# Control of a two-stage mixed suspension mixed product removal crystallizer $\star$

# Marcella Porru<sup>\*</sup> Leyla Özkan<sup>\*</sup>

\* Eindhoven University of Technology, De Zaale, 5612AJ Eindhoven, The Netherlands (e-mail: m.porru;l.ozkan@tue.nl).

Abstract: In this work, we consider the problem of controlling a two-stage cooling mixed suspension mixed product removal (MSMPR) crystallizer. For this process, the temperature in the first crystallizer is manipulated for controlling the average crystal dimension  $(d_{43})$ , while it is desired to maintain the temperature of the second crystallizer at the minimum allowed value to guarantee maximum yield. Due to system nonlinearities and process delays, the performance of traditional PID controllers are poor. A control scheme is proposed to improve the closed loop performance and achieve desired control objectives. The control scheme is based on the coupling of a PI controller and a model-based nonlinear prediction block that serves as delay and disturbance compensator. The proposed scheme has been tested on the system in case of disturbances in the feed concentration, with and without measurement errors. It is observed that the proposed scheme outperforms the PI controller by reducing the output response settling time and overshoot.

Keywords: Model-based control, Nonlinear delay compensation, Series of MSMPR crystallisers

# 1. INTRODUCTION

Crystallization is an important separation process for the production of high-value added chemicals in crystalline form. It has been widely used in pharmaceutical industry and carried out traditionally in batch mode. However, batch operations suffer from disadvantages such as lack of batch to batch reproducibility, long processing times, scale-up issues, poor controllability, and observability (Porru and Özkan (2016); Porru and Özkan (2017)). On the other hand, continuous production offers many advantages such as higher quality, product uniformity and process controllability (Su et al. (2015); Yang and Nagy (2015a)). Therefore, recent research efforts have been directed towards developing continuous crystallisers (Su et al. (2015)). A number of continuous crystallizer types and configurations have been applied, such as single stage or multistage of mixed suspension mixed product removal (MSMPR) crystallisers (Alvarez et al. (2011); Wong et al. (2012); Su et al. (2015); Vetter et al. (2014)), plug flow crystallizers (PFC), with (Alvarez and Myerson (2010)), or without (Ferguson et al. (2013)) static mixers, and more recently, PFC with recycle (Cogoni et al. (2015)), slug flow crystallizers (Rasche et al. (2016)), and periodic flow crystallizers (Su et al. (2017)).

Multistage MSMPR crystallization is the most convenient route of transition from batch to continuous operation, since current crystallizers in industry are of the stirred tank type (Power et al. (2015); Chen et al. (2011)). The two-stage cascade system is the most common configuration because it guarantees a good trade off between operation complexity and performance (Yang and Nagy (2015b)). Multistage MSMPR crystallization steady state and dynamic operation has been widely studied (Randolph and Larson (1962); Shiau and Berglund (1987); Tavare and Chivate (1978); Tavare et al. (1986); Alvarez et al. (2011); Power et al. (2015)). However, only a few papers deal with the control of these units. Su et al. (2015)recommend the use of the concentration (C-)control for operation and start-up control. Yang and Nagy (2015a) use a nonlinear model predictive control (NMPC). Conversely, more studies have been devoted to solve the control problem in single stage MSMPR crystallizers. Multiple papers report the failure of traditional PID controllers due to the system nonlinearities (Damour et al. (2010); Grosch et al. (2008); Yang and Nagy (2015a)). Yang and Nagy (2015a) discourage the use of PID-type controllers due to the low capability of dealing with changing operating conditions. Overall it emerges that the control problem can be successfully solved only by means of advanced process controllers (APC), able to incorporate kinetic crystallization information from measurements (i.e. Process Analytical Technologies (PAT)) (Ward et al. (2010); Randolph et al. (1987); Grosch et al. (2008)) and/or a (first principle) process model (Moldoványi et al. (2005); Damour et al. (2010); Bravi and Chianese (2003); Abonyi et al. (2002)).

In this paper, an alternative scheme for average crystal dimension control in an industrial-scale two-stage MSMPR crystallizers is proposed and tested in simulations. We have chosen a control scheme that combines feedback and prediction elements. This is an effective and simple way to upgrade low level PI controllers to APCs that should not require highly skilled personnel for controller commissioning and maintenance (Shinskey (1990); Porru et al. (2014)). The core of the control scheme is a PI controller which manipulates the temperature setpoint in the first crystallizer jacket such that the average crystal dimension is maintained at the desired specification. Because of the

 $<sup>^{\</sup>star}$  This work has been done within the IMPROVISE project in the Institute for Sustainable Process Technology (ISPT).

 Table 1. Feed and operating conditions, and cooling specifications

| $C_{f}$  | Feed concentration                   | 97.2    | g/kg                 |
|----------|--------------------------------------|---------|----------------------|
| $T_{f}$  | Feed temperature                     | 40      | $^{\circ}\mathrm{C}$ |
| $F_{f}$  | Feed flow rate                       | 100     | kg/min               |
| $T_1$    | Temperature in the $1^{st}$ stage    | 14      | $^{\circ}\mathrm{C}$ |
| $T_2$    | Temperature in the $2^{nd}$ stage    | 5       | $^{\circ}\mathrm{C}$ |
| $	au_1$  | Residence time in the $1^{st}$ stage | 67.2    | $\min$               |
| $	au_2$  | Residence time in the $2^{nd}$ stage | 50.13   | $\min$               |
| $T_{J0}$ | Coolant inlet temperature            | -30     | °C                   |
| $T_{JF}$ | Coolant outlet temperature           | -15     | $^{\circ}\mathrm{C}$ |
| U        | Overall heat transfer coefficient    | 450     | $W/m^2 K$            |
| $Cp_j$   | Specific heat of the coolant         | 3263.52 | J/kg K               |
|          |                                      |         |                      |

large volumes involved, a large time delay between manipulated and controlled variables exists resulting in limitations in the performance of this standard PI controller. Hence, a delay compensator is also used. In this work, the delay compensation block for average crystal dimension prediction consists of the nonlinear dynamic crystallization model with simulation horizon equal to the time delay. Measured disturbances, if available, can be provided to this model-based block. This allows further performance improvements due to the prediction capability of the model.

The paper is organized as follows. Section 2 describes the case study, and presents the dynamic model of the process. In section 3 the control problem is formulated. Section 4 describes the proposed control scheme. Closed loop performance of the proposed scheme is reported in section 5. Conclusions are given in section 6.

#### 2. MODEL OF THE TWO-STAGE MSMPR COOLING CRYSTALLIZATION OF PARACETAMOL

We consider the cooling crystallization of paracetamol from an aqueous isopropanol mixture as case study (Power et al. (2015)). The dominant crystallization kinetics are nucleation and growth. The crystallization is carried out in a series of two MSMPR crystallizers (Fig. 1), with feed condition, operating condition, and specification of the cooling system as in Table 1. The 50% ethylene glycol is a suitable coolant for this system. Physical properties and kinetic parameters are listed in Table 2.

The model of the system consists of material and energy balances for the liquid and solid phase. Under the assumptions of constant volume, no agglomeration and breakage, small variations between the inlet and outlet flow rates, the solid phase dynamics are modelled by means of the moment model (Randolph and Larson (1971)) according to

$$\frac{dm_{j,i}}{dt} = 0^j B_i + j G_i m_{j-1,i} + \frac{1}{\tau_i} (m_{j,i-1} - m_{j,i}); \qquad (1)$$
  

$$j = 0, ..., m_m; \ i = 1, ..., N_c$$

In eq.(1) the subscript j identifies the j-th moment. In this work it is sufficient to model up to the fourth moment (i.e.,  $m_m = 4$ ). The subscript i identifies the i-th crystallizer.  $N_c$  is the number of crystallizers in the series.  $m_{j,i-1} = 0$  for i = 1, because crystal-free feed is considered.  $G_i$ , and  $B_i$  are the crystal growth and birth rate in the crystallizer i respectively, according to the kinetics laws (eqs. 2)

$$G_i = k_{g0} \exp\left(\frac{-E_a}{R T_i}\right) \left(\frac{C_i - C_{sat,i}(T_i)}{C_{sat,i}(T_i)}\right)^g \qquad (2a)$$

Table 2. Physical properties, and kinetic parameters

| $C_p$    | Specific heat of the liquid | 4564        | J/kg K      |
|----------|-----------------------------|-------------|-------------|
| $\rho$   | Liquid density              | 970         | $ m kg/m^3$ |
| $k_v$    | Shape factor                | 0.866       | -           |
| $ ho_c$  | Crystal density             | 1332e + 3   | $ m g/m^3$  |
| $k_{g0}$ | Growth rate constant        | $3.34e{-4}$ | m/s         |
| $E_a$    | Activation energy           | 1.44e + 4   | J/mol       |
| $k_b$    | Nucleation rate constant    | 295         | #/kg s      |
| g        | Growth order                | 1.08        | -           |
| $b_1$    | Nucleation order            | 2.14        | -           |
| $b_2$    | Secondary nucleation order  | 1.6         | -           |
|          |                             |             |             |

$$B_{i} = k_{b} \left( \frac{C_{i} - C_{sat,i}(T_{i})}{C_{sat,i}(T_{i})} \right)^{b_{1}} (k_{v} \ \rho_{c} \ m_{3,i})^{b_{2}}$$
(2b)

The solubility  $C_{sat,i}$  [g-solute/kg-solution] in the stage i as function of the temperature  $T_i$  [°C] is

$$C_{sat,i} = 0.0379 \ T_i^2 + 0.377 \ T_i + 20.7 \tag{3}$$

The material balance in the liquid phase describes the dynamics of the solute concentration  $C_i$  according to

$$\frac{dC_i}{dt} = \frac{1}{\tau_i} (C_{i-1} - C_i) - 3\rho_c \, k_v \, G_i \, m_{2,i}, \ i = 1, ..., N_c \quad (4)$$

$$C_{i-1} = C_f$$
 for  $i = 1$ 

In case of negligible heat of crystallization, constant density  $\rho$  and specific heat Cp, the temperature dynamics are  $\frac{dT_i}{t} = \frac{1}{r}(T_{i-1} - T_i) - \frac{Q_i}{WC}, \ Q_i = m_{c,i} Cp_i (T_{JF} - T_{J0})$ 

$$\frac{1}{dt} = \frac{1}{\tau_i}(T_{i-1} - T_i) - \frac{1}{\rho V_i C_p}, \quad Q_i = m_{c,i} C p_j (T_{JF} - T_{J0})$$
  
where  $Q_i$  is the power absorbed by the jackets for the

cooling. We assume that we are able to supply instantaneously the exact amount of energy required to put the crystallizer temperature at the desired temperature  $T_i^{SP}$ . Then, the following energy balance holds

$$\frac{dT_i}{dt} = 0\tag{5}$$

The average crystal dimension of the solid product is given in terms of  $d_{43}$ 

$$d_{43} = \frac{m_{4,2}}{m_{3,2}} \tag{6}$$

whose dynamics can be obtained with the product rule

$$\frac{d d_{43}}{dt} = \frac{d}{dt} \left( \frac{m_{4,2}}{m_{3,2}} \right) = \frac{1}{m_{3,2}} \frac{d(m_{4,2})}{dt} + m_{4,2} \frac{d(m_{3,2})^{-1}}{dt}$$

$$\frac{d d_{43}}{dt} = \frac{1}{m_{3,2}} \frac{dm_{4,2}}{dt} - \frac{m_{4,2}}{(m_{3,2})^2} \frac{dm_{3,2}}{dt}$$
(7)

The system has initial conditions:  $m_{j,i}(0) = m_{j,i}^{SS}; d_{43}(0) = d_{43}^{SS}; T_i(0) = T_i^{SS}; C_i(0) = C_i^{SS}.$ 

The system (eqs. 1-7) is nonlinear and coupled. If the input-output  $(T_1 - d_{43})$  response is approximated with a first order model plus delay (Ogunnaike and Ray (1994)) one can obtain the following: characteristic time  $\tau_P = 235$  min, process gain  $K_P = 8\mu$  m/°C, and time delay  $t_d = 50$  min. This response is slow with a large time delay. This poses severe limitation on the performance of traditional PI for the control of the crystallization.

The model (eqs. 1-7) will be used for control synthesis, and performance testing.

#### 3. CONTROL PROBLEM

The crystal size distribution (CSD) is an important property of a crystallization process. It can determine the



Fig. 1. The two stages MSMPR crystallizer and its control scheme.

efficiency of the downstream operations, as well as the end-use properties (such as bioavailability). The control of the full CSD is not possible in practice. However some of its attributes (average size, coefficient of variation, fines fraction, etc.) can be controlled. The scope of this work is to achieve the control of the average dimension (mean diameter) of the crystals  $d_{43}$  (eq.6) which is also known the De Brucker mean.

Figure 1 shows a suitable control scheme for the two stage MSMPR crystallization. Assuming that the  $d_{43}$  can be measured (Mesbah et al. (2011); Nagy and Braatz (2003); Jager et al. (1992)) or estimated (Afsi et al. (2016); Ghadipasha et al. (2015); Zhang et al. (2014)), we propose to control it by varying the temperature of the first crystallizer  $(T_1)$  with a cascade controller. The master controller establishes the temperature set-point  $T_1^{SP}$  based on the deviation of the  $d_{43}$  from the desired value and a prediction of the future values of the  $d_{43}$  obtained with the model (eqs. 1-7). This predictor functions as a nonlinear delay compensator. The slave controller manipulates the coolant flow rate to maintain the temperature at the desired value. The temperature of the second crystallizer  $T_2$  is maintained at the minimum allowed value (5°C, see Table 1) to guarantee the maximum yield.

For simplification, we assume perfect slave temperatures control (TC) by manipulating the coolant flow rates, and perfect levels control (LC) by manipulating the product flows. We finally assume perfect control of the feed temperature and flow rate (FC). These loops are depicted in grey in Fig. 1. We also assume no model-plant mismatch. Similar assumptions are adopted also in the paper of Yang and Nagy (2015a).

In the following, we focus on the design of the master  $d_{43}$  controller (black loop in Fig. 1, and Fig. 2).

## 4. CONTROL OF THE $d_{43}$

For the control of the average crystal dimension  $d_{43}$  we propose the use of a PI controller ( $d_{43}$ C) together with a nonlinear delay compensator (NDC). The block diagram of this scheme is summarized in Fig. 2. The control law is

$$T_1^{SP} = T_1^{NOM} + M_1 K_C \left(\epsilon_S + \frac{M_2}{\tau_C} \int_0^t \epsilon_S(\tau) d\tau\right)$$
(8)

In eq.(8)  $K_C = \frac{\tau_P}{K_P t_d}$ , and  $\tau_C = 3.33 t_d$  are the controller tuning parameters according to Ziegler and Nichols (1942) and Smith and Corripio (1985).  $M_1$  and  $M_2$  are multipliers



Fig. 2. Block diagram of the advanced master  $d_{43}$  controller. The block  $d_{43}C$  is the linear PI controller with modified error signal  $\epsilon_S$ ; the block NDC is the nonlinear delay compensator, which can incorporate, if available, exogenous disturbance measurements d.

for tuning refinement that are adjusted by means of an optimization procedure that minimizes the ITAE =  $\int_0^\infty t |d_{43}^{SP} - d_{43}(t)| dt$ .

The feedback controller (eq.8) sees the error signal  $\epsilon_S$  (see Fig. 2)

$$\epsilon_S(t) = d_{43}^{SP} - (d_{43}(t) + \delta(t)) \tag{9}$$

where  $d_{43}$  is the measurement signal, and the signal  $\delta(t)$  is calculated by the NDC block by means of average crystal dimension predictions:

$$\delta(t) = \hat{d}_{43}(t+t_d) - \hat{d}_{43}(t) \tag{10}$$

Practically speaking the NDC block consists of the process dynamic model (eqs. 1-7), and uses the actual control action (eq.8). Based on this information, the process model is run to estimate the actual value of the average crystal size  $d_{43}(t)$ , and the value of average dimension of the crystals  $\hat{d}_{43}(t+t_d)$  after the time delay  $t_d$ . In other words, the model runs with a time horizon  $(t + t_d)$ , and the prediction  $\hat{d}_{43}(t+t_d)$  is compared with the estimation at the current time  $\hat{d}_{43}(t)$  to generate the differential signal  $\delta(t)$ . It must be pointed out that the moment model is not computationally expensive due to the relative low system dimension (13 dynamic states), and the short time horizon. Hence, the proposed dynamic model can be used online. If available, the compensator can incorporate exogenous disturbance measurements, such as variations in the feed concentration. In this way, the delay compensator acts as a feedforward controller without the need to calculate the inverse of the process model. The incorporation of the

model in the control scheme also allows the monitoring of the control input constrains  $(T_1 | G_i > 0$  always) to avoid crystal dissolution.

This NDC can be seen as a nonlinear realization of the Smith Predictor (Smith (1959)). Overall, the APC can be classified as an observer-based controller for delay systems (Richard (2003)).

## 5. RESULTS

The control performance is tested under disturbances in feed concentration, and systematic  $d_{43}$  measurements error for

(i) the PI control strategy (eq.8 and signal  $\delta(t) = 0$ ),

(ii) the PI plus the NDC control strategy (eqs. 8-10),

(iii) and the PI, NDC control strategy (eqs. 8-10) and disturbance measurements.

In each configuration the controller parameters  $M_1, M_2$  minimize the ITAE.

Closed loop responses for the system subjected to a feed concentration disturbance

$$C_f = \begin{cases} C_f & \text{at } t < 200 \text{ min} \\ C_f - 2 & \text{at } t \ge 200 \text{ min} \end{cases}$$
(11)

are depicted in Fig. 3 in the case of  $d_{43}$  measurements free of errors, and in Fig. 4 in case of systematic error in the  $d_{43}$  measurements (+5 $\mu$ m).

In Fig. 3 it can be observed that the PI controller alone (----) has poor closed loop performance, with slow settling time ( $\approx 4.2\tau_p$ , more than 1000 min). This is in agreement with the findings of Ward et al. (2010). Furthermore, the realization of the controller with delay compensation (------) outperforms the PI alone (----) by immediately varying the manipulated variable (Fig. 3b). This control scheme allows to reduce the time to the steady state more than 50% $(\approx 1.7\tau_p)$ . This is because the PI plus NDC accepts a much more aggressive tuning without the destabilization of the closed loop response. If feed concentration measurements are incorporated in the delay compensator, the advanced controller guarantees almost no perturbation of the  $d_{43}$  (--). In this latter case, the predictor is in fact a feedforward element able to fully and very quickly suppress the effect of the disturbance without the need of the inverse of the model.

Also in the case of systematic errors (Fig. 4) the delay compensation, with or without concentration measurements, has a beneficial effect of the closed loop settling time. Optimal tuning of the schemes leads to an ITAE=0.193 for the PI alone, ITAE=0.173 for the PI plus NDC, and ITAE=0.142 for the PI, NDC and disturbance measurements. It could be interesting to exploit the prediction model for measurement bias detection, to further improve the control performance. However, this research question is left for future work, in the understanding that Jager et al. (1992) report that  $d_{43}$  measurements are accurate and reproducible, hence systematic errors can be avoided by using the appropriate PAT.

Finally, we have tested the performance of the controllers with their optimal tuning, without measurement errors, for feed concentration disturbances up to 10% the nominal value:



Fig. 3. (a)  $d_{43}$  closed loop response after disturbance in the feed concentration (eq.11). (b) Manipulated variable ( $T_1$ ) load. PI controller without NDC (—). PI controller with NDC (eq.10), without (—) and with (—) feed concentration measurements. Free of measurements error.

$$C_{f} = \begin{cases} C_{f} & \text{at } t < 200 \text{ min} \\ C_{f} - 2 & \text{at } t \ge 200 \text{ min} \\ C_{f} - 5 & \text{at } t \ge 1200 \text{ min} \\ C_{f} - 10 & \text{at } t \ge 2200 \text{ min} \\ C_{f} - 5 & \text{at } t \ge 3200 \text{ min} \end{cases}$$
(12)

The closed loop performance is presented in Fig. 5a, while the manipulated variable load is depicted in Fig. 5b. One can notice that the designed controllers are able to reject the severe feed concentration disturbances. We observe that the PI alone is very slow in achieving the task leadingto long operating time with off-specification crystal production. The use of the NDC allows to reduce the settling time, and guarantees a lower deviation of the  $d_{43}$  from the desired value. Finally, if disturbance measurements are available, they can be incorporated in the prediction model to reject the disturbance before it causes deviations in  $d_{43}$ .



Fig. 4. (a)  $d_{43}$  closed loop response after disturbance in the feed concentration (eq.11). (b) Manipulated variable ( $T_1$ ) load. PI controller without NDC (—). PI controller with NDC (eq.10), without (—) and with (—) feed concentration measurements. Systematic error (+5  $\mu$ m) in the  $d_{43}$  measurements.

### 6. CONCLUSIONS

In this work, we have designed a controller to maintain the  $d_{43}$  at the desired value under feed concentration disturbances in a two stage MSMPR crystallizer. The controller consists of a PI controller with control action based on a modified error signal. This error signal compares the setpoint with both the  $d_{43}$  measurements and  $d_{43}$ model prediction in order to compensate for dead time and disturbances. The controller achieves decreasing the settling time and the overshoot of the output compared to a traditional PI controller. The work has considered an ideal case of no plant-model mismatch. Further anaylysis is needed for closed loop stability and performance.

#### REFERENCES

- Abonyi, J., Lakatos, B., and Ulbert, Z. (2002). Modelling and control of isothermal crystallizers by self-organising maps. *Chem. Eng. Trans*, 1(3), 1329–1334.
- Afsi, N., Bakir, T., Othman, S., Sheibat-Othman, N., and Sakly, A. (2016). Estimation of the mean crystal size and the moments of the crystal size distribution in batch

crystallization processes. In 2016 4th International Conference on Control Engineering & Information Technology (CEIT), 1–6.

- Alvarez, A.J. and Myerson, A.S. (2010). Continuous plug flow crystallization of pharmaceutical compounds. *Crys. Growth Des.*, 10(5), 2219–2228.
- Alvarez, A.J., Singh, A., and Myerson, A.S. (2011). Crystallization of cyclosporine in a multistage continuous MSMPR crystallizer. *Crys. Growth Des.*, 11(10), 4392– 4400.
- Bravi, M. and Chianese, A. (2003). Neuro-fuzzy control of a continuous cooled MSMPR crystallizer. *Chem. Eng. Technol.*, 26(3), 262–266.
- Chen, J., Sarma, B., Evans, J.M., and Myerson, A.S. (2011). Pharmaceutical crystallization. *Crys. Growth Des.*, 11(4), 887–895.
- Cogoni, G., de Souza, B., and Frawley, P. (2015). Particle size distribution and yield control in continuous plug flow crystallizers with recycle. *Chem. Eng. Sci.*, 138, 592–599.
- Damour, C., Benne, M., Grondin-Perez, B., and Chabriat, J.P. (2010). Nonlinear predictive control based on artificial neural network model for industrial crystallization. J. Food Eng., 99(2), 225–231.
- Ferguson, S., Morris, G., Hao, H., Barrett, M., and Glennon, B. (2013). Characterization of the anti-solvent batch, plug flow and MSMPR crystallization of benzoic acid. *Chem. Eng. Sci.*, 104, 44–54.
- Ghadipasha, N., Romagnoli, J.A., Tronci, S., and Baratti, R. (2015). On-line control of crystal properties in nonisothermal antisolvent crystallization. *AIChE J.*, 61(7), 2188–2201.
- Grosch, R., Mönnigmann, M., and Marquardt, W. (2008). Integrated design and control for robust performance: Application to an MSMPR crystallizer. J. Process Contr., 18(2), 173–188.
- Jager, J., Kramer, H.J., De Jong, E.J., De Wolf, S., Bosgra, O.H., Boxman, A., Merkus, H.G., and Scarlett, B. (1992). Control of industrial crystallizers. *Powder Technol.*, 69(1), 11–20.
- Mesbah, A., Huesman, A.E., Kramer, H.J., and Van den Hof, P.M. (2011). A comparison of nonlinear observers for output feedback model-based control of seeded batch crystallization processes. J. Process Contr., 21(4), 652– 666.
- Moldoványi, N., Lakatos, B.G., and Szeifert, F. (2005). Model predictive control of MSMPR crystallizers. J. Cryst. Growth, 275(1), e1349–e1354.
- Nagy, Z.K. and Braatz, R.D. (2003). Robust nonlinear model predictive control of batch processes. AIChE J., 49(7), 1776–1786.
- Ogunnaike, B.A. and Ray, W.H. (1994). Process dynamics, modeling, and control. Oxford University Press.
- Porru, M., Baratti, R., and Alvarez, J. (2014). Feedforward-feedback control of an industrial multicomponent distillation column. *IFAC Proceedings Volumes*, 47(3), 1266–1271.
- Porru, M. and Ozkan, L. (2016). Systematic observability and detectablity analysis of industrial batch crystallizers. *IFAC-PapersOnLine*, 49(7), 496–501.
- Porru, M. and Ozkan, L. (2017). Monitoring of batch industrial crystallization with growth, nucleation and agglomeration. Part 2: structure design for state esti-



Fig. 5. (a)  $d_{43}$  closed loop response, and (b) manipulated variable  $(T_1)$  load after step disturbances in the feed concentration up to 10% the nominal value (eq.12). PI controller without (--) nonlinear delay compensation. PI controller with nonlinear delay compensator (eq.10), without (--) and with (--) feed concentration measurements. Free of measurement errors.

mation with secondary measurements. Ind. Eng. Chem. Res., 56, 9578–9592.

- Power, G., Hou, G., Kamaraju, V.K., Morris, G., Zhao, Y., and Glennon, B. (2015). Design and optimization of a multistage continuous cooling mixed suspension, mixed product removal crystallizer. *Chem. Eng. Sci.*, 133, 125–139.
- Randolph, A., Chen, L., and Tavana, A. (1987). Feedback control of CSD in a KCl crystallizer with a fines dissolver. *AIChE J.*, 33(4), 583–591.
- Randolph, A. and Larson, M. (1962). Transient and steady state size distributions in continuous mixed suspension crystallizers. AIChE J., 8(5), 639–645.
- Randolph, A.D. and Larson, M.A. (1971). Theory of particulate processes, analysis and techniques of continuous crystallization. Academic Press.
- Rasche, M.L., Jiang, M., and Braatz, R.D. (2016). Mathematical modeling and optimal design of multi-stage slugflow crystallization. *Comput. Chem. Eng.*, 95, 240–248.
- Richard, J.P. (2003). Time-delay systems: an overview of some recent advances and open problems. *Automatica*, 39(10), 1667–1694.
- Shiau, L.D. and Berglund, K.A. (1987). Model for a cascade crystallizer in the presence of growth rate dispersion. *Ind. Eng. Chem. Res.*, 26(12), 2515–2521.
- Shinskey, F.G. (1990). Process control systems: application, design and tuning. McGraw-Hill, Inc.
- Smith, C.A. and Corripio, A.B. (1985). Principles and practice of automatic process control, volume 2. Wiley New York.
- Smith, O.J. (1959). A controller to overcome dead time. ISA J., 6, 28–33.
- Su, Q., Nagy, Z.K., and Rielly, C.D. (2015). Pharmaceutical crystallisation processes from batch to continuous operation using MSMPR stages: Modelling, design, and control. *Chem. eng. and Process.*, 89, 41–53.
- Su, Q., Rielly, C.D., Powell, K.A., and Nagy, Z.K. (2017). Mathematical modelling and experimental validation

of a novel periodic flow crystallization using MSMPR crystallizers. *AIChE J.*, 63(4), 1313–1327.

- Tavare, N.S. and Chivate, M.R. (1978). CSD analysis from a single stage and two stage cascade of MSMPR crystallizers. *Can. J. Chem. Eng.*, 56, 758–761.
- Tavare, N.S., Garside, J., and Larson, M.A. (1986). Crystal size distribution from a cascade of MSMPR crystallizers with magma recycle. *Chem. Eng. Commun.*, 47, 185–199.
- Vetter, T., Burcham, C.L., and Doherty, M.F. (2014). Regions of attainable particle sizes in continuous and batch crystallization processes. *Chem. Eng. Sci.*, 106, 167–180.
- Ward, J.D., Yu, C.C., and Doherty, M.F. (2010). Plantwide dynamics and control of processes with crystallization. *Comput. Chem. Eng.*, 34(1), 112–121.
- Wong, S.Y., Tatusko, A.P., Trout, B.L., and Myerson, A.S. (2012). Development of continuous crystallization processes using a single-stage mixed-suspension, mixedproduct removal crystallizer with recycle. *Cryst Growth Des.*, 12(11), 5701–5707.
- Yang, Y. and Nagy, Z.K. (2015a). Advanced control approaches for combined cooling/antisolvent crystallization in continuous mixed suspension mixed product removal cascade crystallizers. *Chem. Eng. Sci.*, 127, 362– 373.
- Yang, Y. and Nagy, Z.K. (2015b). Combined cooling and antisolvent crystallization in continuous mixed suspension, mixed product removal cascade crystallizers: Steady-state and startup optimization. *Ind. Eng. Chem. Res.*, 54(21), 5673–5682.
- Zhang, B., Willis, R., Romagnoli, J., Fois, C., Tronci, S., and Baratti, R. (2014). Image-based multiresolution-ANN approach for online particle size characterization. *Ind. Eng. Chem. Res.*, 53(17), 7008–7018.
- Ziegler, J.G. and Nichols, N.B. (1942). Optimum settings for automatic controllers. *Trans. ASME*, 64(11).