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Handling Parametric Drift in Batch Crystallization Using Predictive Control with R2R Model Parameter Estimation ⋆

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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. Then, a model predictive controller (MPC) with the proposed parameter estimation scheme is applied to a kinetic Monte Carlo (kMC) simulation model of a batch crystallization process used to produce hen-egg-white (HEW) lysozyme crystals. 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 that of MPC based on the nominal process model.

Keywords: run-to-run control, parameter estimation, moving horizon estimation, model predictive control, batch crystallization, crystal shape control

1. INTRODUCTION

Batch configuration is one of the most widely used reactor and crystallization configurations in the specialty chemicals and pharmaceutical industries. However, unknown systematic trends or drifts in the process parameter values, for example, in initial pH level, operating conditions, and impurity concentrations in raw materials (e.g., Flores-Cerrillo and MacGregor (2004)) may be challenging from the standpoint of 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.

In general, common uncertainties in batch processes include fully stochastic (random) variations (e.g., noise in the measurements) and process drift of repetitive nature. 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 can not be explicitly taken into account in the EKF design Haseltine and Rawlings (2005).

The best known method for handling batch-to-batch drift is the 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 Simith et al. (1998); Chen and Guo (2001); Castillo and Rajagopal (2002); Su and Hsu (2004); Wu and Maa (2011); Kwon et al. (2014a, 2015). 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.

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. Specifically, the key elements of the proposed R2R model parameter estimation scheme based on MHE concepts are: 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., 2^{nd}, 3^{rd} or 4^{th}

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order polynomials) that are 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 manuscript 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. 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. Lastly, the closed-loop performance of the MPC with the proposed R2R model parameter estimation scheme is compared with that of 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 at 4%(w/v) NaCl and pH=4.5, the lysozyme crystals are nucleated according to the following rate expressions Galkin and Vekilov (2001):

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

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

$$\sigma = \ln(C/s) \tag{2}$$

where C is the solute concentration and s is the solubility, which is calculated using the following third-order polynomial equation taken from Ref. Cacioppo and Pusey (1991):

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

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:

$$r_a = K_0^+ \exp(\sigma) \tag{4}$$

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:

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

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., $i = 4$). The migration rate, $r_m(i)$, is shown below:

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

The crystal growth rates obtained from the kMC simulations are calibrated with the experimental data in literature by manipulating a set of E_{pb} and ϕ values for (110) and (101) faces through extensive open-loop kMC simulations. The reader may refer to Kwon et al. (2013) for more details regarding the execution of the kMC simulation.

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:

$$\frac{dC}{dt} = -\frac{\rho_c}{V_{batch}}\frac{dV_{crystal}}{dt} \tag{7}$$

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

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 $\cdot$ kg is the specific heat capacity, $A_c = 0.25$ m^2 and $U_c = 1800$ kJ/m^2·h $\cdot$ K are the area and the overall heat transfer coefficients between the jacket stream T_j and the crystallizer wall, respectively. These values are taken from Shi et al. (2005).

2.4 Moment model

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 moment 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:

$$\frac{dM_0}{dt} = B \tag{9}$$

$$\frac{dM_1}{dt} = G_{vol} M_0 \tag{10}$$

where $M_j(t) = \int_0^\infty V^j n(V,t) dV$ is the j^{th} 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:

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

where $\langle h_{110}\rangle$ and $\langle h_{101}\rangle$ are the average crystal heights in the direction of the (110) and (101) faces, G_{110} and G_{101} are the crystal growth rates in the direction of the

(110) and (101) faces, which can be obtained through the following expressions:

$$\begin{aligned} G_{110} &= 0.1843\sigma^3 - 1.1699\sigma^2 + 2.8885\sigma - 2.5616 \\ G_{101} &= 0.1893\sigma^3 - 1.2264\sigma^2 + 2.9887\sigma - 2.5348 \end{aligned} \tag{12}$$

and

$$\begin{aligned} \frac{d\langle h_{110}\rangle}{dt} &= G_{110} - \frac{BV_{batch}\langle h_{110}\rangle}{M_0} \\ \frac{d\langle h_{101}\rangle}{dt} &= G_{101} - \frac{BV_{batch}\langle h_{101}\rangle}{M_0} \end{aligned} \tag{13}$$

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

$$\langle\alpha\rangle \approx \frac{\langle h_{110}\rangle}{\langle h_{101}\rangle} \qquad \langle V\rangle = \frac{M_1}{M_0} \tag{14}$$

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).

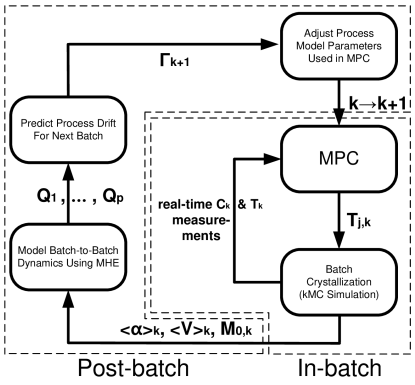

Fig. 1. Model predictive control with R2R model parameter estimation.

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 temperature 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:

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

$$\text{s.t.} \quad \text{Eqs. } (1)-(3) \text{ and } (7)-(14) \tag{15b}$$

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

where $p = 10$ is the length of the prediction horizon, Δ=40 seconds is the sampling time, $t_i = t + i\Delta$ and $T_{j,i}$ are the time and the jacket temperature of the i^{th} 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.

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 n^{th} batch run is formulated as follows:

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

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

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

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

$$\hat{G}_{101}(k) = \gamma_{101}(k)G_{101}(k) \tag{16e}$$

$$\gamma_x(k) = \sum_{r=1}^{p} q_{(x,r)} \left[\gamma_x(k-1)\right]^r \tag{16f}$$

$$\forall\gamma_x \in [\gamma_{110}\ \gamma_{101}\ \gamma_s\ \gamma_\alpha\ \gamma_V] \tag{16g}$$

where 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.

Referring to Eq. (16), we note that Eq. (16g) is used in order to approximate the batch-to-batch parameter drift from the $k-m+1$ to k batch run with a p^{th} order polynomial through the manipulation of the decision variables, $\underline{Q}_1 = [q_{(110,1)}\ q_{(101,1)}\ q_{(s,1)}\ q_{(\alpha,1)}\ q_{(V,1)}]$, $\cdots$, $\underline{Q}_p = [q_{(110,p)}\ q_{(101,p)}\ q_{(s,p)}\ q_{(\alpha,p)}\ q_{(V,p)}]$ in a moving horizon fashion. For example, the p^{th} order polynomial for the correction factor $\gamma_s(k)$ can be written in the form of $\gamma_s(k) = \sum_{r=1}^{p} q_{(s,r)} [\gamma_x(k-1)]^r$. Then, the batch-to-batch dynamics of the process drift is estimated by using Eq. (16g) 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, $\widehat{\langle\alpha(t_f)\rangle}$ and $\widehat{\langle V(t_f)\rangle}$, 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).

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 k^{th} batch run, the post-batch measurements of the product qualities such as the number of crystals and the average size and 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 over the last m measurements (i.e., moving horizon length) are used to compute $\underline{Q}_1$, $\cdots$, $\underline{Q}_p$ that minimize the cost function, Eq. (16a).
(3) The one-step-ahead correction factors for the $k+1$ batch run, $\hat{\underline{\Gamma}}_{k+1}$, are predicted through the use of $\underline{Q}_1$, $\cdots$, $\underline{Q}_p$ obtained from Step 2. Then, the process model parameters are updated through $\hat{\underline{\Gamma}}_{k+1}$ 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.

The controller performance of the MPC with the proposed R2R model parameter estimation scheme is evaluated in response to a process drift whose rate fluctuates from batch-to-batch (see, e.g., Fig. 2). 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 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 $(\langle\alpha(t_f)\rangle_i - \alpha_{\text{set}})$ between the measured average crystal shape after the i^{th} batch run and the set-point value is introduced as follows:

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

where n is the total number of batch runs.

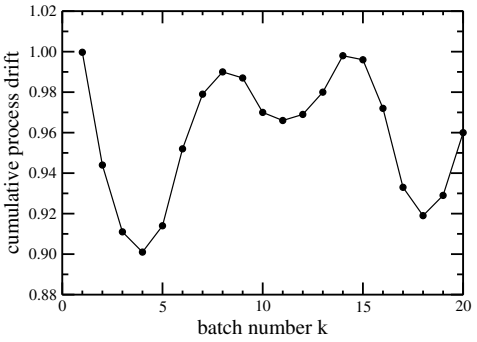

Fig. 2. The evolution of the cumulative process drift where its rate changes from batch-to-batch. Please note that the y-axis implies how much the batch system is perturbed from a nominal batch system (nominal batch system corresponds to y-axis value equal to 1).

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 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:

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

where $\widetilde{\langle\alpha(t_f)\rangle}_k$ is the predicted average crystal shape at the end of the k^{th} batch, $\widehat{\langle\alpha(t_f)\rangle}_k$ 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 k^{th} 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:

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

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

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

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

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.

Please 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 Sensitivity to process drift

In this section, we consider a complicated drift. As is shown in Fig. 2, the rate of this process drift changes rapidly from batch-to-batch (e.g., the system drifts from 1 to 0.9 over the first 4 batch runs), 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. In Fig. 3, it is evident that the MPC with the proposed R2R model parameter estimation scheme is able to handle the process drift described in Fig. 2, and as a result the production of crystals whose shapes are relatively closer to a desired set-point is compared to those achieved under the dEWMA-based MPC and MPC with the nominal process model. We summarize the performance of three different control schemes in response to the process drift described in Fig. 2 by comparing their MSE values in Table 1.

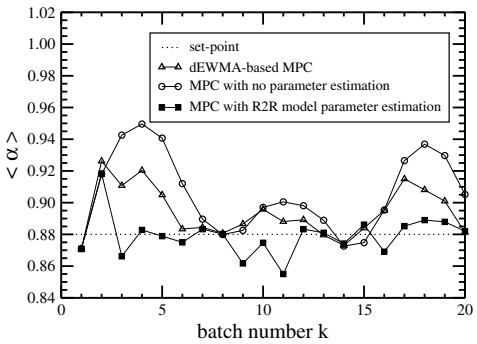

Fig. 3. The evolution of the average crystal shape obtained from the kMC simulations from batch-to-batch under different control schemes, for the process drift described in Fig. 2.

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}

Table 1. Comparison among different control schemes in response to the process drift described in Fig. 2.

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, $\langle\alpha_{\text{set}}\rangle = 0.88$. Therefore, the process drift described in Fig. 2 was properly modeled by the proposed R2R model parameter estimation scheme based on MHE concepts with a 3rd order polynomial for the moving horizon length of 5.

Finally, for the purpose of a test of the control performance with respect to unmodeled uncertainty in the nucleation rate from a controller point of view, the nucleation rate in the kMC simulation is dropped by 10% by multiplying 0.9 to Eq. 1. Since this uncertainty is not modeled in the process model used in the parameter estimation scheme (Eq. (16)), the other parameters $\underline{\Gamma}=[\gamma_{110}\ \gamma_{101}\ \gamma_s\ \gamma_\alpha\ \gamma_V]$ have to be adjusted to compensate for the unmodeled uncertainty in the nucleation rate. As a result, it is shown in Fig. 4 that the controller model parameters are appropriately adjusted and thus the effect of the unmodeled uncertainty to the control performance is properly suppressed achieving the production of crystals with a shape which is close to the desired set-point. The remaining offset from a desired set-point is sometimes expected because of

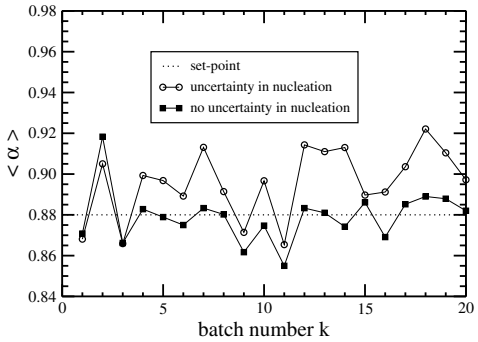

Fig. 4. The evolution of the average crystal shape obtained from the kMC simulations from batch-to-batch under the MPC with the proposed R2R model parameter estimation scheme for two cases when there is an unmodeled uncertainty in the nucleation rate vs. no uncertainty in the nucleation rate, for the process drift described in Fig. 2. The desired set-point is $\langle \alpha_{\text{set}} \rangle = 0.88$.

the nonlinear nature of the unmodeled uncertainty in the nucleation rate. The crystal shape distribution obtained by the proposed R2R model parameter estimation scheme in Fig. 5 is closer to the desired set-point than that of case when there is an unmodeled uncertainty. To deal with this problem, a correction factor for the uncertainty in the nucleation rate can be directly introduced in order to improve the robustness of the MPC with the proposed R2R model parameter estimation scheme with respect to unmodeled uncertainties.

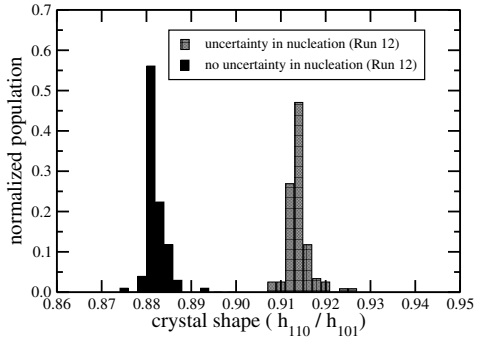

Fig. 5. The normalized crystal shape distributions at $t = 20000$ seconds obtained from the kMC simulations under the MPC with the proposed R2R model parameter estimation scheme. The desired set-point is $\langle \alpha_{\text{set}} \rangle = 0.88$.

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 MPC with the proposed estimation scheme is applied to a kMC simulation of a batch crystallization process used to produced HEW lysozyme crystals. 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.

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