Chemical Engineering Science 127 (2015) 210–219

Contents lists available at ScienceDirect

Chemical Engineering Science

journal homepage: www.elsevier.com/locate/ces

A method for handling batch-to-batch parametric drift using moving horizon estimation: Application to run-to-run MPC of batch crystallization

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HIGHLIGHTS

- Model parameter estimation using moving horizon approach from post-batch measurements.
- Prediction of parameter estimates for next batch.
- Estimation-based model predictive control of end-of-batch crystal shape distribution.
- Proper handling of batch-to-batch drift and measurement noise.

ARTICLE INFO

Article history:
Received 24 August 2014
Received in revised form
17 December 2014
Accepted 16 January 2015
Available online 29 January 2015

Keywords:
Run-to-run control
Parameter estimation
Moving horizon estimation
Model predictive control
Batch crystallization
Crystal shape control

ABSTRACT

In this work, we develop a run-to-run (R2R) model parameter estimation scheme based on moving horizon estimation (MHE) concepts for the modeling of batch-to-batch process model parameter variation using a polynomial regression scheme in a moving horizon fashion. Subsequently, the batch process model parameters computed via the proposed R2R model parameter estimation scheme are used in a model predictive controller (MPC) within each batch to compute a set of optimal jacket temperatures for the production of crystals with a desired shape distribution in a batch crystallization process. The ability of the proposed method to suppress the inherent variation in the solubility caused by batch-to-batch parametric drift and handle the noise in post-batch measurements is demonstrated by applying the proposed parameter estimation and control method to a kinetic Monte Carlo (kMC) simulation model of a batch crystallization process used to produce hen-egg-white (HEW) lysozyme crystals. Furthermore, the performance of the proposed R2R model parameter estimation scheme is evaluated with respect to different orders of polynomials and different moving horizon lengths in order to calculate the best parameter estimates. The average crystal shape distribution of crystals produced from the closed-loop simulation of the batch crystallizer under the MPC with the proposed R2R model parameter estimation scheme is much closer to a desired set-point value compared to those of the double exponentially weighted moving average-based MPC (dEWMA-based MPC) and that of MPC based on the nominal process model.

1. Introduction

Batch configuration is one of the most widely used reactor and crystallization configurations in the specialty chemicals and pharmaceutical industries. However, due to unknown systematic trends or drifts in the process parameter values, for example, in initial pH level, operating conditions, and impurity concentrations in raw materials, the values of the parameters used in batch process models (employed for control and estimation purposes) may significantly deviate from the actual parameter values resulting in poor control and estimation performance (e.g., FloresCerrillo and MacGregor, 2004). Such a drift in the pH level of a feedstock container, for example, may be challenging from the standpoint of

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http://dx.doi.org/10.1016/j.ces.2015.01.033
0009-2509/

operating batch crystallization processes because even a small change in the pH level may have a significant influence on the size and shape distribution of crystal products, and thereby, on the bioavailability of crystals produced from a batch crystallization process. As another example, in a chemical–mechanical planarization process, a negative drift may occur when the interior diameter of a spray nozzle decreases due to clogging, thereby causing a decrease in the amount of liquid passing through the nozzle. On the other hand, positive drift may occur when process equipment gradually wears out. These issues can be addressed by cleaning the spray nozzle or replacing the part, but certainly make difficult the consistent production of parts (Rahim and Banerjee, 1988).

In general, common uncertainties in batch processes include fully stochastic (random) variations (e.g., noise in the measurements) and process drift of repetitive nature. There are previous contributions that have considered parameter uncertainty in batch crystallization processes. Specifically, while stochastic filtering techniques such as Kalman filtering and its variants such as the extended Kalman filter (EKF) are known for their ability to handle stochastic fluctuations effectively (Mesbah et al., 2011), the ability of Kalman filtering to handle process drift is limited as batch-to-batch parametric drift cannot be explicitly taken into account in the EKF design (Haseltine and Rawlings, 2005). Additionally, the kinetic parameters may be estimated by Bayesian inference from batch data collected from in situ measurements (Hermanto et al., 2008). The difficulty in making in situ measurements for real-time control during each batch run and the high sensitivity of the product quality on the feedstock stream have led to numerous implementations of run-to-run (R2R) control on batch processes to deal with random variations and drift (e.g., Sachs et al., 1990, 1995). Several significant efforts have been made to the parameter estimation of multiscale models. For example, a maximum likelihood scheme was used for the estimation of the process parameters (Kannan et al., 2000), and modeling and control of thin film morphology using uncertain processing parameters was studied in Gallivan et al. (2001) and Lou and Christofides (2003). Additionally, parameter estimation for other multiscale chemical processes was investigated in Raimondeau and Vlachos (2002) and Gunawan et al. (2003).

The best known method for handling batch-to-batch drift, particularly in the application of run-to-run control to batch semiconductor manufacturing processes, is the exponentially weighted moving average (EWMA) control scheme because of its ability to detect mean shifts in the presence of strong autocorrelation from batch-to-batch (Castillo and Yeh, 1998; Moyne et al., 2001; Campbell et al., 2002; Lee and Dorsey, 2004; Wang et al., 2009; Kwon et al., 2014a). While significant efforts have been devoted to the improvement of the stability and sensitivity in response to process noise of the EWMA scheme (e.g., Wang, 2010; Wang et al., 2010), this scheme becomes insufficient for processes subject to highly nonlinear batch-to-batch dynamics of the process drift. Motivated by this, several authors have proposed using a double exponentially weighted moving average (dEWMA) formula, which can capture the changes in the rate of the process drift, and thus, forecast the process drift in the next batch run (Bulter and Stefani, 1994; Simith et al., 1998; Castillo, 1999; Chen and Guo, 2001; Castillo and Rajagopal, 2002; Su and Hsu, 2004; Tseng and Hsu, 2005; Wu and Maa, 2011).

However, when the batch-to-batch dynamics of the process drift is nonlinear, the effectiveness and convergence speed of the dEWMA scheme are highly restricted, and thus, the remaining parametric mismatch between the process model used in the controller and the actual process variables may significantly affect the controller performance. While higher-order EWMA schemes such as triple EWMA schemes may improve the control performance in batch systems (Fan et al., 2002), they are impractical due to their tuning complexity because of the trade-off between the convergence speed and the stability of the closed-loop system, which has to be evaluated by a trial-and-error procedure. Furthermore, the dEWMA is a suboptimal filter for stochastic processes, no matter how the process gains in the dEWMA are tuned off-line (Ramaswamy and Lee, 2003).

Motivated by the above considerations, in this work, a run-to-run model parameter estimation scheme based on moving horizon estimation concepts is proposed in order to model the batch-to-batch dynamics of the process drift and compute improved estimates of process model parameters, utilizing post-batch measurements from multiple batch runs. The MHE approach is employed because it provides improved parameter estimation and greater robustness to poor guesses for initial states because of its capability to incorporate physical constraints into the optimization problem used for parameter estimation. Specifically, the key elements of the proposed R2R model parameter estimation scheme based on MHE concepts are the following: first, the variation of the process model parameters from batch-to-batch is estimated by solving an R2R model parameter estimation scheme along with the post-batch measurements from multiple batch runs. Second, the batch-to-batch parametric drift is modeled through the use of a nonlinear function (e.g., second-, third- or fourth-order polynomials), and used to update the parameters of the model predictive controller (MPC) model (used for real-time feedback control within each batch) to suppress the undesired effect of the process drift in the next batch run.

The paper is structured as follows: we initially discuss the model of our case study, a batch crystallization process used to produce tetragonal hen-egg-white (HEW) lysozyme crystals, focusing on the nucleation and crystal growth processes in the direction of (110) and (101) faces. Then, we develop an R2R model parameter estimation scheme in order to identify the batch-to-batch dynamics of the process drift by solving a multivariable optimization problem along with the post-batch measurements from multiple batch runs in a moving horizon fashion. The computed model parameters are used in an MPC for the computation of a set of optimal jacket temperatures that drive the average shape of the entire crystal population at the end of the batch to a desired value. The performance of the proposed R2R model parameter estimation scheme is evaluated with respect to the different orders of polynomials and different moving horizon lengths in order to find the best parameter estimates. Lastly, the closed-loop performance of the MPC with the proposed R2R model parameter estimation scheme is compared with those of a double exponentially weighted moving average-based MPC (dEWMA-based MPC) and MPC with no model parameter update.

2. Modeling of batch crystallization process

To present and evaluate the proposed technique for process model parameter estimation, we will focus on a batch crystallization process used to produce HEW lysozyme crystals.

2.1. Crystal nucleation

At 4%(w/v) NaCl and pH=4.5, the lysozyme crystals are nucleated according to the following rate expressions (Galkin and Vekilov, 2001)

$$B = \begin{cases} 0.041\sigma + 0.063 & \text{for } \sigma \geq 3.11 \\ 8.0 \times 10^{-8} \exp(4.725\sigma) & \text{for } \sigma < 3.11 \end{cases} \quad (1)$$

where B is the nucleation rate with units [$cm^{-3}\,s^{-1}$], and the supersaturation level σ is defined as follows:

$$\sigma = \ln(C/s) \quad (2)$$

where C is the solute concentration and s is the solubility, which is calculated using the following third-order polynomial equation taken

from Cacioppo and Pusey (1991):

$$s(T) = 2.88 \times 10^{-4}T^3 - 1.65 \times 10^{-3}T^2 + 4.62 \times 10^{-2}T + 6.01 \times 10^{-1} \quad (3)$$

where the temperature in the crystallizer, T, is in degrees Celsius.

2.2. Crystal growth

The crystal growth is modeled through the kMC simulation using the following rate equations, which are adopted from Durbin and Feher (1991). The adsorption rate, r_a, is independent of each lattice site and is defined as follows:

$$r_a = K_0^+ \exp(\sigma) \quad (4)$$

where K_0^+ is the adsorption coefficient. On the other hand, the desorption and migration rates depend on the surface micro-configuration (i.e., the number of particles that surround the particle of interest). Thus, the desorption rate for a lattice site with i nearest neighbors, $r_d(i)$, is given by

$$r_d(i) = K_0^+ \exp\left(\frac{\phi}{k_B T} - i\frac{E_{pb}}{k_B T}\right) \quad (5)$$

where E_{pb} is the average bonding energy per bond, ϕ is the total binding energy when chemical bonds of a molecule are fully occupied by nearest neighbors (i.e., $i=4$). In order to account for the fact that the migration rate is higher than the desorption rate, the migration rate, $r_m(i)$, is defined by multiplying an additional term to Eq. (5) and is shown below

$$r_m(i) = K_0^+ \exp\left(\frac{\phi}{k_B T} - i\frac{E_{pb}}{k_B T} + \frac{E_{pb}}{2k_B T}\right) \quad (6)$$

The crystal growth rates obtained from the kMC simulations are calibrated with the experimental data (Durbin and Feher, 1991) by manipulating a set of E_{pb} and ϕ values for the (110) and (101) faces through extensive open-loop kMC simulations. The parameters for the kMC simulation are listed in Table 1.

2.3. Mass and energy balance equations

The mass and energy balance equations that calculate the amount of the protein solute remaining in the continuous phase, C, and the temperature in the crystallizer, T, are given by the following ordinary differential equations:

$$\frac{dC}{dt} = -\frac{\rho_c}{V_{batch}}\frac{dV_{crystal}}{dt}, \quad C(0) = C_0 \quad (7)$$

$$\frac{dT}{dt} = -\frac{\rho_c \Delta H_c}{\rho C_p V_{batch}}\frac{dV_{crystal}}{dt} - \frac{U_c A_c}{\rho C_p V_{batch}}(T - T_j), \quad T(0) = T_0 \quad (8)$$

where $V_{crystal}$ is the total volume of crystals in the crystallizer, $C_0 = 42$ mg/cm^3 is the initial protein solute concentration, $\rho_c = 1400$ mg/cm^3 is the crystal density, and $V_{batch} = 1$ L is the volume of the batch crystallizer, $T_0 = 17$ °C is the initial crystallizer temperature, $\Delta H_c = -4.5$ kJ/kg is the enthalpy of crystallization, $\rho(t) = 1000 + C(t)$ mg/cm^3 is the density of the continuous phase, $C_p = 4.13$ kJ/K kg is the specific heat capacity, $A_c = 0.25$ m^2 and $U_c = 1800$ kJ/m^2 h K are the area and the overall heat transfer coefficients between the jacket stream T_j and the crystallizer wall, respectively.

Table 1
Parameters for the faces (110) and (101) at 42 mg/mL NaCl and pH=4.5% at $T=18$ °C. Additionally, $K_o^+ = 0.211$ s^{-1}.

Face	E_{pb}/k_B	ϕ/k_B
(110)	1077.26	227.10
(101)	800.66	241.65

2.4. Moment models

Due to the complexity of a population balance equation (PBE), it cannot be directly used for the computation of a crystal volume distribution in real-time. Motivated by this, a moments model is used to describe the zero and first moments of the evolution of the number and the total volume of crystals in the batch crystallization process in the process model used in the controller of the form

$$\frac{dM_0}{dt} = B \quad (9)$$

$$\frac{dM_1}{dt} = G_{vol} M_0 \quad (10)$$

where $M_j(t) = \int_0^\infty V^j n(V,t)\, dV$ is the jth moment for $j=0, 1$, $n(V,t)$ is the number of crystals with volume V at time t, and G_{vol} is the volumetric crystal growth rate, which is formulated as follows:

$$G_{vol} = 2G_{110}\langle h_{110}\rangle\langle h_{101}\rangle + G_{101}\langle h_{110}\rangle^2 \quad (11)$$

where the crystal growth rates in the direction of (110) and (101) faces, G_{110} and G_{101}, can be obtained through the following expressions:

$$G_{110} = 0.1843\sigma^3 - 1.1699\sigma^2 + 2.8885\sigma - 2.5616$$
$$G_{101} = 0.1893\sigma^3 - 1.2264\sigma^2 + 2.9887\sigma - 2.5348 \quad (12)$$

which are calibrated with the experimental data (Durbin and Feher, 1986). Similarly, the average crystal heights, $\langle h_{110}\rangle$ and $\langle h_{101}\rangle$, are calculated by using the following ordinary differential equations:

$$\frac{d\langle h_{110}\rangle}{dt} = G_{110} - \frac{BV_{batch}\langle h_{110}\rangle}{M_0}$$
$$\frac{d\langle h_{101}\rangle}{dt} = G_{101} - \frac{BV_{batch}\langle h_{101}\rangle}{M_0} \quad (13)$$

and thereby the average crystal shape, $\langle\alpha\rangle$, and size, $\langle V\rangle$, can be computed as follows:

$$\langle\alpha\rangle \approx \frac{\langle h_{110}\rangle}{\langle h_{101}\rangle}, \quad \langle V\rangle = \frac{M_1}{M_0} \quad (14)$$

A more detailed description regarding the derivation of the moment model that accounts for the dynamic evolution of the crystal volume distribution for the batch crystallization process can be found in Kwon et al. (2014b).

3. MPC with R2R model parameter estimation

3.1. MPC formulation

In this subsection, a model predictive controller (MPC) is presented for in-batch control. Specifically, the dominant dynamic behavior of the evolution of crystal shape distribution in the batch crystallization process is modeled through the process model (cf. Eqs. (1)–(3) and (7)–(14)), which are used to compute a set of optimal jacket temperatures that minimizes the squared deviation of the average crystal shape from a set-point value over the entire prediction horizon. Constraints on the rate of change of the jacket temperature (i.e., manipulated input) and the temperature in the crystallizer are imposed. The resulting MPC formulation is given by the following optimization problem:

$$\min_{T_{j,1},\ldots,T_{j,i},\ldots,T_{j,p}} \quad \sum_{i=1}^{p} (\langle\alpha(t_i)\rangle - \alpha_{set})^2 \quad (15a)$$

s.t. Eqs. (1)–(3) and (7)–(14) (15b)

$$4\ ^\circ\mathrm{C} \le T \le 25\ ^\circ\mathrm{C} \quad \left|\frac{T_{j,i+1}-T_{j,i}}{\Delta}\right| \le 2\ ^\circ\mathrm{C/min} \tag{15c}$$

where $p=10$ is the length of the prediction horizon, T is the crystallizer temperature, $\Delta = 40$ is the sampling time, α_{set} is the desired average crystal shape (i.e., set-point), $t_i = t + i\Delta$, $T_{j,i}$, and $\langle\alpha(t_i)\rangle$ are the time, the jacket temperature, and the average crystal shape of the ith prediction step, respectively. At every sampling time, the real-time measurements for the solute concentration in the continuous phase and the temperature in the crystallizer are used to compute a set of optimal jacket temperatures, $(T_{j,1}, T_{j,2}, \ldots, T_{j,p})$, by solving Eq. (15) where the first value, $T_{j,1}$, is applied to the crystallizer over the next sampling time.

3.2. MPC with R2R model parameter estimation scheme

For the batch crystallization process with changes in the process model parameters owing to a process drift, an R2R model parameter estimation scheme based on MHE concepts is proposed and used along with post-batch measurements from multiple batch runs in a moving horizon fashion to estimate parameters of the batch crystallization model (cf. Eqs. (1)–(3) and (7)–(14)). Then, the updated process model parameters are used in the MPC for the computation of control inputs applied to a batch crystallization process.

3.2.1. R2R model parameter estimation scheme based on MHE concepts

There are many different formulations for an R2R parameter estimation scheme and the design of the observer significantly affects the estimator performance. In this work, an optimization-based parameter estimation scheme is proposed in order to estimate the process model parameters using several sets of post-batch measurements. Specifically, the uncertainty in the solubility of the protein solute is accounted for by multiplying a correction factor, γ_s, to the nominal third-order polynomial equation for solubility, Eq. (3). The uncertainty associated with the crystal growth rates in the direction of (110) and (101) faces is taken into account by multiplying the parameters γ_{110} and γ_{101} to the nominal growth rate expressions for the (110) and (101) faces, respectively. Furthermore, to account for the remaining offset between the predicted and measured values for the average crystal shape and size, a set of correction factors (γ_α and γ_V) is directly introduced to the objective function.

Specifically, the optimization problem for the proposed R2R model parameter estimation scheme based on MHE concepts after the nth batch run is formulated as follows:

$$\min_{\underline{Q}_1,\ldots,\underline{Q}_p} \sum_{k=n-m+1}^{n} w_\alpha\left(\langle\widehat{\alpha(t_f)}\rangle_k + \gamma_\alpha(k) - \langle\alpha(t_f)\rangle_k\right)^2 + w_V\left(\langle\widehat{V(t_f)}\rangle_k + \gamma_V(k) - \langle V(t_f)\rangle_k\right)^2 \tag{16a}$$

$$\text{s.t.} \quad \text{Eqs. (1)–(3) and (7)–(14)} \tag{16b}$$

$$\hat{s}(k) = \gamma_s(k)s(k) \tag{16c}$$

$$\hat{G}_{110}(k) = \gamma_{110}(k)G_{110}(k), \quad \hat{G}_{101}(k) = \gamma_{101}(k)G_{101}(k) \tag{16d}$$

$$\gamma_x(k) = \sum_{r=1}^{p} q_{(x,r)}\left[\gamma_x(k-1)\right]^r \quad \forall \gamma_x \in [\gamma_{110}\ \ \gamma_{101}\ \ \gamma_s\ \ \gamma_\alpha\ \ \gamma_V] \tag{16e}$$

where s is the solubility, and G_{110} and G_{101} are the crystal growth rate in the direction of (110) and (101) faces, respectively. Note that $\hat{X}_k$ is a predicted variable X for the kth batch run and X_k represents a measured variable X after the kth batch run. Furthermore, the correction factors are initially $\underline{\Gamma}(0) = [1\ 1\ 1\ 0\ 0]$ which are the nominal values of the process model for the batch crystallization process, and more details about correction factors are described below.

Referring to Eq. (16), we note that Eq. (16e) is used in order to approximate the batch-to-batch parameter drift from the $k-m+1$ to k batch run with a pth order polynomial through the manipulation of the decision variables, $\underline{Q}_1 = [q_{(110,1)}\ q_{(101,1)}\ q_{(s,1)}\ q_{(\alpha,1)}\ q_{(V,1)}]$, …, $\underline{Q}_p = [q_{(110,p)}\ q_{(101,p)}\ q_{(s,p)}\ q_{(\alpha,p)}\ q_{(V,p)}]$ in a moving horizon fashion. For example, the pth order polynomial for the solubility correction factor $\gamma_s(k)$ can be written in the form of $\gamma_s(k) = \sum_{r=1}^{p} q_{(s,r)}[\gamma_s(k-1)]^r$. Then, the batch-to-batch dynamics of the process drift is estimated by using Eq. (16e) to predict a set of correction factors for the $k+1$ batch run, $\underline{\Gamma}(k+1) = [\gamma_{110}(k+1)\ \gamma_{101}(k+1)\ \gamma_s(k+1)\ \gamma_\alpha(k+1)\ \gamma_V(k+1)]$. The objective function (cf. Eq. (16a)) consists of sum of squared errors between the predicted average crystal size and shape, $\langle\widehat{\alpha(t_f)}\rangle$ and $\langle\widehat{V(t_f)}\rangle$, and the measured ones, $\langle\alpha(t_f)\rangle$ and $\langle V(t_f)\rangle$, which are obtained at the end of the batch crystallization process from the $k-m+1$ to k batch run where m is the moving horizon length. In the beginning of the batch-to-batch estimation, the number of post-batch measurements is allowed to grow until it reaches the length of the horizon (i.e., until the batch number becomes equal to m).

We note that the sensitivity of the proposed R2R model parameter estimation scheme based on MHE concepts with respect to the different orders of polynomials and different moving horizon lengthes is further discussed in Section 4 below in order to find the best parameter estimates for the batch crystallization process.

Remark 1. While the sign and the magnitude of the rate of the process drift change from batch-to-batch, if the overall batch-to-batch dynamics of the process drift can be described by a smooth function, Eq. (16e) in the proposed R2R model parameter estimation scheme should be able to capture such a drift, which should lead to good parameter estimates for the next batch run. Furthermore, the idea of the proposed R2R model parameter estimation scheme based on MHE concepts is related to that of least square estimation in that the relationship between the independent variables and the dependent variables is modelled through a pth order polynomial and is used to find the best fit polynomial of multiple data points. Other nonlinear functions besides polynomials could be also used if necessary.

Remark 2. A short horizon length allows the proposed model parameter estimation scheme to follow fast batch-to-batch dynamics of the process drift while a longer horizon length (i.e., post-batch measurements from multiple batch runs) is able to better deal with the noise in the process and post-batch measurements.

3.2.2. MPC with R2R model parameter estimation scheme: implementation algorithm

An MPC with the proposed R2R model parameter estimation scheme is implemented to a batch crystallization process for the computation of the control inputs as follows:

1. At the end of the kth batch run, the post-batch measurements of the product qualities such as the number of crystals and the average size and the shape of the crystals are measured.
2. Then, the real-time measurements of the solute concentration in the continuous phase and the temperature in the crystallizer ($[C_{k-m+1}(t), T_{k-m+1}(t)], \ldots, [C_k(t), T_k(t)]\ \forall t \in [0, t_f]$) over the last m measurements (i.e., moving horizon length) are used to compute $\underline{Q}_1, \ldots, \underline{Q}_p$ that minimize the cost function, Eq. (16a).
3. The one-step-ahead correction factors for the $k+1$ batch run, $\underline{\hat{\Gamma}}_{k+1}$, are predicted through the use of $\underline{Q}_1, \ldots, \underline{Q}_p$ obtained from Step 2. Then, the process model parameters are updated through $\underline{\hat{\Gamma}}_{k+1}$ and they are used in the model employed in the MPC to compute a set of optimal jacket temperatures T_j which will drive the temperature T in the crystallizer to a desired value.
4. Increase k by 1 and repeat Step 1 to Step 4.

We note that the real-time measurements of the solute concentration and the temperature in the crystallizer are assumed to be available at each sampling time. A schematic representation of the MPC with the proposed R2R model parameter estimation scheme is shown in Fig. 1.

4. Application of MPC with R2R model parameter estimation to batch crystallization

One of the reasons that the control of the size and shape distributions of crystals produced from a batch process may be difficult is because even minor contaminations in the feedstock container (e.g., variations in the pH and added electrolyte concentration levels) may lead to a significant drift of key process parameters from batch-to-batch. Furthermore, minor contaminations in the feedstock container cannot be identified immediately, and thus, their undesired effect on the product quality continues to the next batch runs until the feedstock container is replaced by a new one. To tackle this problem, we initially use the proposed R2R model parameter estimation scheme based on MHE concepts where a polynomial regression scheme is applied in a moving horizon fashion to approximate the batch-to-batch dynamics of the drift and adjust the MPC model parameters at the beginning of each batch. Then, the MPC with the updated process model parameters is used to compute the optimal jacket temperature by suppressing the effect of the process drift in the next batch. In the proposed estimation scheme, we note that only post-batch measurements are used for the parameter estimation scheme. Furthermore, process noise (approximately 2%) due to the stochastic nature of the crystal growth mechanisms and measurement noise (approximately 8%) are intrinsically modeled through the kMC simulation. In order to simulate the operation of each batch run, a single kMC simulation is executed and used for the analysis per batch run.

The controller performance of the MPC with the proposed R2R model parameter estimation scheme is initially evaluated in response to an exponentially decaying process drift whose rate decays exponentially from 1 (i.e., nominal system) to 0.95 over 10 batch runs (see, e.g., Fig. 2). Additionally, a more complicated process drift whose rate fluctuates is considered in order to evaluate the robustness of the MPC with the proposed R2R model parameter estimation scheme for a more realistic environment for the operation of the batch crystallization process (see, e.g., Fig. 3). For comparison purposes, the dEWMA-based MPC that captures the changes in the rate of the process drift and properly adjusts outputs in the process model and

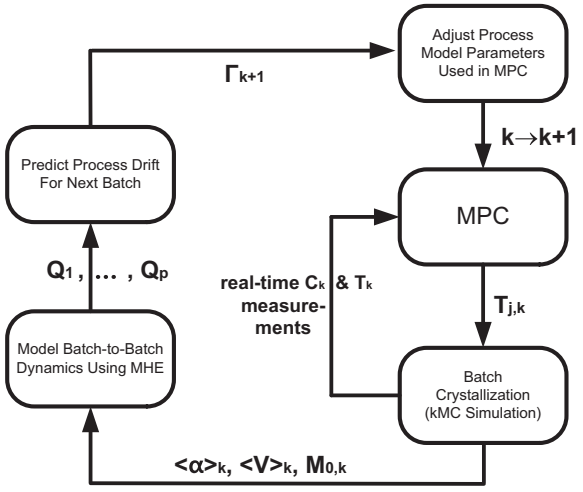

Fig. 1. Model predictive control with R2R model parameter estimation.

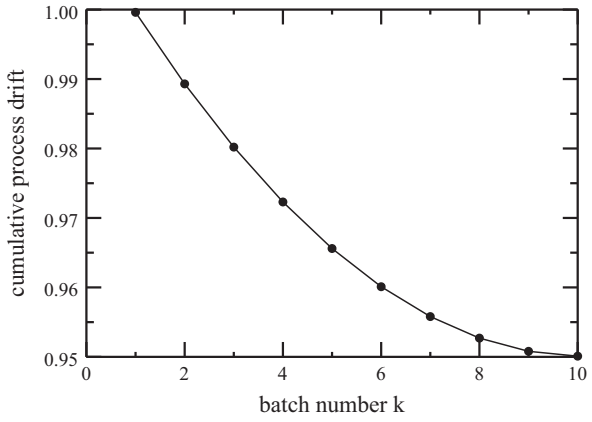

Fig. 2. The evolution of the cumulative process drift with an exponentially decaying rate from batch-to-batch. Note that the *y*-axis shows how much the batch system is perturbed from a nominal batch system (nominal batch system corresponds to the *y*-axis value equal to 1).

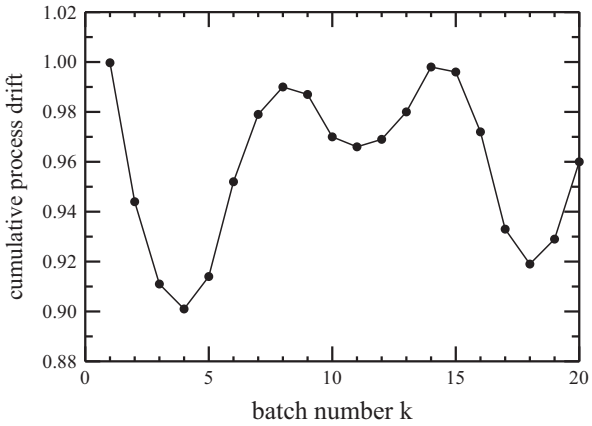

Fig. 3. The evolution of the cumulative process drift where its rate changes from batch-to-batch. Note that the *y*-axis implies how much the batch system is perturbed from a nominal batch system (nominal batch system corresponds to the *y*-axis value equal to 1).

the MPC that uses the nominal process model are also applied to the batch crystallization process model. To evaluate the controller performance, the mean squared error (MSE) of the offset $(\langle\alpha(t_f)\rangle_i - \alpha_{set})$ between the measured average crystal shape after the *i*th batch run and the set-point value is introduced as follows:

$$\mathrm{MSE} = \frac{\sum_{i=1}^{n} \left(\langle\alpha(t_f)\rangle_i - \alpha_{set}\right)^2}{n} \tag{17}$$

where n is the total number of batch runs.

4.1. dEWMA-based model predictive control

For the sake of comparison, a double exponentially weighted moving average (dEWMA) scheme, which is known for its ability to capture batch-to-batch dynamics of the process drift (Bulter and Stefani, 1994; Simith et al., 1998; Chen and Guo, 2001; Wang et al., 2010), is integrated with the MPC and its closed-loop performance is presented along with that of the MPC with the proposed R2R model parameter estimation scheme. In the dEWMA scheme, the predicted average crystal shape for the *k*th batch run can be written as follows:

$$\langle\widetilde{\alpha(t_f)}\rangle_k = \langle\widehat{\alpha(t_f)}\rangle_k + \hat{e}_k + \Delta\hat{e}_k \tag{18}$$

where $\langle\widetilde{\alpha(t_f)}\rangle_k$ is the predicted average crystal shape at the end of the kth batch, $\langle\widehat{\alpha(t_f)}\rangle_k$ is the predicted average crystal shape using only the nominal process model that consists of Eqs. (1)–(3) and (7)–(14), $\hat{e}_k$ is the estimated model prediction error, and $\Delta\hat{e}_k$ is used to compensate for the error in the parameter estimation caused by the change in the rate of the process drift. For a dEWMA-based MPC, the process model used in MPC (cf. Eqs. (1)–(3) and (7)–(14)) is not directly adjusted but its offset from the actual process model is approximated by $\hat{e}_k+\Delta\hat{e}_k$. The following control scheme is implemented for the computation of inputs in the proposed dEWMA-based MPC as follows:

1. At the end of the kth batch run, the post-batch measurements of the product variables such as average crystal size and shape of crystals are obtained.
2. Then, the average crystal shape measured from Step 1, $\langle\alpha(t_f)\rangle_k$, is used to compute the estimated model prediction error, $\hat{e}_k$, and the estimated change in the rate of the process drift, $\Delta\hat{e}_k$, through the following equation:

$$\hat{e}_{k+1}=\omega_1\left[\langle\alpha(t_f)\rangle_k-\langle\widehat{\alpha(t_f)}\rangle_k\right]+(1-\omega_1)\hat{e}_k \tag{19a}$$

$$\Delta\hat{e}_{k+1}=\omega_2\left[\langle\alpha(t_f)\rangle_k-\langle\widehat{\alpha(t_f)}\rangle_k-\hat{e}_k\right]+(1-\omega_2)\Delta\hat{e}_k \tag{19b}$$

   where $0<\omega_1\le 1$ and $0<\omega_2\le 1$ are the learning factors.
3. Then, the predicted average crystal shape for the $k+1$ batch run, $\langle\widetilde{\alpha(t_f)}\rangle_{k+1}$, that accounts for the change in the rate of the process drift is obtained by

$$\langle\widetilde{\alpha(t_f)}\rangle_{k+1}=\langle\widehat{\alpha(t_f)}\rangle_{k+1}+\hat{e}_{k+1}+\Delta\hat{e}_{k+1} \tag{20}$$

   and is used in the model employed in the MPC to compute a set of optimal jacket temperatures T_j which will drive the temperature T in the crystallizer to a desired value.
4. Increase k by 1 and repeat Step 1 to Step 5.

Note that the first equation, Eq. (19a), is used to estimate the offset in the average crystal shape (i.e., output) and the second equation, Eq. (19b), is used to capture an additional offset in the average crystal shape due to the change in the rate of the process drift.

4.2. Exponentially decaying process drift

When the process drift decays with an exponential rate (Fig. 2), the closed-loop performance of the MPC with the nominal process model becomes progressively worse (Fig. 4) as runs are repeated due to the increasing mismatch between the process model and actual batch crystallization process. In Fig. 4, it is also shown that the dEWMA-based MPC is able to produce crystals with a desired shape distribution compared to that of the MPC with the nominal process model, however, its convergence speed is so slow that there still remains an offset from the desired crystal shape. On the other hand, the crystal shape distribution obtained by the MPC with the proposed R2R model parameter estimation scheme (Fig. 4) converges fast (after 5 batch runs) and becomes much closer to a desired set-point value compared to those of the MPC with the nominal process model and dEWMA-based MPC, because the exponentially decaying process drift can be better captured by the proposed R2R model parameter estimation scheme based on MHE. Specifically, the change in the solubility induced by the process drift introduced to the batch crystallization process is properly predicted by the proposed R2R model parameter estimation scheme as is shown in Fig. 5. The superiority is due to more accurate estimates of the process model parameters which are obtained by solving Eq. (16). Lastly, we summarize the performances of the MPC with the proposed R2R model parameter estimation, dEWMA-based MPC, and MPC with no parameter estimation in response to the process drift described in Fig. 2 by comparing their MSE values in Table 2.

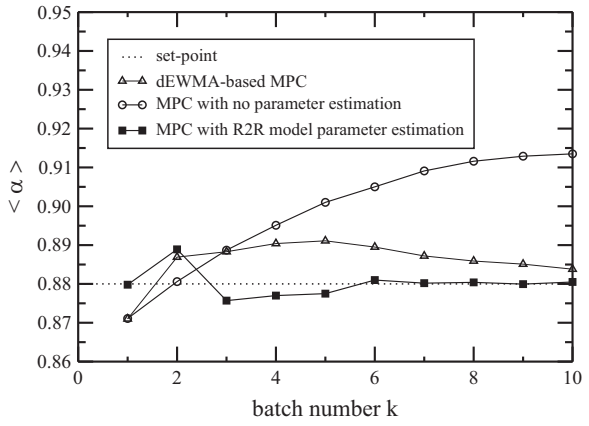

Fig. 4. The evolution of the average crystal shape at $t=20{,}000$ s obtained from the kMC simulations from batch-to-batch under the MPC with the nominal process model, the dEWMA-based MPC with $(w1,w2)=(0.5,0.5)$, and the proposed MPC with R2R model parameter estimation, with the desired set-point $\langle\alpha_{set}\rangle=0.88$.

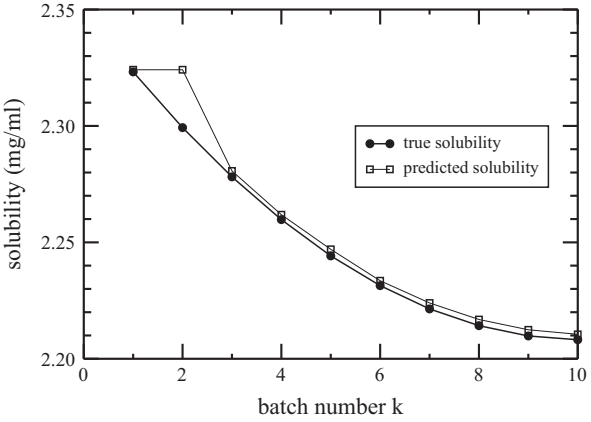

Fig. 5. The evolution of the predicted and true solubilities in the beginning of batch runs. The predicted solubility is calculated using the proposed R2R model parameter estimation scheme. Note that the average discrepancy between the two profiles from run 3 to run 10 (i.e., after the estimation scheme is applied to the batch system) is about 0.2%.

4.3. Sensitivity to different drift types and tuning parameters

In this section, we consider a more complicated drift. As is shown in Fig. 3, the rate of this process drift changes more rapidly from batch-to-batch (e.g., the system drifts from 1 to 0.9 over the first 4 batch runs) compared to the process drift with an exponentially decaying rate (see, e.g., Fig. 2), and 5 inflection points (i.e., a point of a curve at which a change in the direction of the curvature occurs) are introduced in order to model a significant fluctuation in the rate of the process drift.

For a given polynomial order, although longer horizon length provides better attenuation of random fluctuations, fast batch-to-batch drift dynamics may not be captured effectively, therefore, an optimal horizon length should be chosen to balance the trade-off between noise handling and capturing fast drift dynamics. A comparative study of using different moving horizon lengths for the proposed R2R model parameter estimation scheme is carried out. A third-order polynomial is chosen for Eq. (16e) for the comparison because it is the lowest order polynomial to effectively describe a curve with a pair of inflection points. Specifically, it is shown in Fig. 6 that the closed-loop performance initially improves with increasing horizon length (from $m=4$ to $m=5$) due to the better handling of noise in the post-batch measurements, then decreases with further increase of the horizon length (from $m=5$ to $m=7$) because fast

Table 2
Comparison among the MPC with R2R model parameter estimation, dEWMA-based MPC, and MPC with no parameter estimation in response to the process drift with an exponentially decaying rate.

Control schemes	MSE
MPC with R2R model parameter estimation	1.14×10^{-5}
dEWMA-based MPC	8.17×10^{-5}
MPC with no parameter estimation	5.51×10^{-4}

batch-to-batch dynamics of the process drift (e.g., drastic batch-to-batch fluctuations) are not captured with $m=7$. Therefore, the closed-loop simulation under the MPC with the proposed R2R model parameter estimation scheme with $m=7$ leads to the production of more off-spec crystals while crystals whose shapes are closer to a desired set-point value are produced under the MPC with $m=5$. Additionally, it is presented in Fig. 7 that the solubility at the beginning of each batch predicted by the proposed R2R model parameter estimation scheme with a horizon length of 5 is much closer to the true value than those with the moving horizon lengths of 4 and 7 for the given third-order polynomial.

For a given horizon length, the performance for parameter estimation increases with the order of polynomials due to additional degrees of freedom, then its performance decreases with the order increase as a higher order polynomial overfits the process and measurement noise. For a horizon length of $m=5$, which is found to be optimal from the previous analysis, the performance of the proposed R2R model parameter estimation scheme is tested with respect to different functions for Eq. (16e) such as second-, third-, and fourth-order polynomials. Subsequently, it is shown in Fig. 8 that the average crystal shape of the crystals produced from a batch process under the MPC with the proposed R2R model parameter estimation scheme with a third-order polynomial is closer to a desired set-point value compared to those of the MPC with second- and fourth-order polynomials. Additionally, it is presented in Fig. 9 that the solubility predicted by the proposed R2R model parameter estimation scheme based on MHE concepts with a third-order polynomial is much closer to the true value than those with second- and fourth-order polynomials for a given horizon length. Therefore, we can conclude that a horizon length of $m=5$ and a third-order polynomial is indeed optimal. We note that the proposed R2R model parameter estimation scheme is not applied to the batch crystallization process until the second batch run because at least two post-batch measurements are required to apply the polynomial regression scheme for the prediction of the batch-to-batch dynamics of the process drift. Additionally, it is possible that, if a process drift in a particular batch is significantly off from the dominant trend in the batch-to-batch dynamics of a process drift, it cannot be easily modeled by a function. For example, the 11th batch run in Figs. 7 and 9 cannot be appropriately modeled by any polynomial, which results in a poor controller performance by the MPC with the proposed R2R model parameter estimation scheme as is shown in Fig. 10.

The controller performance of the MPC with the proposed R2R model parameter estimation scheme is also compared with those of the dEWMA-based MPC and MPC with the nominal process model. In Fig. 10, it is evident that the MPC with the nominal process model is not able to handle the process drift described in Fig. 3, and as a result it may lead to the production of crystals with an undesired shape distribution. Furthermore, the production of crystals whose shapes are relatively closer to a desired set-point is achieved under the dEWMA-based MPC, which demonstrates that this scheme is more suitable for process drifts of a more random nature. We summarize the performance of the MPC with the proposed R2R model parameter estimation, dEWMA-based MPC, and MPC with the nominal process model in response to the process drift described in Fig. 3 by comparing their MSE values in Table 3.

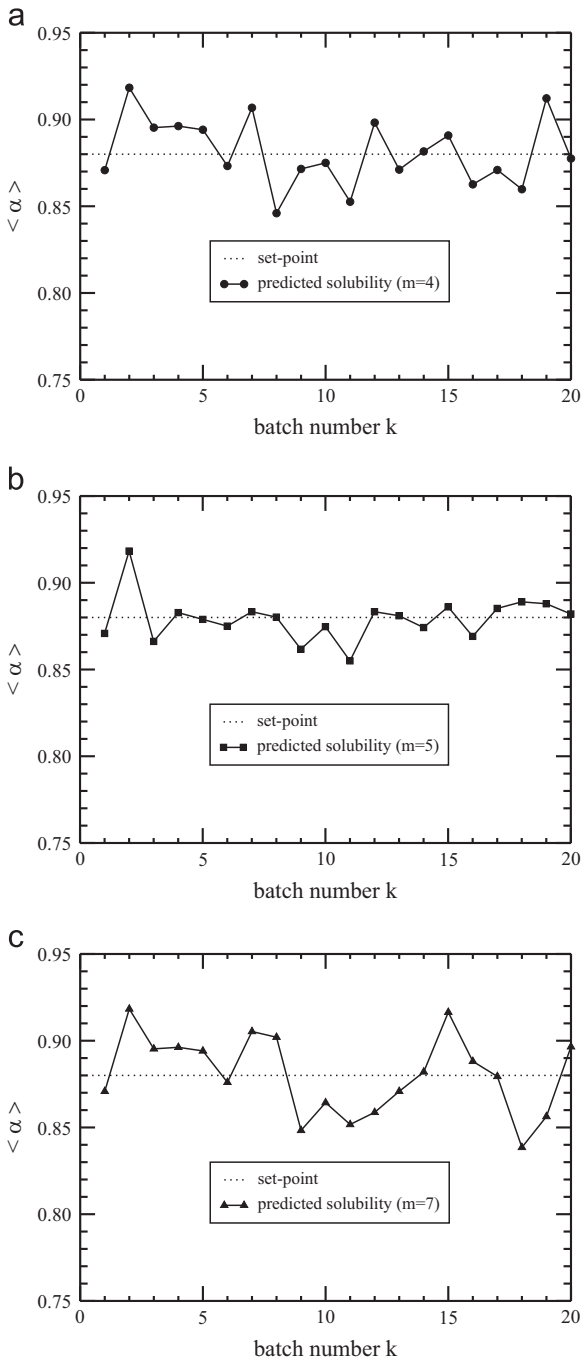

Fig. 6. The evolution of the average crystal shape obtained from the kMC simulations from batch-to-batch under the MPC with the proposed R2R model parameter estimation for the process drift described in Fig. 3. Different moving horizon lengthes ($m=4$, 5, and 7) are used in order to estimate the batch-to-batch dynamics of the process drift.

Since each batch has its own average crystal shape at the end of the process, there is a distribution for the average crystal shapes from all the batches (from 1st to 20th batch runs). In this work, we define the distribution as a batch-wise crystal shape distribution as follows: a good batch-wise crystal shape distribution should have small batch-to-batch variations and its average should be close to a set-point value, while a poor batch-wise crystal shape distribution has large batch-to-batch variations and its average is away from a set-point value. In order to compare the batch-wise crystal shape distributions obtained from the closed-loop simulations under different control schemes, a quantile plot is presented

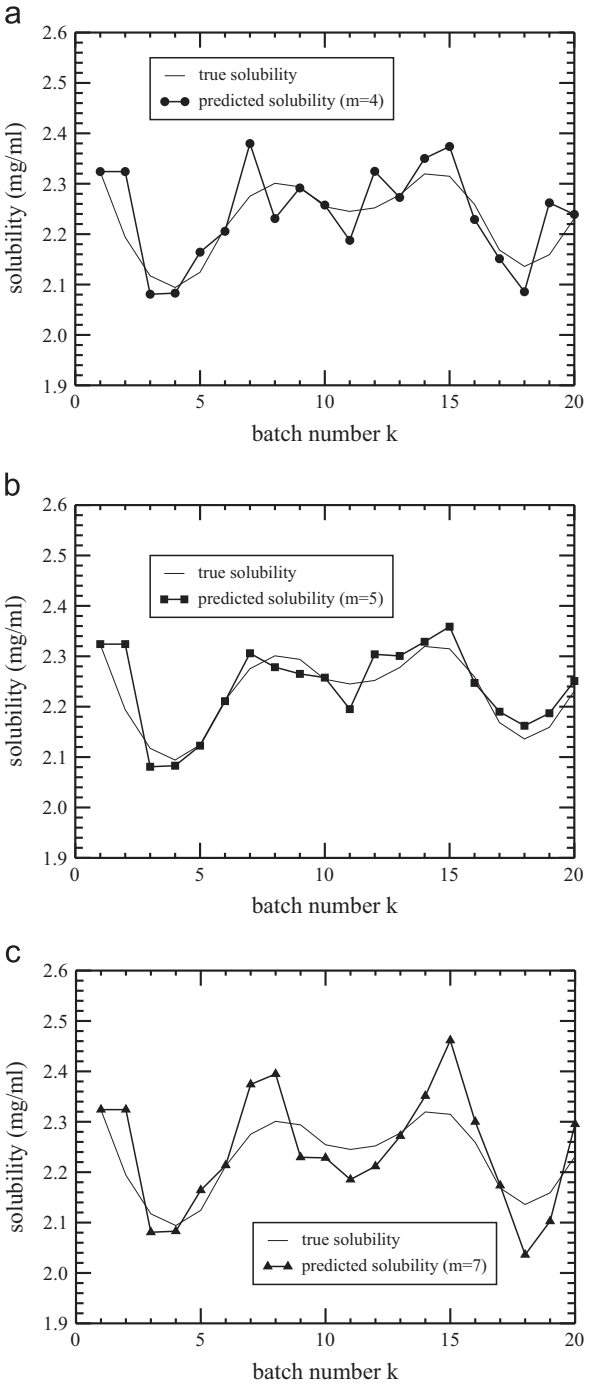

Fig. 7. The evolution of the predicted and true solubilities in the beginning of batch runs. The predicted solubility is calculated using the proposed R2R model parameter estimation scheme. Different moving horizon lengthes (m=4, 5, and 7) are used in order to estimate the batch-to-batch dynamics of the process drift.

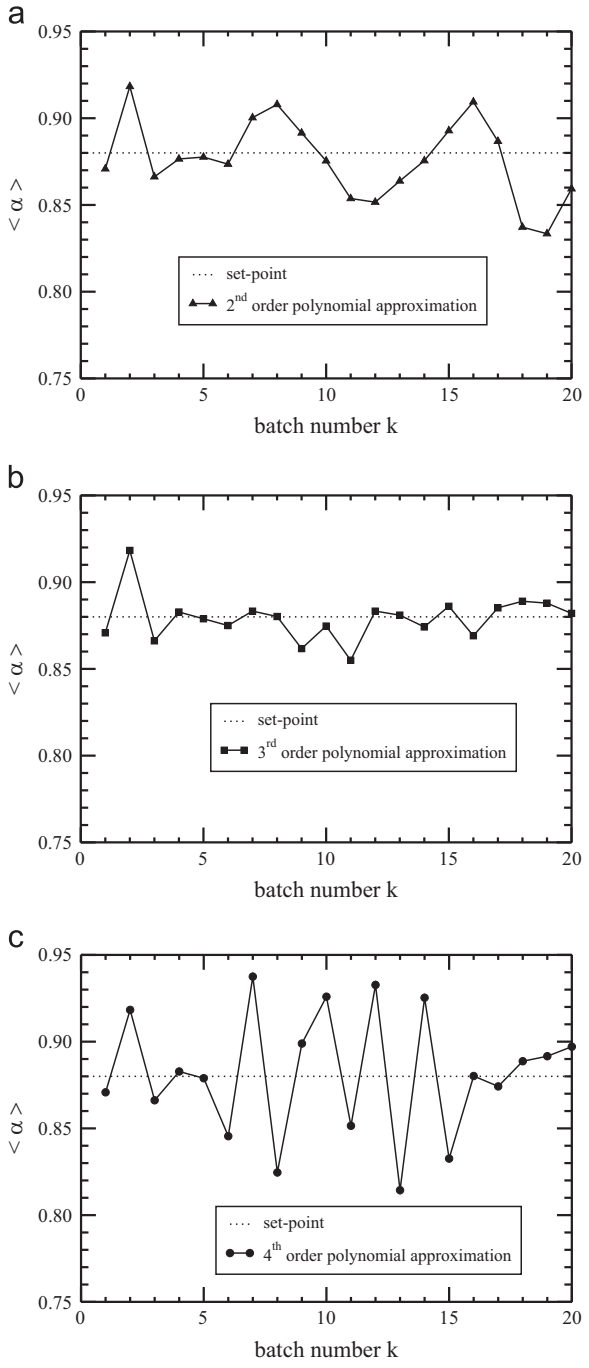

Fig. 8. The evolution of the average crystal shape obtained from the kMC simulations from batch-to-batch under the MPC with the proposed R2R model parameter estimation for the process drift described in Fig. 3. Different orders of polynomial expressions are used in order to estimate the bath-to-batch dynamics of the process drift. (a) Second-order polynomial approximation. (b) Third-order polynomial approximation. (c) Fourth-order polynomial approximation.

in Fig. 11 where the batch-wise crystal shape distribution obtained under the MPC with the proposed R2R model parameter estimation scheme is found to be better than those of the MPC with the nominal process model and dEWMA-based MPC. Furthermore, the quantile plot indicates that the average of the points obtained under the proposed MPC with R2R model parameter estimation scheme is very close to a desired set-point value, $\langle \alpha_{set} \rangle = 0.88$. Therefore, the process drift described in Fig. 3 was properly modeled by the proposed R2R model parameter estimation scheme based on MHE concepts with a third-order polynomial for the moving horizon length of 5.

Remark 3. The implementation of the proposed R2R model parameter estimation scheme based on MHE concepts can guarantee the best performance for a given moving horizon length when an appropriate function is chosen for the modeling of the batch-to-batch dynamics of the process drift. Once the batch-to-batch dynamics of the process drift is modeled well using a function, the proposed scheme becomes robust with respect to a rapidly changing process drift, while the dEWMA scheme may suffer from convergence issues given the difficulty in choosing the learning factors, w_1 and w_2.

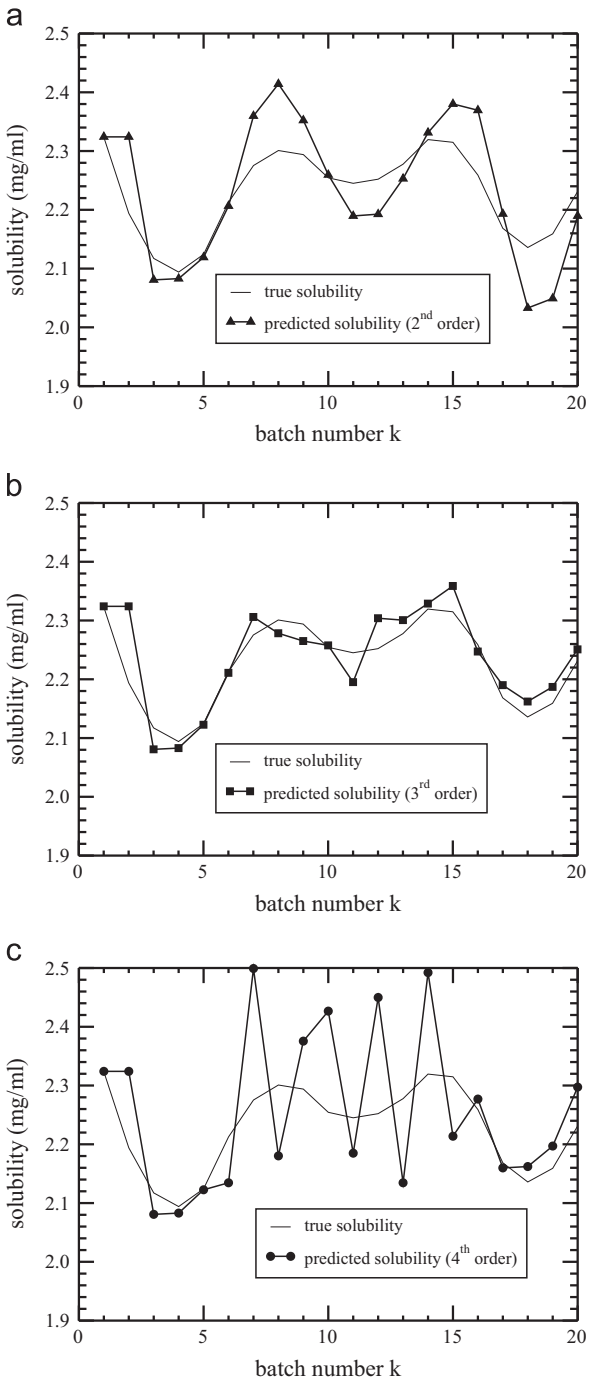

Fig. 9. The evolution of the predicted and true solubilities in the beginning of batch runs. The predicted solubility is calculated using the proposed R2R model parameter estimation scheme. Different orders of polynomial expressions are used in order to estimate the batch-to-batch dynamics of the process drift. (a) Second-order polynomial approximation. (b) Third-order polynomial approximation. (c) Fourth-order polynomial approximation.

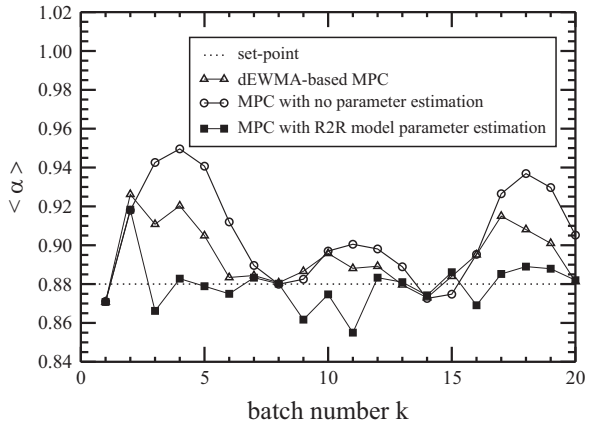

Fig. 10. The evolution of the average crystal shape obtained from the kMC simulations from batch-to-batch under the MPC with the proposed R2R model parameter estimation scheme, dEWMA-based MPC with ($w1$,$w2$)=(0.5,0.5), and MPC with no parameter estimation, for the process drift described in Fig. 3.

Table 3
Comparison among the MPC with R2R model parameter estimation, dEWMA-based MPC, and MPC with no parameter estimation in response to the process drift described in Fig. 3.

Control schemes	MSE
MPC with R2R model parameter estimation	3.62×10^{-4}
dEWMA-based MPC	4.45×10^{-4}
MPC with no parameter estimation	1.25×10^{-3}

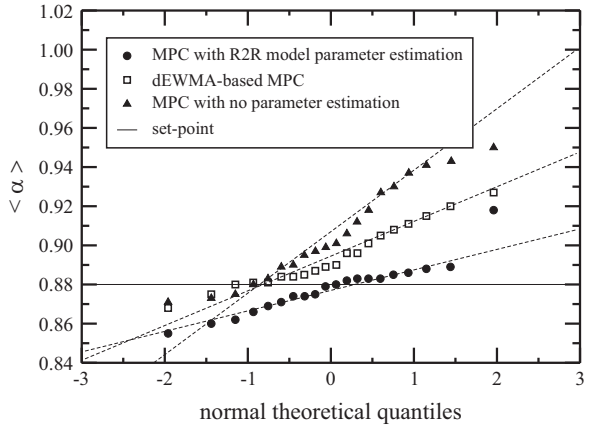

Fig. 11. The quantile plot for the distributions of the average crystal shapes obtained from the kMC simulations from batch-to-batch under the MPC with the proposed R2R model parameter estimation scheme, dEWMA-based MPC with ($w1$, $w2$)=(0.5,0.5), and MPC with no parameter estimation, for the process drift described in Fig. 3. Note that the dotted lines represent standard normal distributions for each data set and the unit for the x-axis is in standard deviation.

5. Conclusions

In this work, we proposed an R2R model parameter estimation scheme based on a moving horizon approach in order to model batch-to-batch parametric drift using a polynomial regression scheme. Then, the batch process model parameters computed by the proposed parameter estimation scheme are used in an MPC within each batch to compute a set of optimal jacket temperatures for the production of crystals with a desired shape distribution. The ability of the proposed parameter estimation scheme to suppress the inherent variation in the solubility incurred by batch-to-batch drift and deal with the noise in real-time and post-batch measurements was demonstrated by applying the MPC with the proposed estimation scheme to a kMC simulation of a batch crystallization process used to produce HEW lysozyme crystals. The performance of the proposed R2R model parameter estimation scheme was evaluated with respect to the use of different orders of polynomials and different moving horizon lengths. Lastly, for comparison purposes, the performance of the MPC with the proposed R2R model parameter estimation scheme was favorably compared with those of the MPC based on the nominal process model and dEWMA-based MPC.

Acknowledgments

The authors gratefully acknowledge the financial support from the Extreme Science and Engineering Discovery Environment (TG-CCR120003), the National Science Foundation (CBET-0967291), the National Science Foundation of China (Grant no. 61473287) and the NSF Graduate Research Fellowship (DGE-1144087) given to Michael Nayhouse.

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