimized temperature setpoints were predicted for a future horizon, the freshly trained RBF model was then used to predict the corresponding chord count profile \( \hat{CLD}_{RBF} \) for each basis function and used in the MAPE calculations together with the experimental data, \( CLD_{Exp} \). In an experiment, after the RBF driven control was activated, the RBF network model was re-trained total approximately 44 times until the end of a crystallization experiment. The comparison of the calculated MAPE for the performance evaluation of different basis functions can be found in Supplementary Material. The best performance was observed in biharmonic, multi quadratic and thin plate spline basis functions, respectively. In this study, the biharmonic function was employed as the radial basis function, which is the simplest and resulted in the best process input-output approximation compared to other basis functions. Moreover, the performance of the continuously trained model based on biharmonic RBF was quantified for all the experiments (DoE 01-10) also by means of MAPE and can be seen in Fig. 6.
Figure 6: Mean absolute percentage error calculated for the performance evaluation of the RBF model predictions during the experiments.

At the beginning of each experiment, the calculated error between the RBF predicted and experimental CLD profile was higher and this error tended to decrease below 5% as the experiment continued. As the experiments continued, the RBF network was constantly retrained with the increasing amount of experimental data, which was rich in terms of current dynamics and that’s why the performance of the RBF predictions tends to perfection.

Fig. 7 shows $CLD_{Exp}$ and temperature trajectory during the RBF driven control experiment, numbered as DoE 09 in Table 2. In this experiment, the positive disturbances on initial supersaturation and water content of the ethanol and negative disturbances on the impeller speed and seed size were given. When the RBF driven control took the control of the crystallization operation (or deciding temperature) at 90 minutes, $CLD_{Exp}$ profile in the experiment was below the $CLD_{Ref}$. The RBF driven control took actions towards cooling the system until approximately $CLD_{Ref}$ profile was being caught. Afterward, it continued to cool down the system with a different rate ($\Delta T/\Delta t$) corresponding to a slower cooling profile. It can be clearly seen that the control strategy smoothly drove the system (measured $CLD_{Exp}$ profile) along with the reference chord count profile. Chord count profiles of all the RBF driven control experiments are plotted in Fig. 8. In the experiments during the initial open-loop cooling phase (first 45 minutes), the disturbances resulted in majorly a higher square weighted chord count profile of the 10-500 µm range ($CLD_{Exp}$) than the reference profile ($CLD_{Ref}$) except for the experiments DoE 01 and DoE 10. However, at
the end of the initial open-loop heating phase (between 45-90 minutes) following the cooling phase (or when the RBF control was activated), $CLD_{Exp}$ in all the experiments was lower than the $CLD_{Ref}$. Herein, the RBF control switched immediately from the heating mode to the cooling in order to increase the $CLD_{Exp}$ and the system was being cooled down. In some cases such as in DoE 03 and DoE 07, upon cooling the $CLD_{Exp}$ became higher than the $CLD_{Ref}$. In such circumstances, the RBF control switched again to the heating shortly to decrease the $CLD_{Exp}$ and after continued to cool down the system. It can be clearly seen that the RBF control was able to take the right actions (without overcooling triggering the spontaneous nucleation) to achieve the reference profile. Overall, the proposed control strategy was able to handle all disturbance scenarios. Less than 10 % deviation from the $CLD_{Ref}$ profile was achieved not only at the end of the crystallization experiment, but also during the last approximately 3 hours in 8 out of 10 scenarios. In the remaining 2 out of 10 experiments (DoE 01 and DoE 10), approximately 17 % deviation from the $CLD_{Ref}$ profile was obtained. In both experiments, a negative disturbance was applied to the initial supersaturation, so there was no supersaturation at the beginning of the experiment. This means essentially there was no driving force available or very low during the experiment. This might be the reason why the experimental chord count profile was lower than the reference chord count profile. Never the less, $CLD_{Ref}$ profile was being smoothly followed with an offset. In such situations, one way to deal with might be that the system can be sub-cooled so that nucleation is promoted. However, this method can have two major shortcomings: i) it might not be economic to sub-cool and heat again especially for large scale systems e.g. in the industry, ii) nucleated crystals also consume the supersaturation, so the growth can be still hindered due to the low supersaturation available.
On the other hand, in all experiments, the final temperature was above the final temperature of the reference batch. But still $CLD_{Ref}$ profile was being followed by the control strategy. The final temperature offset might bring the concern of percentage yield loss in comparison with the reference experiment (GBE). The percentage yield loss can be calculated based on the Eq. [16]

$$\text{Percentage Yield [\%]} = \frac{\text{Actual yield}}{\text{Theoretical yield}} \times 100 = \frac{C_0 - C_{f,\text{Exp}}}{C_0 - C_{Sat,T_f}} \quad (16)$$

where $C_0$ is the initial solute concentration, $C_f$ is the final solute concentration in the control experiments and $C_{Sat,T_f}$ is the saturated solution concentration at the final temperature of the reference batch experiments, which was 10 $^\circ$C in this case. Since the concentration was not measured in the experiments, the final solute concentration ($C_{f,\text{Exp}}$) was
assumed to be same as the saturated solution concentration at the final temperature of the experiment. This assumption is valid in most cases, since the crystallization process is slow and the mother liquor is in contact with sufficiently large crystal surface areas [79]. Accordingly, if the temperature at the end of the experiment is higher than 10 °C, the percentage yield will decrease. To overcome this issue, the constraints of the objective function can be updated. To illustrate $T_{\text{max}}$ set as 35 °C during the experiment can be decreased to a lower value during the final stages of the experiment. Instead of updating the constraint, one can also add a yield-related term into the previously described objective function. In this study, in order to test the yield constraints, we decreased $T_{\text{max}}$ constrain to 13 °C at the end of 5.5 hours (330 minutes) crystallization, and allowed RBF driven system to continue for a half hour more (until 360 minutes). In this case, as seen also in Fig. 8, the final temperature of approximately 10 °C was achieved in DoE 1 and DoE 7.

Figure 8: Chord count (Above) and temperature (below) trajectories of all RBF driven control experiments (DoE 01-10).
Finally, the performance of the control strategy in *DoE 01–10* with respect to the set-point tracking and total actuator variation was also compared by means of IAE (Eq. 12) and TV (Eq. 13), respectively and shown in Table 3. Calculated IAE values indicate that *DoE 01* and *DoE 10* showed the worst performance with respect to the set-point tracking, while total actuator variations in these experiments were minimum. On the other hand, *DoE 09*, *DoE 07* and *DoE 08* performed the best set-point tracking, respectively. The highest actuator variation appeared in *DoE 03*, in which all the positive disturbances were introduced.

Table 3: Performance metrics of the control strategy in *DoE 01–10* with respect to set-point tracking (IAE) and total actuator variation (TV).

<table>
<thead>
<tr>
<th>Performance Metrics</th>
<th>Unit</th>
<th>01</th>
<th>02</th>
<th>03</th>
<th>04</th>
<th>05</th>
<th>06</th>
<th>07</th>
<th>08</th>
<th>09</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>IAE</td>
<td>$[10^{10} , #\mu m^2]$</td>
<td>5.6</td>
<td>1.1</td>
<td>1.0</td>
<td>1.6</td>
<td>2.0</td>
<td>2.3</td>
<td>0.8</td>
<td>0.9</td>
<td>0.7</td>
<td>5.4</td>
</tr>
<tr>
<td>TV</td>
<td>$[^\circ C]$</td>
<td>51.5</td>
<td>75.5</td>
<td>85.2</td>
<td>62.9</td>
<td>65.5</td>
<td>67.3</td>
<td>74.5</td>
<td>79.8</td>
<td>71.3</td>
<td>53.4</td>
</tr>
</tbody>
</table>

3.3. Critical comparison and discussion

In the context of previous data-driven control studies, we can formulate the strength of presented work as follows:

- A data-driven control strategy based on the RBF network was applied experimentally to a pharmaceutical crystallization process and comprehensively evaluated under various sources of process disturbances.

- The proposed strategy is simple, easy to implement and requires very limited data. Besides, the RBF network embodies a single hidden layer that eliminates the effort for optimization of the number of hidden layers.

- On the contrary to the previous studies, in which a large amount of experimental data was used to train the model offline, the application of the presented strategy to the different scales is more straightforward. It is also possible in the absence of historical data. Because, training of the data-driven model is in real-time with online experimental data and a reference batch data.
On the other hand, in the context of previous model-based and model-free control studies, the new features of the presented work can be formulated as follows:

- The time and effort required to develop a process model-based control with high accuracy are much higher compared with data-driven strategies. However, there is already a high number of available and free sources/toolboxes of data-based models. Besides, the trade-off between the accuracy and computational time of the models based on the population balances is much drastic that challenges the use in real-time optimization and control. For instance, an MPC applied in silico to the seeded batch cooling crystallization of ibuprofen took about 36 hours to complete the simulation [70]. To overcome this challenge, code optimization strategies in combination with the parallel computing/increasing number of cores are often needed.

- Control of supersaturation throughout the process (as in the SSC technique) is an indirect control of critical solid-state attributes. It also requires solubility curve knowledge in advance. The proposed data-driven strategy is much more robust compare to the SSC techniques, especially in the presence of disturbances (or impurities) changing the solubility curve.

- In the DNC technique, several heating and cooling cycles are performed to determine the primary and secondary nucleation limits. Then the crystallization is further operated below these metastable limits so that the growth of the crystals is dominated (constant crystal number). These metastable limits of the API-solvent system are highly dependent on the specific conditions of the crystallizer such as geometry, impeller type, scale, impurities, etc. Hence, when the process is scaled-up, the DNC-based operation might necessitate to be redesigned. However, the proposed data-driven control strategy, due to its data-based adaptive nature, has the potential to handle such system uncertainties.
4. Conclusion

A data-driven control strategy based on the RBF networks was presented and applied experimentally to the crystallization process of ibuprofen from ethanol solvent. The RBF network was trained in real-time with online experimental data and a reference batch data of temperature and chord count profile measured by the FBRM. The objective of the control strategy was to optimize the operation of the cooling crystallization (temperature profile) for a future horizon in order to achieve the desired reference chord count profile. In other words, the aim was to minimize the offset from the reference chord count profile not only at the end, but also throughout the operation. Comprehensive laboratory experiments in the presence of various disturbances were performed to test and demonstrate the robustness of the control strategy. Initial supersaturation, impeller speed, water composition (as solvent impurity) and seed size were considered as the sources of the disturbances in the process. The experiments were designed based on the fractional factorial design method yielding 10 experimental condition scenarios. Experimental results showed that the implemented fully-automated data-based control was able to easily handle all case scenarios. In 8 out of 10 cases, the experimental chord count profile caught and followed the reference chord count profile with an offset of less than 10 %. In the remaining 2 cases, the supersaturation was absent as a negative disturbance. In both cases, the reference chord count profile was still being followed smoothly with an offset of 17 %. This comprehensive study showed that the RBF network-driven control is a promising strategy that is easy to implement, fully automated and relies on limited data. The proposed control strategy could be especially useful for supporting a quick process development and control, where comprehensive process understanding and historical data are not readily available. However, independent of the implemented control strategy (model-based, model-free or data-based), all techniques have some parameters that need to be identified. This requires measurements from the crystallization system. Availability and variability of more data through advanced sensor technologies (PAT tools) enhance understanding of the dynamics of the system. They provide opportunities for advanced strategies and therefore improve the reliability of the control
strategy as well as the efficiency of the manufacturing process.

Acknowledgement

We would like to thank the Danish Council for Independent Research (DFF) for financing the project with grant ID: DFF-6111600077B. We are grateful for the cooperation with the pilot plant group (Z11) at LEO Pharma A/S for all the crystallization experiments.

Supplementary Material

Supplementary material associated with this article can be found in the online version.

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