Integrated B2B-NMPC Control Strategy for Batch/Semibatch Crystallization Processes

Qinglin Su
Dept. of Chemical and Biomolecular Engineering, National University of Singapore, 117576, Singapore

Davidson School of Chemical Engineering, Purdue University, West Lafayette, IN 47906

Min-Sen Chiu
Dept. of Chemical and Biomolecular Engineering, National University of Singapore, 117576, Singapore

Richard D. Braatz
Dept. of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139

DOI 10.1002/aic.15810
Published online June 15, 2017 in Wiley Online Library (wileyonlinelibrary.com)

The uncertainty in crystallization kinetics is of major concern in manufacturing processes, which can result in deterioration of most model-based control strategies. In this study, uncertainties in crystallization kinetic parameters were characterized by Bayesian probability distributions. An integrated B2B-NMPC control strategy was proposed to first update the kinetic parameters from batch to batch using a multiway partial least-squares (MPLS) model, which described the variances of kinetic parameters from that of process variables and batch-end product qualities. The process model with updated kinetic parameters was then incorporated into an NMPC design, the extended prediction self-adaptive control (EPSAC), for online control of the final product qualities. Promising performance of the proposed integrated strategy was demonstrated in a simulated semibatch pH-shift reactive crystallization process to handle major crystallization kinetic uncertainties of L-glutamic acid, wherein smoother and faster convergences than the conventional B2B control were observed when process dynamics were shifted among three scenarios of kinetic uncertainties. © 2017 American Institute of Chemical Engineers *AIChE J*, 63: 5007–5018, 2017
Keywords: B2B-NMPC, crystallization, pH-shift, semibatch, process control

Introduction

In industrial manufacturing practice, batch process is repeatedly proceeded with routine recipes to produce various customized products, for example, batch/semibatch crystallization is repeated with a cooling or antisolvent addition trajectory to separate and purify pharmaceutical and fine chemical ingredients. The repetitive nature in turn helps to boost the learning-type control strategies, such as iterative learning control (ILC) and batch-to-batch (B2B) or run-to-run (R2R) controls.[1] Batch-to-batch control uses information obtained from previous batches to optimize operation for the next batch with an aim to improve the tracking of final product qualities, which can also address the problems of process uncertainties or unmeasured disturbances in batch processes.[2] The latter is of great significance when common uncertainties in crystallization kinetics due to mixing conditions, impurities, fouling, and so forth often downgrade the performances of most solely model-based control strategies.

Batch-to-batch control, which was first proposed in the beginning of 1990s,[3,4] has been studied extensively in the past decades (see Refs. 5, 6 and the references cited therein). For example, Clarke-Pringle and MacGregor (1998) introduced batch-to-batch adjustments to optimize polymer molecular-weight distributions.[7] Doyle et al. (2003) developed a batch-to-batch control based on hybrid model to realize particle-size distribution control.[8] Zhang (2008) reported a batch-to-batch optimal control of a batch polymerization process based on stacked neural network models.[9] However, B2B control strategies often suffer from its open-loop nature, as the correction is not made until the next batch. Conversely, with the ability of online control strategies, such as model predictive control (MPC) to respond to disturbances occurring during the batch, and the batch-to-batch control to correct bias left uncorrected, integration of both strategies becomes interesting to researchers.[10,11] Recent implementations of the integrated batch-to-batch and online control for product quality improvement of batch crystallizers were reported in Refs. 12 and 13. For example, an integrated B2B-NMPC design in the form of a hybrid model was recently developed for a batch polymorphic crystallization process.[13] The hybrid model, consisting of a nominal first-principles model and a series of correction factors based on batch-to-batch updated partial least square (PLS) models, was used to predict the process variables and final product qualities. The major benefit of such hybrid model was its ability to harness the extrapolative prediction capability of

Correspondence concerning this article should be addressed to M.-S. Chiu at checms@nus.edu.sg.

the first-principles model while the PLS models provided a means for simple model updating.

Encouraged by the previous works and the benefits of integrated B2B-NMPC control strategy, a new integrated B2B-NMPC control strategy is proposed in this study. Note that previous efforts tend to concentrate on the update of model prediction in the form of a hybrid process model. For example, a bias term or a correction factor for final product quality is measured after the finish of a batch or calculated from a historical operating database, respectively, and is added to the model prediction of that quality variable to be used in the online control of the next batch.[9,13] Addition of these accessional terms assumes that same deviations will persist during the next batch. Though simple and efficient in some batch processes, it may not work properly for a nonlinear or complex batch process, particularly when online control is combined with a B2B control scheme as they work at a relatively different time scale.

To the contrary, the batch-to-batch update of the process model in our proposal of B2B-NMPC framework considered a more direct manner. Hereby, we first assumed that major process dynamics can be described by a first-principle process model and any uncertainties in the process system dynamics were reflected as the uncertainties in the corresponding kinetic parameters, viz., the model structure is correct and the process kinetic parameters are observable.[14,15] Therefore, it is of practical importance for model-based control strategies to detect the change of system dynamics due to process uncertainties and re-estimate the model parameters. Specifically, the recent works by Kwon et al. (2015) and Mockus et al. (2015) also added to the importance of detecting the kinetic shift or variations in batch operations.[16,17] Other than perform the routine model parameter estimation which is really time consuming, a multiway partial least-squares (MPLS) model utilizing measurements of the previous batch, for example, initial conditions, process variable trajectories, and final product qualities, was adopted to re-estimate the kinetic parameters.[18] The MPLS is a typical multivariate statistical process control (MSPC) tool and has been commonly used to monitor the batch process with a special predictive capability for final product qualities. Instead of predicting the final product qualities, herein it is assumed that the variance in the process kinetic parameters can be explained and predicted together by the variance of the process operating conditions during the batch and the final product qualities at the batch end. In such, the proposed framework performs the online control during the batch with batch-to-batch updated model kinetic parameters to achieve consistent final product qualities and to handle constraints and disturbances/uncertainties within the batch.[12,13]

This article is organized as follows. First, the MPLS method is briefly described in the next section. Then a conventional B2B control strategy based on the MPLS model is introduced, which is followed by the proposed integrated B2B-NMPC control strategy. Applications of the B2B and integrated B2B-NMPC to a semibatch pH-shift reactive crystallization of L-glutamic acid are illustrated in the Results and Discussion section. Lastly, concluding remarks based on their control performances are given.

Multiway Partial Least Squares

A historical database with nominal process data is usually needed when implementing multivariate statistical process control (MSPC) methods, like principal component analysis

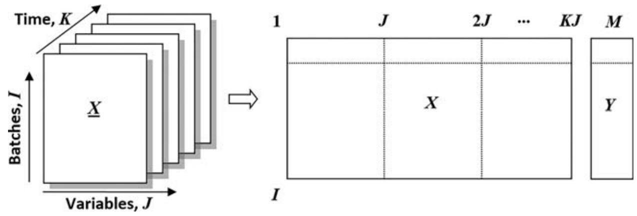

Figure 1. Batch-wise unfolding of batch process data.

(PCA) or partial least squares (PLS), for process monitoring purpose.[19] The variation within the database serves as a reference distribution, against which the performance of independent new batches can then be compared and thus monitored.[20] In batch manufacturing, process data are composed of three dimensional array $\underline{X}$ ($I \times J \times K$), where I is the number of batches, J is the number of variables, and K is the number of sampling times in a given batch. To apply the MSPC methods, $\underline{X}$ should be rearranged into a 2-D dataset X ($I \times JK$) as shown in Figure 1 by the widely applied batch-wise unfolding method, which captures the correlation information of the variables both within-time and time to time.[21] Besides, measurements of batch-end product quality variables, for example, $\mathbf{Y}$ ($I \times M$), where M is the number of final quality variables, could also be considered in the database.

The multiway partial least squares (MPLS) is equivalent to performing ordinary PLS on the unfolded 2-D measurement data $\mathbf{X}$ and product quality data $\mathbf{Y}$. For example, MPLS decompose the $\mathbf{X}$ and $\mathbf{Y}$ matrices into a summation of np scores vectors ($\mathbf{t}_r$) and loading vectors ($\mathbf{p}_r$ and $\mathbf{q}_r$), plus residual matrices $\mathbf{E}$ and $\mathbf{F}$

$$\mathbf{X}=\sum_{r=1}^{r=np}\mathbf{t}_r\mathbf{p}_r^T+\mathbf{E} \tag{1}$$

$$\mathbf{Y}=\sum_{r=1}^{r=np}\mathbf{t}_r\mathbf{q}_r^T+\mathbf{F} \tag{2}$$

This decomposition summarizes and compresses the data of $\mathbf{X}$ and $\mathbf{Y}$ into low dimensional spaces that describe the operation of the process.[18] In addition, it also provides predictions of the final product qualities, as by the predictive capability of the PLS model. Applications and extensions of this method have also been reported extensively. For example, to address the uneven batch time problem, handling methods were reported, such as using rescaled batch time as a maturity index, tracking the batch progress with an indicator variable, or using local batch time as the response vector.[20]

With the recent development of *in situ* real-time measurements for crystallization processes,[22,23] such as attenuated total reflection Fourier transform infrared spectroscopy (ATR-FTIR) for solute concentration, focused beam reflectance measurement (FBRM) and particle vision measurement (PVM) for crystal size and shape, and Raman spectroscopy for polymorphic purity, more and more process data are now becoming readily available for developing multivariate statistical tools, such as MPLS, to efficiently monitor, diagnose, and control of crystallization processes, which are critically important for various reasons such as safety, consistency, and quality improvement.[24]

Batch-to-Batch Control Strategy

A conventional batch-to-batch control strategy based on the interaction of a first-principles process model and a multiway partial least squares model is introduced in this section, the benefit of which lies in its ability to exploit the extrapolative power of a first-principles model to optimize the process operation while the inevitable model-plant mismatch resulting from process uncertainties is addressed through a batch-to-batch model refinery by MPLS model.

From the perspective of Baye's theory, unknown model parameter shows a probability distribution (**Pr**) of certain shape,[25] which is distinct from the classical notion of treating a model parameter as a fixed but unknown quantity. Rigorous procedures, such as design of experiments (DoE), are generally required to describe these probability distributions.[26] Although effective they are not efficient to be used online, particularly, for large and complex systems due to the heavy cost in experimental and computational efforts.[27] To this end, an alternative simple but efficient method based on a multivariate statistical tool is proposed for the B2B scheme in this study.

Frist, when provided with enough system dynamic information from proper experiments, for example, *in situ* online measurement profiles and batch-end product qualities of batch crystallization processes, probability distributions of unknown kinetic parameters in the process model could be estimated by Bayesian inference.[27] The main idea of Bayesian inference lies in Bayes' rule

$$\mathrm{Pr}\,(\boldsymbol{\theta}|\mathbf{x})=\frac{\mathrm{Pr}(\mathbf{x}|\boldsymbol{\theta})\mathrm{Pr}\,(\boldsymbol{\theta})}{\mathrm{Pr}\,(\mathbf{x})} \tag{3}$$

where $\boldsymbol{\theta}$ is a vector of unknown parameters and $\mathbf{x}$ is a vector of the observations, such as measurements of state variables at different time points, to be used to infer $\boldsymbol{\theta}$. $\mathrm{Pr}\,(\boldsymbol{\theta})$ is the prior distribution of $\boldsymbol{\theta}$; $\mathrm{Pr}(\mathbf{x}|\boldsymbol{\theta})$ is referred as the sampling distribution for fixed parameters $\boldsymbol{\theta}$; and $\mathrm{Pr}\,(\boldsymbol{\theta}|\mathbf{x})$ is the Bayesian posterior distribution of $\boldsymbol{\theta}$ provided the measurement of $\mathbf{x}$; $\mathrm{Pr}\,(\mathbf{x})$ acts as a normalizing constant to ensure that the Bayesian posterior integrates to unity. One of the merits of Bayesian inference is that it can update existing probability distribution with new observation, that is, the existing posterior distribution $\mathrm{Pr}\,(\boldsymbol{\theta}|\mathbf{x})$ can act as the prior distribution of $\mathrm{Pr}\,(\boldsymbol{\theta})$ when new measurement $\mathbf{x}$ arrives. In such way, when a batch is finished, theoretically it is possible to update the model parameters' probability distributions and use their mode values in the distributions as new parameters. However, the Bayesian inference based on the classical Markov Chain Monte Carlo (MCMC) simulation would take too many samplings to reach a converged distribution,[27] making it impractical to be used with on-line control strategies and swift batch-to-batch model update.

Hereinto, another way to conveniently deal with the process model and its corresponding Bayesian parameter probability distributions is to use the multivariate statistical tools, that is, the MPLS. The MPLS model, which was previously used for process monitoring and batch-end product quality prediction, could now serve similar purpose in that it interprets, statistically, the relationship between process dynamics and its model parameters' probability distributions, viz., the MPLS uses the initial conditions, measurement trajectories, and batch-end product qualities to form an unfolded dataset $\mathbf{X}$ to predict the model parameters $\boldsymbol{\theta}$ which forms the vector $\mathbf{Y}$.[18]

The initial database for such MPLS model could be simply generated by running the first-principles process model repeatedly with combinations of kinetic parameters sampled from their probability distributions $\mathrm{Pr}\,(\boldsymbol{\theta}|\mathbf{x})$ and with nominal operating conditions subject to normal disturbances. As this database is generated offline, selections of measurement profiles

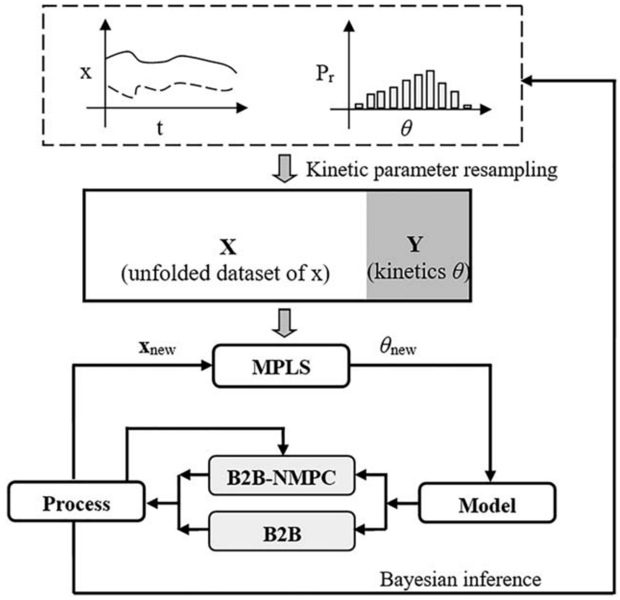

Figure 2. The schemes of B2B and B2B-NMPC control strategies based on a MPLS model and Bayesian inference.

and product quality variables, as well as the size of the database and number of principle components used in MPLS, can be well trained to give predictions of model parameters with good accuracy. Herein, the assumption is that the nominal variations of kinetic parameters are within a modest range and can be predicted using the linear MPLS model, otherwise other nonlinear and complex empirical or data-based method should be considered, for example, neural network model.

When it comes to the prediction of kinetic parameters after each batch, similar procedures of MPLS as that used for process monitoring are considered.[18,20] For example, as illustrated in Figure 2, when the batch process reaches its end point, the measurement profiles are unfolded to form a 2-D array $\mathbf{x}_{\mathrm{new}}$, the corresponding $\boldsymbol{\theta}_{\mathrm{new}}$ will be calculated as follows

$$\mathbf{t}_{\mathrm{new}}=\left(\mathbf{W}_{np}^{T}\mathbf{P}_{np}\right)^{-1}\mathbf{W}_{np}\mathbf{x}_{\mathrm{new}} \tag{4}$$

$$\boldsymbol{\theta}_{\mathrm{new}}=\sum_{r=1}^{r=np}\mathbf{t}_{\mathrm{new},r}\mathbf{q}_{r}^{T} \tag{5}$$

Where $\mathbf{W}$ ($KJ \times np$) is the weight matrix in the PLS algorithm. Nevertheless, to avoid abrupt substantial changes in model parameters, averages of parameter predictions obtained from the previous batches are usually adopted as follows

$$\overline{\boldsymbol{\theta}}_{j}=\frac{1}{m}\sum_{k=j-m+1}^{j}\boldsymbol{\theta}_{k} \tag{6}$$

where $\overline{\boldsymbol{\theta}}_{j}$ is an average of parameter predictions for the jth batch based on those from the previous m batches, which is then incorporated into the first-principles process model embedded in the B2B control strategy as also illustrated in Figure 2. Furthermore, similar to other MPLS models for batch process monitoring,[24] the above model can also monitor the changes of kinetic parameters $\boldsymbol{\theta}$ whether they are within their nominal variations. If not, new historical process data can be collected and inferred with Bayesian inference to update the parameter probability distributions.

In the conventional B2B control framework, the following objective function to be minimized for the jth batch is considered

$$J_{\mathrm{B2B}}=\min_{\mathbf{U}}\ (\mathbf{P}-\mathbf{P}_d)^T\mathbf{W}_p(\mathbf{P}-\mathbf{P}_d)+\Delta\mathbf{U}^T\mathbf{W}_{\Delta\mathrm{U}}\Delta\mathbf{U}+d\mathbf{U}^T\mathbf{W}_{d\mathrm{U}}d\mathbf{U} \tag{7}$$

where

$$\mathbf{U}=\left[\mathbf{u}_{j,0}^T,\mathbf{u}_{j,1}^T,\cdots,\mathbf{u}_{j,N-1}^T\right]^T$$

$$\Delta\mathbf{U}=\left[\mathbf{u}_{j,1}^T-\mathbf{u}_{j,0}^T,\mathbf{u}_{j,2}^T-\mathbf{u}_{j,1}^T,\cdots,\mathbf{u}_{j,N-1}^T-\mathbf{u}_{j,N-2}^T\right]^T$$

$$d\mathbf{U}=\left[\mathbf{u}_{j,0}^T-\mathbf{u}_{j-1,0}^T,\mathbf{u}_{j,1}^T-\mathbf{u}_{j-1,1}^T,\cdots,\mathbf{u}_{j,N-1}^T-\mathbf{u}_{j-1,N-1}^T\right]^T$$

and $\mathbf{P}$ and $\mathbf{P}_d$ are the predicted and desired final product qualities, respectively, $\mathbf{u}_{j,k}$ is the input vector (e.g., antisolvent addition flowrate or jacket cooling temperature in crystallization process) at the kth sampling instant of jth batch, N is the total number of samples in one batch, $\mathbf{W}_p$ is the weight vector corresponding to the final product quality, $\mathbf{W}_{\Delta U}$ and $\mathbf{W}_{dU}$ are the weight matrices to penalize excessive changes in the input variables for within-batch and interbatch, respectively.

The above minimization problem is subject to the first-principles process model updated with $\boldsymbol{\theta}_{\mathrm{new}}$ after each batch and inequality constraints $\mathbf{H}(\mathbf{U})\leq 0$ if any. Differential evolution (DE),[13,28,29] or sequential quadratic programming (SQP) technique can be implemented to solve the above minimization problem.[30] The resulting optimal input $\mathbf{U}$ obtained is then implemented in an open-loop manner for the next batch.

Integrated B2B-NMPC Control Strategy

The main drawback of a conventional batch-to-batch control strategy results from its open-loop nature, where the correction is not made until the next batch. Therefore, the control performance of the current batch depends only on the accuracy of the process model, which is updated based on the information of previous batch. Consequently, its control performance may become sluggish or even diverging when the updated model is still not accurate, which is very likely the case in the first few batches when process dynamics shift.[13] In light of this, combinations of the best efforts of B2B and online control strategies receive great interest decade ago. In particular, it is possible and beneficial to couple the nonlinear model predictive control (NMPC) technique with the B2B control strategy to develop an integrated B2B-NMPC control strategy, wherein both control strategies complement each other in an interactively way such that the online control issue can be tackled effectively by NMPC whose embedded nonlinear process model is refined through the B2B control by re-estimating model parameters from previous batches.[12]

In the proposed integrated control strategy, the updating policy of the first-principles model in B2B as shown in Figure 2 remains the same. Whereas, the objective function to be minimized at every sampling time by NMPC is as follows

$$\begin{aligned}J_{\mathrm{B2B-NMPC}}=\min_{\mathbf{U}}\ &(\mathbf{P}-\mathbf{P}_d)^T\mathbf{W}_p(\mathbf{P}-\mathbf{P}_d)\\&+\Delta\mathbf{U}^T\mathbf{W}_{\Delta\mathrm{U}}\Delta\mathbf{U}+d\mathbf{U}^T\mathbf{W}_{d\mathrm{U}}d\mathbf{U}\end{aligned} \tag{8}$$

where

$$\mathbf{U}=\left[\mathbf{u}_{j,k}^T,\mathbf{u}_{j,k+1}^T,\cdots,\mathbf{u}_{j,N-1}^T\right]^T$$

$$\Delta\mathbf{U}=\left[\mathbf{u}_{j,k}^T-\mathbf{u}_{j,k-1}^T,\mathbf{u}_{j,k+1}^T-\mathbf{u}_{j,k}^T,\cdots,\mathbf{u}_{j,N-1}^T-\mathbf{u}_{j,N-2}^T\right]^T$$

$$d\mathbf{U}=\left[\mathbf{u}_{j,k}^T-\mathbf{u}_{j-1,k}^T,\mathbf{u}_{j,k+1}^T-\mathbf{u}_{j-1,k+1}^T,\cdots,\mathbf{u}_{j,N-1}^T-\mathbf{u}_{j-1,N-1}^T\right]^T$$

and obviously, the online control of NMPC is implemented in the way of shrinking horizon, by which control actions from current kth to the end of (N-1)th sampling time are optimized. The above minimization problem of **(8)** is also subject to process model and inequality constraints $\mathbf{H}(\mathbf{U})\leq 0$ if any.

The NMPC strategy considered here is based on the Just-in-Time Learning-extended prediction self-adaptive control (JITL-EPSAC) technique[31–33] to achieve the desired final product qualities in batch process. The JITL-EPSAC has improved the original EPSAC method reported in Ref. 13 in the aspect of weight tuning and final product qualities control. In this NMPC design framework, the model prediction of future trajectory consists of a base and an optimized term. The base term is computed from a nominal first-principles process model using the current values of input variables obtained from the predefined base input trajectory and the corresponding output variables, while the optimized term is computed from a set of local state-space models identified by JITL method along its base trajectory.[34,35] The key idea of EPSAC is to predict nonlinear process variables by iterative optimization with respect to future trajectories so that they converge to the same nonlinear optimal solution. For example, in the JITL-EPSAC, representations of $\mathbf{P}$, $\Delta\mathbf{U}$, and $d\mathbf{U}$ in the minimization problem of **(8)** can be decomposed as follows

$$\mathbf{P}=\mathbf{P}_b+\mathbf{G}_{pl}\delta\mathbf{U} \tag{9}$$

$$\Delta\mathbf{U}=\Delta\mathbf{U}_b+\mathbf{C}\delta\mathbf{U} \tag{10}$$

$$d\mathbf{U}=\mathbf{U}_b+\delta\mathbf{U}-\mathbf{U}_{\mathrm{prev}} \tag{11}$$

where $\mathbf{P}_b$ is the product quality calculated using the first-principles model with updated model parameters and with predetermined future inputs $\mathbf{U}_b=\left[\mathbf{u}_{b,k}^T,\mathbf{u}_{b,k+1}^T,\cdots,\mathbf{u}_{b,N-1}^T\right]^T$, $\mathbf{G}_{pl}$ is the state-space model coefficients matrix corresponding to the product quality and is obtained from JITL method, $\delta\mathbf{U}=\left[\delta\mathbf{u}_k^T,\delta\mathbf{u}_{k+1}^T,\cdots,\delta\mathbf{u}_{N-1}^T\right]^T$ is the incremental control actions, $\mathbf{U}_{\mathrm{prev}}=\left[\mathbf{u}_{j-1,k}^T,\mathbf{u}_{j-1,k+1}^T,\cdots,\mathbf{u}_{j-1,N-1}^T\right]^T$ is the input sequence implemented in the previous batch, $\Delta\mathbf{U}_b=\left[\Delta\mathbf{u}_{b,k}^T,\Delta\mathbf{u}_{b,k+1}^T,\cdots,\Delta\mathbf{u}_{b,N-1}^T\right]^T$ is the change in the predetermined future inputs, and matrix $\mathbf{C}$ is as shown below.

$$\mathbf{C}=\begin{bmatrix}\mathbf{I}&\mathbf{0}&\cdots&\mathbf{0}&\mathbf{0}\\-\mathbf{I}&\mathbf{I}&\cdots&\mathbf{0}&\mathbf{0}\\\vdots&\vdots&\ddots&\vdots&\vdots\\\mathbf{0}&\mathbf{0}&\cdots&-\mathbf{I}&\mathbf{I}\end{bmatrix} \tag{12}$$

Therefore, the minimization problem **(8)** becomes

$$J_{\mathrm{B2B-NMPC}}=\min_{\delta\mathbf{U}}\ \delta\mathbf{U}^T\Gamma\delta\mathbf{U}+\Phi^T\delta\mathbf{U} \tag{13}$$

where

$$\Gamma = \mathbf{G}_{pl}^T \mathbf{W}_p \mathbf{G}_{pl} + \mathbf{C}^T \mathbf{W}_{\Delta u} \mathbf{C} + \mathbf{W}_{dU}$$

$$\Phi = 2\left[(\mathbf{P}_b - \mathbf{P}_d)^T \mathbf{W}_p \mathbf{G}_{pl} + \Delta \mathbf{U}_b^T \mathbf{W}_{\Delta u} \mathbf{C} + (\mathbf{U}_b - \mathbf{U}_{prev})^T \mathbf{W}_{dU} \right]^T$$

Analogously, the inequality constraints $\mathbf{H}(\mathbf{U})$ can be decomposed into

$$\mathbf{H}_b + \mathbf{G}_{hl} \delta \mathbf{U} \leq 0 \tag{14}$$

where $\mathbf{G}_{hl}$ is the state-space model coefficient matrix corresponding to the constraints and $\mathbf{H}_b$ is the constraints calculated using the updated first-principles model with predetermined future inputs $\mathbf{U}_b$. In this study, the soft-constraints approach[13] is utilized and the minimization problem is modified as follows

$$\min_{\delta U, \varepsilon} J_{\text{sc, B2B-NMPC}} \tag{15}$$

subject to

$$\mathbf{H}_b + \mathbf{G}_{hl} \delta \mathbf{U} \leq \boldsymbol{\varepsilon} \tag{16}$$

$$\boldsymbol{\varepsilon} \geq \mathbf{0} \tag{17}$$

where $J_{\text{sc, B2B-NMPC}} = J_{\text{B2B-NMPC}} + \boldsymbol{\varepsilon}^T \mathbf{W}_\varepsilon \boldsymbol{\varepsilon} + \boldsymbol{\varepsilon}^T \mathbf{w}_\varepsilon$, $\boldsymbol{\varepsilon}$ is a vector of slack variables, $\mathbf{W}_\varepsilon$ is a diagonal matrix of positive weight, and $\mathbf{w}_\varepsilon$ is a vector of positive elements.

Hence, the solution to the modified minimization problem is shown as follows

$$\begin{aligned} J^*_{\text{sc, B2B-NMPC}} &= \min_{\delta \mathbf{U}, \boldsymbol{\varepsilon}} \delta \mathbf{U}^T \Gamma \delta \mathbf{U} + \Phi^T \delta \mathbf{U} + \boldsymbol{\varepsilon}^T W_\varepsilon \boldsymbol{\varepsilon} + \boldsymbol{\varepsilon}^T \mathbf{w}_\varepsilon \\ &= \min_{\delta \mathbf{U}, \boldsymbol{\varepsilon}} \begin{bmatrix} \delta \mathbf{U}^T & \boldsymbol{\varepsilon}^T \end{bmatrix} \begin{bmatrix} \Gamma & \mathbf{0} \\ \mathbf{0} & \mathbf{W}_\varepsilon \end{bmatrix} \begin{bmatrix} \delta \mathbf{U} \\ \boldsymbol{\varepsilon} \end{bmatrix} + \begin{bmatrix} \Phi^T & w_\varepsilon^T \end{bmatrix} \begin{bmatrix} \delta \mathbf{U} \\ \boldsymbol{\varepsilon} \end{bmatrix} \\ &= \min_{\Pi} \Pi^T \Lambda \Pi + \boldsymbol{\tau}^T \Pi \end{aligned} \tag{18}$$

subject to

$$\begin{bmatrix} \mathbf{H}_b \\ \mathbf{0} \end{bmatrix} + \begin{bmatrix} \mathbf{G}_{hl} & -\mathbf{I} \\ \mathbf{0} & -\mathbf{I} \end{bmatrix} \Pi \leq \mathbf{0} \tag{19}$$

where $\Pi = \begin{bmatrix} \delta \mathbf{U}^T & \boldsymbol{\varepsilon}^T \end{bmatrix}^T$, $\Lambda = \begin{bmatrix} \Gamma & \mathbf{0} \\ \mathbf{0} & \mathbf{W}_\varepsilon \end{bmatrix}$, and $\boldsymbol{\tau} = \begin{bmatrix} \Phi^T & \mathbf{w}_\varepsilon^T \end{bmatrix}^T$

In summary, the procedure of implementing the integrated B2B-NMPC control strategy for each batch j and sampling time k is as follows

Step 1 Prepare the database matrices $\mathbf{X}$ and $\mathbf{Y}$ for the MPLS model as follows:

- if $j = 1$, the database matrices $\mathbf{X}$ and $\mathbf{Y}$ for the MPLS model can be obtained by offline simulation runs. For example, input sequences around the optimal input trajectory for the nominal first-principles model and a combination of model parameters sampled from their probability distributions, are implemented to the process model and the resulting state variables profiles are used to construct the database.

Table 1. Variations in Model Kinetic Parameters for B2B Control Study: Case 1 is the Nominal Model; Case 2 has Fast Nucleation and Slow Growth Rate Parameters; Case 3 has Slow Nucleation and Fast Growth Rate Parameters

Cases	$k_{b,\alpha 1}$	$k_{g,\alpha 1}$	$E_{g,\alpha 2}$	$k_{g,\beta 1}$
1	1.00×10^{11}	9.84×10^{-7}	0.888	1.07×10^{-7}
2	1.20×10^{11}	7.87×10^{-7}	1.066	0.86×10^{-7}
3	0.80×10^{11}	1.18×10^{-6}	0.710	1.28×10^{-7}

Table 2. Tuning Parameters for Two Controllers

B2B Control	B2B-NMPC Control
$\mathbf{W}_p = 1$	$\mathbf{W}_p = 1$
$(\mathbf{W}_{\Delta U})_{i,i} = 1\times10^{-5}$[a]	$(\mathbf{W}_{\Delta U})_{i,i} = 1\times10^{-5}$
$(\mathbf{W}_{dU})_{i,i} = 1\times10^{-4}$	$(\mathbf{W}_{dU})_{i,i} = 1\times10^{-4}$
	$\mathbf{W}_\varepsilon = \mathbf{I}$
	$\mathbf{w}_\varepsilon = [1, 1, \cdots 1]^T$

[a]The diagonal elements of matrices, where $i = 1, \ldots, N$.

- if $j > 1$, update the database matrices by including the previous simulation runs computed by NMPC during the online control into the database. In this study, the moving window approach is adopted, viz., the dataset from the earliest runs is removed every time a new dataset is included.
- Step 2 Update the process model: collect the initial conditions, measurement trajectories, and batch-end product qualities from previous batch to form vector $\mathbf{x}_{\text{new}}$ and predict the model parameters $\boldsymbol{\theta}_{\text{new}}$ through the updated MPLS model, as in Figure 2. And average the prediction of model parameters by Eq. 6.
- Step 3 Obtain $\mathbf{U}_b$ by the following method:
- If $k = 0$ and $iter = 1$, $\mathbf{U}_b$ is chosen from the nominal operating point which was used in the previous batches;
- If $k > 0$ and $iter = 1$, $\mathbf{U}_b$ is set as the $\mathbf{U}_{\text{optimal}}$ obtained in the previous sampling instance;
- If $iter > 1$, the updated $\mathbf{U}_b$ from the previous iteration is used; where $iter$ is the iteration count in the EPSAC algorithm.
- Step 4 Obtain $\mathbf{P}_b$ and $\mathbf{H}_b$ by using $\mathbf{U}_b$ as the input to the updated first-principles process model. In this study, it is assumed that the state variables are measured or observed.
- Step 5 Obtain the state space model coefficient matrices $\mathbf{G}_{pl}$ and $\mathbf{G}_{hl}$ using JITL method.
- Step 6 Obtain $\Pi^* = \begin{bmatrix} \delta \mathbf{U}^{*T} & \boldsymbol{\varepsilon}^{*T} \end{bmatrix}^T$ from the solution to the minimization problem **(18)** and **(19)**, then update the element of $\mathbf{U}_b$ using

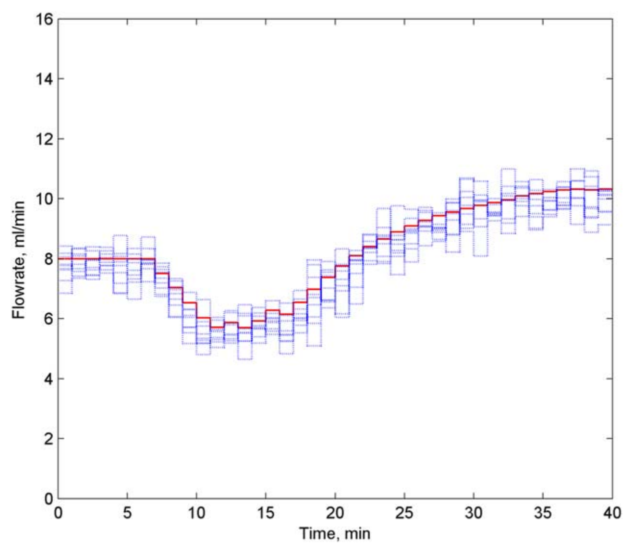

Figure 3. Flowrate profiles for initial database generation of MPLS model (solid line: nominal optimal flowrate trajectory; dash line: random flowrate profiles around the nominal one).

[Color figure can be viewed at wileyonlinelibrary.com]

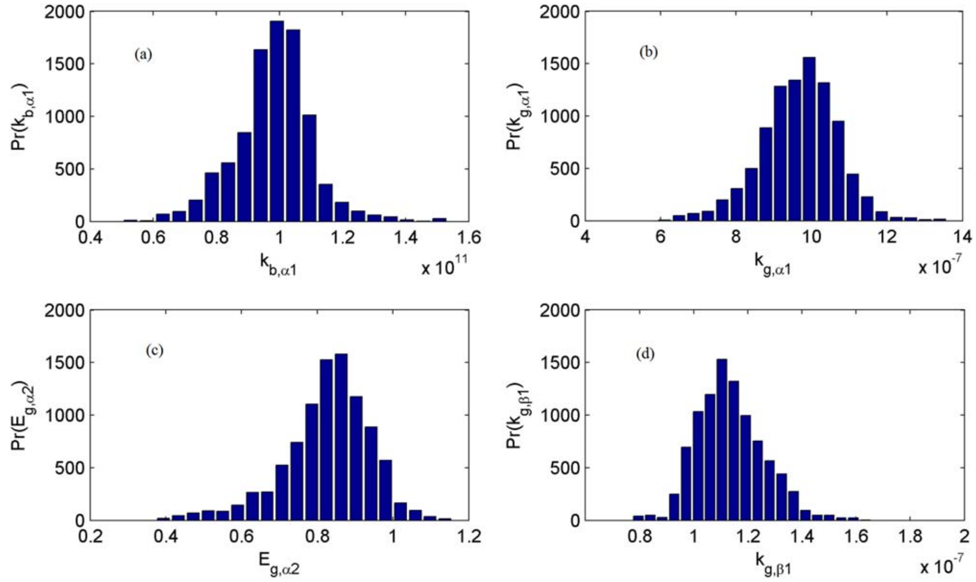

Figure 4. The probability distributions of uncertain kinetic parameters.

[Color figure can be viewed at wileyonlinelibrary.com]

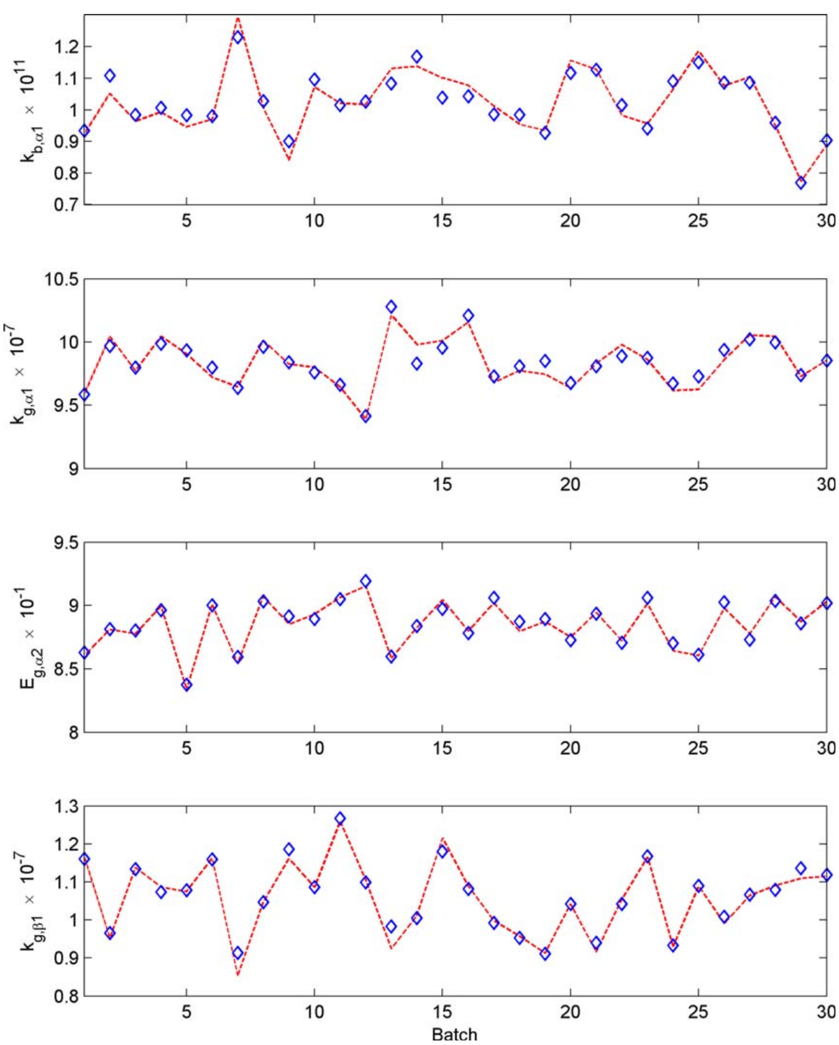

Figure 5. Validation result of MPLS model for kinetic parameters estimation (dash line: process value; symbol: predicted data by MPLS).

[Color figure can be viewed at wileyonlinelibrary.com]

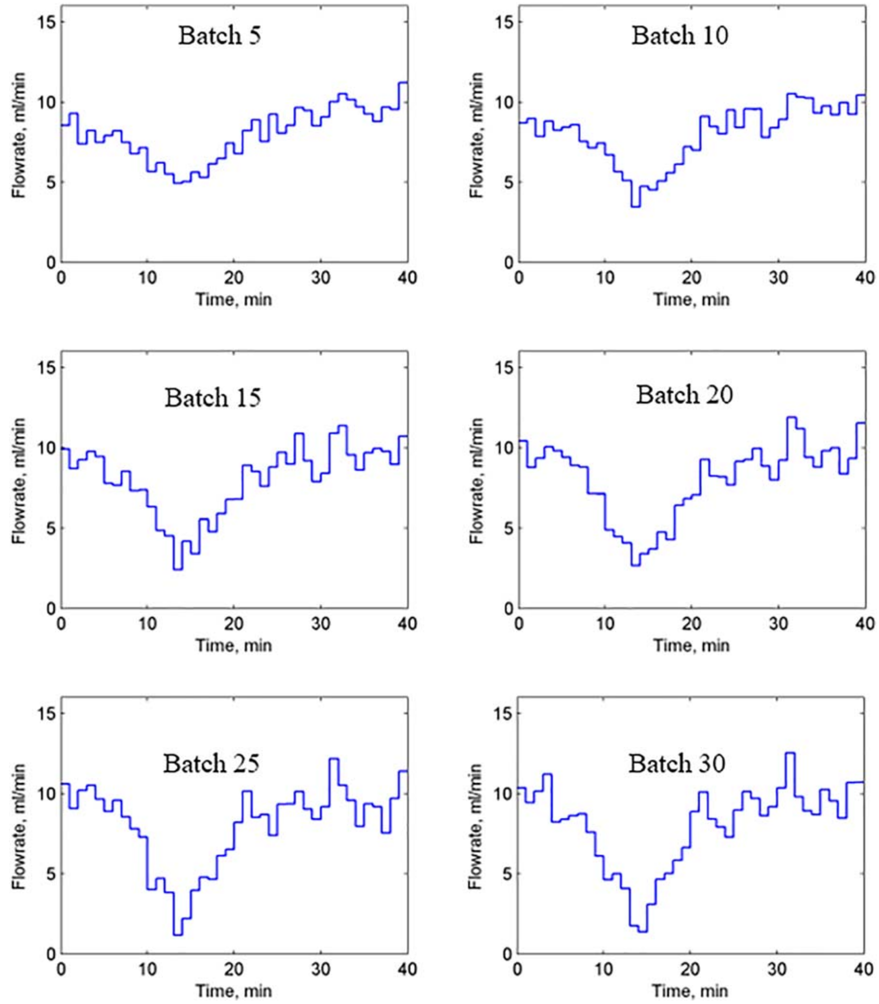

Figure 6. Flowrate profiles of B2B control strategy from nominal process of Case 1 to abnormal Case 2.

[Color figure can be viewed at wileyonlinelibrary.com]

$$\mathbf{u}_{b,k+j}=\mathbf{u}_{b,k+j}+\delta\mathbf{u}_{k+j} \tag{20}$$

where $j=0, \cdots, N-1$

- Step 7 Calculate $\text{err}=\left\|\begin{bmatrix}\mathbf{G}_{pl}\\ \mathbf{G}_{hl}\end{bmatrix}\delta\mathbf{U}^*\right\|$. If *err* is greater than a specified tolerance, iter = iter + 1, and go back to Step 3. Otherwise, set $\mathbf{U}_{\text{optimal}}=\mathbf{U}_b$ and implemented the first element of $\mathbf{U}_{\text{optimal}}$ to the process.
- Step 8 If the end of the current batch is reached, repeat from step 1 and go to the next batch.

Results and Discussion

To illustrate and compare the control performances of the conventional B2B and integrated B2B-NMPC control strategies, their applications to a semibatch pH-shift reactive crystallization of L-glutamic acid were investigated. More details of the reactive crystallization process can be found in Refs. 23 and 24 with some of the features briefly defined as follows.

Process and control specifications

A first-principles mathematical model consisting of population balance models for both α and β polymorphs, as well as their respective crystallization mechanisms and kinetics was developed from the reported experiments of Refs. 23 and 24. This model was used in this study to simulate the semibatch pH-shift reactive crystallization of L-glutamic acid, whose model parameters were estimated using the Bayesian inference.[19] The nominal operating procedures are summarized here. The crystallizer is initially half-filled with 0.65 L monosodium glutamate (MSG, 1.0 mol/L). Then sulfuric acid (SA, 1.0 mol/L) is continuously added to produce glutamic acid and induce crystallization of α and/or β polymorphic form without seeding. The additional flow rate of SA is constrained between 0 and 16 ml/min with a maximum crystallizer volume of 0.97 L. The default batch time and sampling interval are 40 and 1 min, respectively. A nominal flow rate profile for SA is selected to produce an on-spec product with respect to polymorphic purity of α-form (P_α), volume-based mean crystal size (M_s), and product yield of crystals (P_y), which are chosen from a Pareto front of a multiobjectives optimization problem.[36]

Three scenarios of the crystallization process uncertainties are summarized in Table 1 with four crystallization kinetic parameters of α and β polymorphs were taken into account for demonstration purpose here, which affects their nucleation and crystal growth rates. The other process parameters were remained the same as the mode values in their probability distributions in the Table 2 of Ref. 19. Of the three scenarios, the

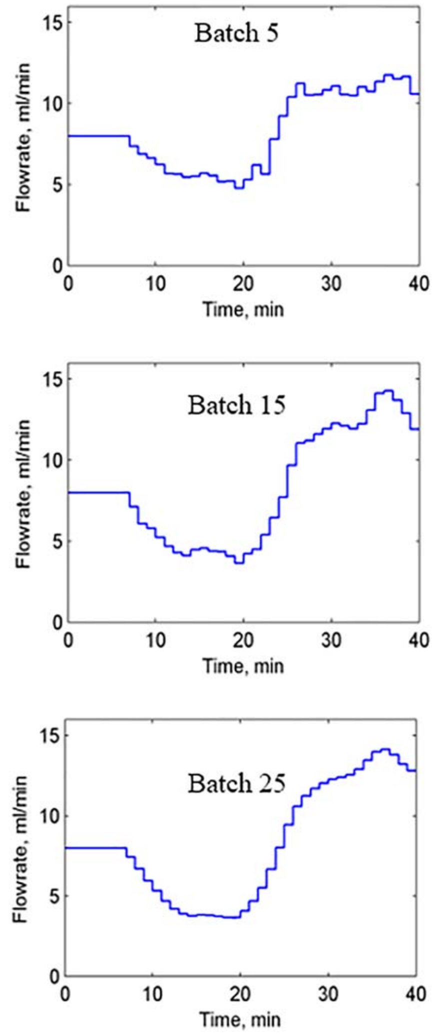

Figure 7. Flowrate profiles of B2B-NMPC control strategy from nominal process of Case 1 to abnormal Case 2.

[Color figure can be viewed at wileyonlinelibrary.com]

Case 1 considers a nominal crystallization process, Case 2 has fast nucleation and slow growth rate parameters, while Case 3 has slow nucleation and fast growth rate parameters. The process was first started in Case 1 and then shifted to abnormal Case 2 after the first batch and stayed at this scenario until the 30th batch. From batch 31 to batch 60, the process entered the Case 3, after which it resumed to the nominal Case 1 from the 61th batch till the 90th batch.

The first batch was initialized with a nominal optimal flowrate profile as shown in Figure 3, which was obtained under a nominal process by JITL-EPSAC to achieve a desired α-form polymorphic purity, P_{α}, of 0.8255. This is because

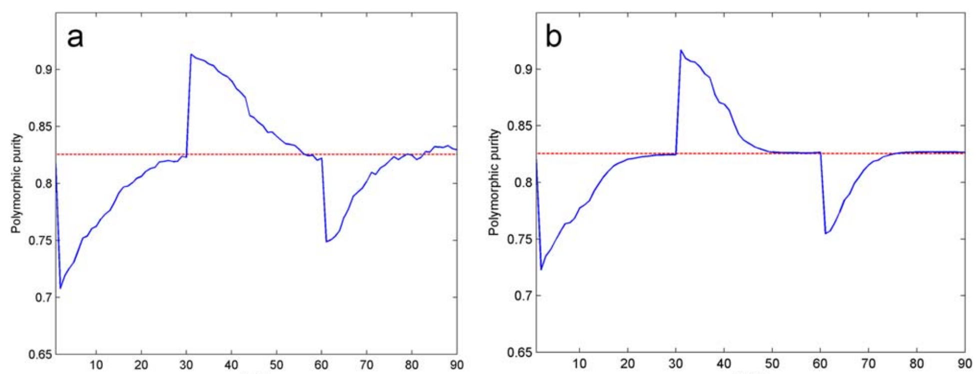

Figure 8. Polymorphic purity of B2B (top) and B2B-NMPC (bottom) control strategies for Case 1, Case 2, and Case 3 (dash line: final quality setpoint; solid line: final quality).

[Color figure can be viewed at wileyonlinelibrary.com]

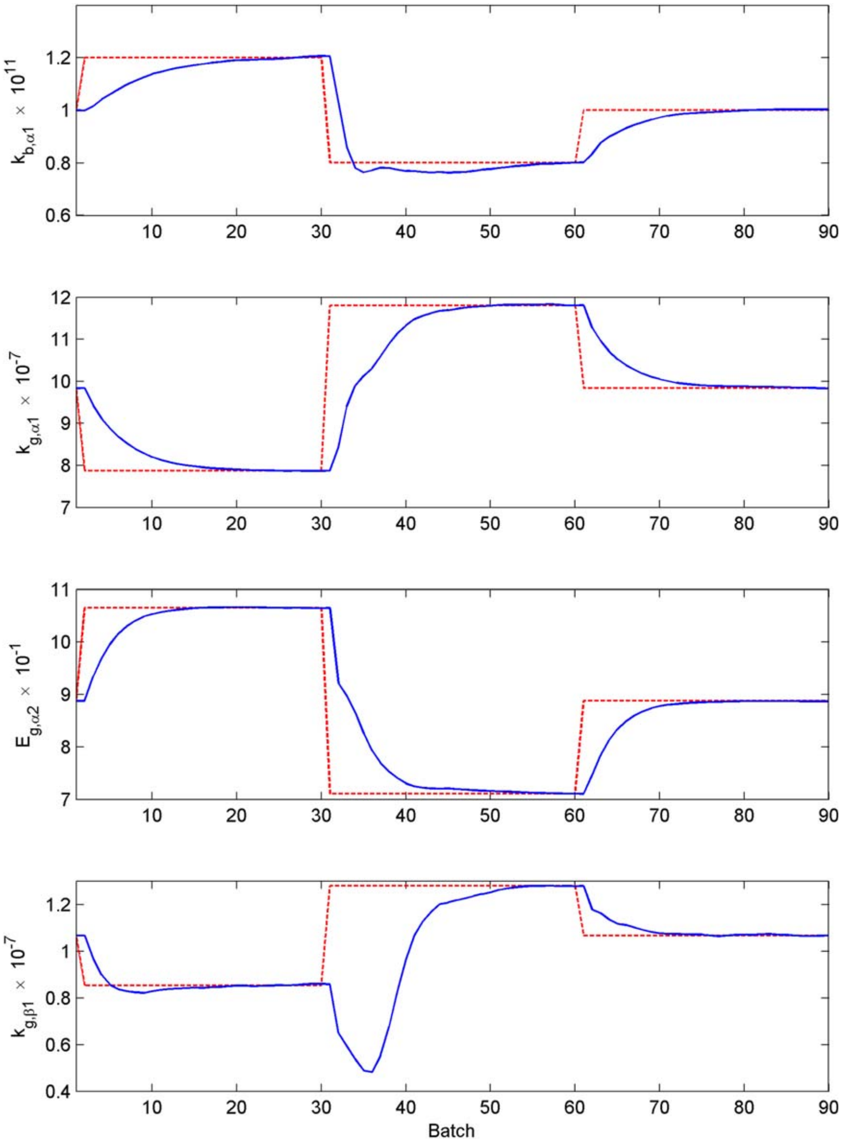

Figure 9. Kinetic parameters updating of B2B control strategies for Case 1, Case 2, and Case 3 (dash line: process value; solid line: estimated value).

[Color figure can be viewed at wileyonlinelibrary.com]

polymorphic purity was found to be the most important product quality and also determining the other two final qualities of mean crystal size M_s and product yield P_y.[36] Furthermore, an initial database for MPLS model was generated by introducing random disturbances of N (0, 0.5) to this nominal optimal flowrate profile at each sampling instant, with some of them depictured in Figure 3. Besides, resampling of the four studied kinetic parameters from their probability distributions, as shown in Figure 4, were also introduced during the offline simulation runs for initial database generation. With the recent development in process analytical techniques (PAT), more abundant process data are now available, though correlated to each other. Nevertheless, initial concentrations of monosodium glutamate and sulfuric acid, complete state variable trajectories of pH value, crystallizer volume, solute concentrations by ATR-FTIR, mean crystal size by FBRM or PVM, the zeroth and first moments of crystal size distribution by FBRM, and polymorphic purity of α-form by Raman spectroscopy, as well as the batch-end product yield, are all collected to construct the unfolded dataset **X** for process monitoring. While the four kinetic parameters formed the dataset **Y**. Totally 200 batches of the simulation runs were used to construct the MPLS model with the number of principle components fine-tuned as seven by cross-validation. Incidentally, during the online application, here we assumed that all these state variables in **X** are either measured or observed by state estimators, such as extended Kalman filter (EKF) or unscented Kalman filter (UKF).[32,37–39] Additional unseen 30 batches were used for validation test as given in Figure 5, which shows the MPLS model is capable of inferring the kinetic parameters from the provided system dynamic information.

It should be pointed out that this initial database was used for both B2B and B2B-NMPC control strategies and was then updated by their control techniques individually during online implementation for all the 90 batches, from which the merit of the batch-to-batch control can be demonstrated by gradually learning, from the previous batches, the system dynamic information while the process suffered from shifting among scenarios of abnormality.

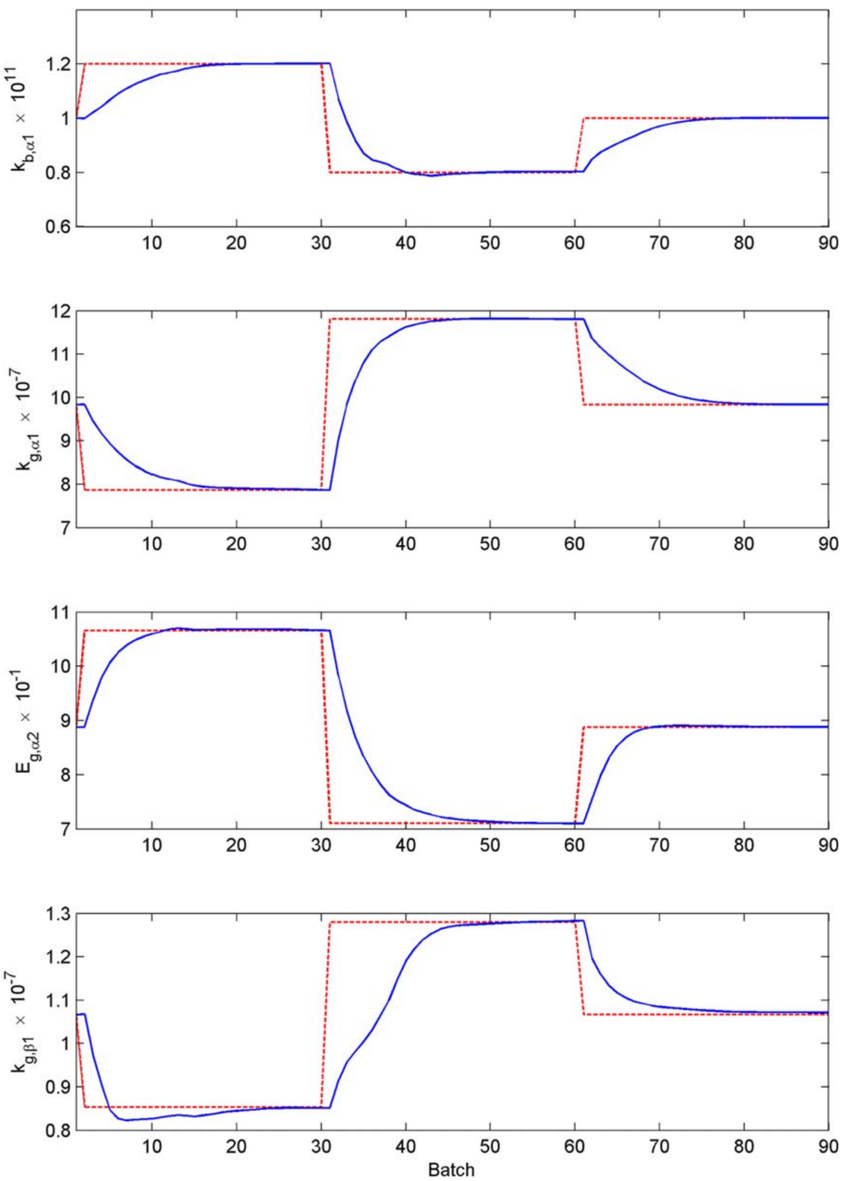

Figure 10. Kinetic parameters updating of B2B-NMPC control strategies for Case 1, Case 2, and Case 3 (dash line: process value; solid line: estimated value).

[Color figure can be viewed at wileyonlinelibrary.com]

For the controller implementation, the minimization problem of **(7)** for conventional B2B was solved by the DE method,[13,29] while the integrated B2B-NMPC was transferred to a soft-constrained problem of **(8)** and therefore a time-saving quadratic programming method was conveniently adopted.[13,32] The tuning parameters for the studied two controllers are listed in Table 2.

Results comparison and discussion

For the batch-end product quality control of α-form polymorphic purity, performances of the B2B and integrated B2B-NMPC control strategies, when crystallization process underwent from Case 1 to 2 during the first 30 batches, are illustrated in Figures 6 and 7 for additional flowrate profiles of sulfuric acid, respectively. Figure 8 shows the final product quality, while Figures 9 and 10 demonstrate the convergences of the four kinetic parameters.

It is observed that the integrated B2B-NMPC shows smoother and faster convergences in both flowrate profile and final product quality compared to the standard B2B control strategy, even though not only the penalty weights for excessive changes inter and within the batches are the same for both control strategies, as shown in Table 2, but also the kinetic parameters updated by MPLS model converged at nearly the same rate, as can be seen from Figures 9 and 10. This well explains the fact that the open-loop nature of B2B results into the unsatisfied control performance when the model-plant mismatch resulted from process uncertainties is large. Conversely, the performance of the proposed JITL-EPSAC in Ref. 33 is further enhanced since under large model-plant mismatch, the JITL-EPSAC gradually improved the final polymorphic purity with the embedded first-principles model refined by MPLS model from batch to batch. Incidentally, the tuning parameter of $m = 4$ in Eq. 6 is used for both control strategies here to adjust the convergence rate of kinetic parameters. In pharmaceutical industries, high economic penalties are suffered so that if one batch fails and the next must be on target. Thus, it is intended to reduce the convergence rate here, such that if only a single batch fails due to large random disturbance within the batch, then it will have limited effects on the model updating and then on the following batches. The main focus of the batch-to-batch control is to deal with the process uncertainties that show a clear trend of process dynamic changes among batches. Whereas the abrupt disturbances within a single batch can be tackled by on-line control.[33]

The second simulation study considered the crystallization kinetics shifted from Case 2 to 3 in the 31st batch and continued the Case 3 till the 60th batch. Interestingly, the standard B2B slowly reached the final product quality set point, however, it then slightly diverged as shown in Figure 8. To the contrary, the integrated B2B-NMPC more steadily reduced the unexpected high polymorphic purity, for example, about 10 batches faster, to the set point to maintain a constancy of the other two product quality, that is, mean crystal size and product yield.[33] What's more, the convergences of the four kinetic parameters by MPLS model can also be found in Figures 9 and 10, respectively.

Lastly, the crystallization process returned to the nominal Case 1 from abnormal Case 3 after the 61th batch. Consistent better performance of the B2B-NMPC are also observed, for example, about 15 batches faster, as given in Figures 9 and 10 for batches from 61 to 90. Worth to note is that the initial database for MPLS model at Batch 1 was only generated around the nominal optimal flowrate profile, but it can be renewed by gradually incorporating the simulation runs computed by B2B or the integrated B2B-NMPC control strategies. This really shows the capability of the proposed Batch-to-Batch framework to learn from previous batch information when it is subject to process uncertainties, provided that the variances in the process kinetics are captured by the Bayesian probability distributions. Otherwise, when it is detected to be exciting the nominal varying range (cases not considered here), that is, by Hotelling's T^2 statistics or squared prediction error (SPE),[25] in the MPLS model, a new parameter estimation step has to be taken, as schemed in Figure 2.

Conclusions

A new integrated B2B-NMPC control strategy based on a MPLS model and the JITL-EPSAC technique was proposed in this study. The MPLS model is capable of inferring the model kinetic parameters from the system dynamic information obtained from previous batches, which updates the first-principles model for the JITL-EPSAC. At the meantime, the robustness of the JITL-EPSAC can help to improve the batch-end product quality online even under large model-plant mismatch. The proposed integrated B2B-NMPC was applied to a semi-batch pH-shift reactive crystallization process and was also compared to a conventional B2B control strategy. The simulation results showed that the proposed integrated control strategy performed a much smoother and faster convergence to the final product quality set point under multiple shifts of abnormal scenarios, showing its capability to maintain consistent production of on-spec product in batch manufacturing process, which has never been demonstrated in previous works.

Literature Cited

1. Wang Y, Gao F, Doyle III F. Survey on iterative learning control, repetivite control, and run-to-run control. *J Process Control*. 2009; 19:1589–1600.
2. Xiong Z, Zhang J, Wang X, Xu Y. Tracking control for batch processes through integrating batch-to-batch iteractive learning control and within-batch on-line control. *Ind Eng Chem Res*. 2005;44:3983–3992.
3. Zafiriou E, Adomaitis RA, Gattu G. An approach to run-to-run control for rapid thermal processing. In: *Paper presented at Proceedings of the American Control Conference*. Seattle, Washington USA, 1995.
4. Bonvin D. Optimal operation of batch reactors - a personal view. *J Process Control*. 1998;8:355–368.
5. Forgione M, Mesbah A, Bombois X, Van den Hof PMJ. Iterative learning control of supersaturation in batch cooling crystallization. In: *Paper presented at Proceedings of the American Control Conference*. Montreal, Canada, 2012.
6. Forgione M, Birpoutsoukis G, Bombois X, Mesbah A, Daudey PJ, Van den Hof PMJ. Batch-to-batch model improvement for cooling crystallization. *Control Eng Pract*. 2015;41:72–82.
7. Clarke-Pringle TL, MacGregor JF. Optimization of molecular-weight distribution using batch-to-batch adjustments. *Ind Eng Chem Res*. 1998;37:3660–3669.
8. Doyle FJ, III, Harrison CA, Crowley TJ. Hybrid model-based approach to batch-to-batch control of particle size distribution in emulsion polymerization. *Comput Chem Eng*. 2003;27:1153–1163.
9. Zhang J. Batch-to-batch optimal control of a batch polymerisation process based on stacked neural network models. *Chem Eng Sci*. 2008;63:1273–1281.
10. Chin IS, Lee KS, Lee JH. A technique for integrated quality control, profile control, and constraint handling of batch processes. *Ind Eng Chem Res*. 2000;39:693–705.
11. Lee K, Lee JH, Yang DR, Mahoney AW. Integrated run-to-run and on-line model-based control of particle size distribution for a semi-batch precipitation reactor. *Comput Chem Eng*. 2002;26:1117–1131.
12. Paengjuntuek W, Arpornwichanop A, Kittisupakorn P. Product quality improvement of batch crystallizer by batch-to-batch optimization and nonlinear control approach. *Chem Eng J*. 2008;139:344–350.
13. Hermanto MW, Braatz RD, Chiu MS. Integrated batch-to-batch and nonlinear model predictive control for polymorphic transformation in pharmaceutical crystallization. *AIChE J*. 2011;57:1008–1019.
14. Perrier M, Feyo de Azevedo S, Ferreira EC, Dochain D. Tuning of observer-based estimators: theory and application to the on-line estimation of kinetic parameters. *Control Eng Pract*. 2000;8:377–388.
15. Kravaris C, Hahn J, Chu Y. Advances and selected recent developments in state and parameter estimation. *Comput Chem Eng*. 2013; 51:111–123.
16. Kwon JS, Nayhouse M, Christofides PD. Detection and isolation of batch-to-batch parametric drift in crystallization using in-batch and post-batch measurements. *Ind Eng Chem Res*. 2015;54:5514–5526.
17. Mockus L, Peterson JJ, Lainez JM, Reklaitis GV. Batch-to-Batch variations: a key component for modeling chemical manufacturing processes. *Org Process Res Dev*. 2015;19:908–914.
18. Nomikos P, MacGregor JF. Multi-way partial least squares in monitoring batch processes. *Chemometr Intell Lab Syst*. 1995;30:97–108.
19. Geladi P, Kowalski B. Partial least squares regression: a tutorial. *Anal Chim Acta*. 1986;185:1–17.
20. Zhao C, Mo S, Gao F, Lu N, Yao Y. Statistical analysis and online monitoring for handling multiphase batch processes with varying durations. *J Process Control*. 2011;21:817–829.
21. Camacho J, Pico J, Ferrer A. The best approaches in the on-line monitoring of batch processes based on PCA: does the modelling structure matter? *Anal Chim Acta*. 2002;642:59–68.
22. Alatalo H, Kohonen J, Qu H, Hatakka H, Reinikainen SP, Louhi-Kultanen M, Kallas J. In-line monitoring of reactive crystallization process based on ATR-FTIR and Raman spectroscopy. *J Chemometr*. 2008;22: 644–652.
23. Qu H, Alatalo H, Hatakka H, Kohonen J, Louhi-Kultanen M, Reinikainen SP, Kallas J. Raman and ATR FTIR spectroscopy in reactive crystallization: simultaneous monitoring of solute concentration and polymorphic state of the crystals. *J Cryst Growth*. 2009;311:3466–3475.
24. Su QL, Chiu MS. Monitoring pH-shift reactive crystallization of L-glutamic acid using moving window MPCA. *J Chem Eng Jap*. 2016;49:680–688.
25. Gelman A, Carlin JB, Stern HS, Rubin DB. *Bayesian Data Analysis*. New York: Chapman & Hall/CRC, 2004.
26. Englezos P, Kalogerakis N. *Applied Parameter Estimation for Chemical Engineers*. New York: Marcel-Dekker, 2000.
27. Su QL, Braatz RD, Chiu MS. Modeling and Bayesian parameter estimation for semi-batch pH-shift reactive crystallization of L-glutamic acid. *AIChE J*. 2014;60:2828–2838.

28. Storn R, Price K. Differential evolution-a simple and efficient heuristic for global optimization over continuous spaces. *J Global Optim.* 1997;11:341–359.
29. Lampinen J. A constraint handling approach for the differential evolution algorithm. In: *Paper presented at Proceedings of the 2002 Congress on Evolutionary Computation*, Washington DC, 2002.
30. Nocedal J, Wright S. *Numerical Optimization*. New York: Springer; 2006.
31. De Keyser R. Model based predictive control for linear systems. In: Unbehauen H, editor. *UNESCO Encyclopaedia of Life Support System (EoLSS), Vol* XI. Oxford: Eolss Publishers, 2003.
32. Hermanto MW, Chiu MS, Braatz RD. Nonlinear model predictive control for the polymorphic transformation of L-glutamic acid crystals. *AIChE J*. 2009;55:2631–2645.
33. Su QL, Hermanto MW, Braatz RD, Chiu MS. Just-in-time-learning based extended prediction self-adaptive control for batch processes. *J Process Control*. 2016;43:1–9.
34. Cheng C, Chiu MS. A new data-based methodology for nonlinear process modeling. *Chem Eng Sci*. 2004;59:2801–2810.
35. Su Q, Kano M, Chiu MS. A new strategy of locality enhancement for Just-in-time learning method. *Comput Aided Chem Eng*. 2012;31:1662–1666.
36. Su QL, Braatz RD, Chiu MS. JITL-based concentration control for semi-batch pH-shift reactive crystallization of L-glutamic acid. *J Process Control*. 2014;24:415–421.
37. Mesbah A, Huesman AE, Kramer HJ, Nagy ZK, Van de Hof PM. Real-time control of a semi-industrial fed-batch evaporative crystallizer using different direct optimization strategies. *AIChE J*. 2011;57:1557–1569.
38. Li H, Grover MA, Kawajiri Y, Rousseau RW. Development of an empirical method relating crystal size distributions and FBRM measurements. *Chem Eng Sci*. 2013;89:142–151.
39. Li H, Kawajiri Y, Grover MA, Rousseau RW. Application of an empirical FBRM model to estimate crystal size distributions in batch crystallization. *Cryst Growth Design*. 2014;14:607–616.

Manuscript received Feb. 17, 2017, and revision received May 1, 2017.