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A Multiway Gaussian Mixture Model based Adaptive Kernel Partial Least Squares Regression Approach for Inferential Quality Predictions of Batch Processes

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Abstract: Soft sensor technique has become increasingly important to provide reliable on-line measurements, facilitate advanced process control and improve product quality in process industries. The conventional soft sensors are normally single-model based and thus may not be appropriate for processes with shifting operating conditions or phases. In this study, a multiway Gaussian mixture model (MGMM) based kernel partial least squares (PLS) method is proposed to handle multiple operating phases in batch or semibatch processes. The measurement data are first projected onto high-dimensional kernel feature space to account for the process nonlinearity. Then the multiway Gaussian mixture model is estimated with multiple Gaussian clusters in the kernel space. Thus various localized PLS models can be built within each Gaussian cluster to characterize the dynamics in the particular operating phase. Using Bayesian inference strategy, the soft sensor models for all the test samples are adaptively selected from the multiple localized kernel PLS models representing different phases and further used for online quality predictions. The presented soft sensor method is applied to the multiphase penicillin fermentation process and the computational results demonstrate that its performance is superior to the conventional multiway kernel PLS model.

1. INTRODUCTION

Batch or semi-batch processes have been widely used to produce low-volume and high-value-added products in different industrial sectors including chemical, materials, food, pharmaceutical, biotechnology and semiconductor industries. Batch operations often face the challenge of lacking accurate real-time measurements of key product quality variables that are essential for implementing advanced process control in the plant and continuously improving the product quality [1, 2, 3]. In recent years, soft sensor techniques have become popular in industry to provide reliable online measurements on critical process or quality variables based upon predictive models instead of hardware instruments or offline lab analysis [4, 5].

In literature work, soft sensor development is typically based on either first-principle or data-driven statistical models [4]. The former type of approaches require in-depth process knowledge, which may not be available in real applications especially like complex industrial processes. Furthermore, the model development can be quite tedious and time-consuming [5, 6]. In contrast, the data-driven techniques are more desirable for industrial applications as very minimal process knowledge is needed while the plant historians provide abundant process data for soft sensor modeling [4, 7, 8]. The most popular data-driven soft sensor methods are multivariate statistical techniques including principal component analysis (PCA) [9], partial least squares (PLS) [10], Fisher discriminant analysis (FDA) [3, 11] and independent component analysis (ICA) [12, 13]. This class of methods usually project the original measurement data onto the linear subspace to extract variable features and then identify the predictive model within the lower-dimensional subspace. In addition to multivariate statistical analysis, the machine learning methods such as support vector regression (SVR) have witnessed some success in soft sensor modeling of batch processes [6, 14, 15].

Though different kinds of soft sensor techniques have been developed for batch processes, they are typically based upon a single regression model with the assumption of constant operating scenario and phase throughout the entire process. In practice, however, batch processes often have shifting operation phases, which lead to changing process dynamics. Thus, the performance of soft sensor predictions will degrade as the operating phase and underlying dynamics switch. In this paper, a new multiway Gaussian mixture model based adaptive kernel partial least square (MGMM-AKPLS) method is proposed for soft sensor development and quality variable predictions of batch or semibatch processes. The multiway process measurement data matrix is first preprocessed and unfolded into two-dimensional matrix. Then the Gaussian mixture model is adopted to isolate the multiple phases in batch operation. With each identified phase, the data are further projected onto high-dimensional kernel feature space so that a localized PLS regression model is built between the process variables and quality variables. With the Bayesian inference base posterior probabilities estimated on the test samples, their operating phases can be determined so that the corresponding localized PLS models are automatically selected for on-line quality variable predictions.

The organization of the paper is as follows. Partial least square regression and multiway Gaussian mixture model are briefly described in Section II. Then Section III presents the MGMM based adaptive kernel PLS method for soft sensor modeling and prediction in batch processes. The proposed approach is applied to the fed-batch penicillin fermentation process and the results

are compared with those of conventional multiway kernel PLS model in Section IV. Finally, the concluding remarks are drawn in Section V.

2. PRELIMINARIES

2.1 PLS regression model

Consider an input and an output data matrices $X(I \times J_X)$ and $Y(I \times J_Y)$, where I represents the number of observations, J_X and J_Y denote the numbers of input and output variables. The input and output data can be projected onto the S-dimensional latent variable subspace as follows

$$X = T_X P_X^T + E_X \tag{1}$$

and

$$Y = T_Y P_Y^T + E_Y \tag{2}$$

where $T_X(I \times S)$ and $T_Y(I \times S)$ are the score matrices, $P_X(J_X \times S)$ and $P_Y(J_Y \times S)$ represents the loading matrices, and $E_X(I \times J_X)$ and $E_Y(I \times J_Y)$ are the residual matrices in the input and output spaces. The objective in PLS model is to maximize the correlation between the score vectors of the input and output data and the PLS based regression model is expressed as

$$Y = X\Gamma + \Gamma_0 \tag{3}$$

with

$$\Gamma = W(P_X^T W)^{-1} P_Y^T Y \tag{4}$$

where Γ is the regression coefficient matrix, Γ_0 denotes the bias matrix and W represents the input weighting matrix involved in the following equation

$$T_x = XW \tag{5}$$

The above PLS model can be solved from the nonlinear iterative partial least squares (NIPALS) algorithm [16].

2.2 Multiway Gaussian mixture model for phase isolation of batch processes

Multiway Gaussian mixture model has been proven effective in isolating multiple phases of batch operation for process monitoring and fault detection [17, 18]. Consider a three-way input data matrix $X^{(B)}(I^{(B)} \times J^{(B)} \times L^{(B)})$ with $I^{(B)}$, $J^{(B)}$ and $I^{(B)}$ representing the numbers of batches, process variables and sampling instants, respectively. Firstly it is converted into a two-dimensional matrix $\overline{X}^{(B)}(I^{(B)} \times J^{(B)}L^{(B)})$ via batch-wise unfolding. Then each column vector of $\widehat{X}^{(B)}$ can be mean-centered and the formed matrix $\overline{\widehat{X}}^{(B)}(I^{(B)}L^{(B)} \times J^{(B)})$ is further rearranged to $\widetilde{X}^{(B)}$ through variable-wise unfolding as illustrated in Fig. 1. The multiway output data matrix of quality variables can be unfolded in the same fashion.

For the unfolded data matrix $\widetilde{X}^{(B)}$, each row vector $\widetilde{x}_{j.}^{(B)}$ can be assumed to follow a Gaussian mixture distribution as shown below

$$p(\widetilde{x}_{j.}^{(B)}|\theta) = \sum_{i=1}^{C} \omega_i p(\widetilde{x}_{j.}^{(B)}|\theta_i) \tag{6}$$

where ω_i is the prior probability of the i-th Gaussian component and the corresponding distribution parameter θ_i includes the mean vector μ_i and covariance matrix Σ_i. The above Gaussian mixture model can be estimated from the modified expectation-maximization (E-M) algorithm [15], which involves the following two-step iterations

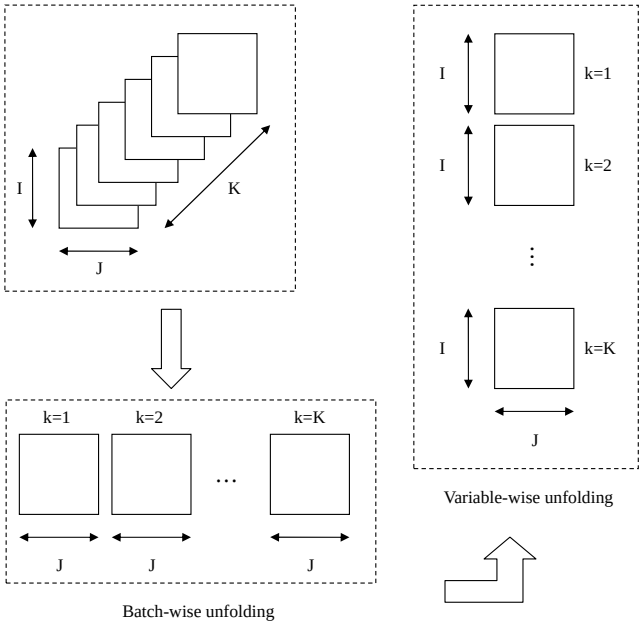

Fig. 1. Illustration of three-way data matrix unfoldings

• E-step:

$$P^{(s)}(\theta_i|\widetilde{x}_{j.}^{(B)}) = \frac{P_i^{(s)} p(\widetilde{x}_{j.}^{(B)}|\mu_i^{(s)}, \Sigma_i^{(s)})}{\sum_{l=1}^{L^{(B)}} P_l^{(s)} p(\widetilde{x}_{j.}^{(B)}|\mu_l^{(s)}, \Sigma_l^{(s)})} \tag{7}$$

and

• M-step:

$$\mu_i^{(s+1)} = \frac{\sum_{j=1}^{I^{(B)}L^{(B)}} P^{(s)}(\theta_i|\widetilde{x}_{j.}^{(B)})\widetilde{x}_{j.}^{(B)}}{\sum_{j=1}^{I^{(B)}L^{(B)}} P^{(s)}(\theta_i|\widetilde{x}_{j.}^{(B)})} \tag{8}$$

$$\Sigma_i^{(s+1)} = \frac{\sum_{j=1}^{I^{(B)}L^{(B)}} P^{(s)}(\theta_i|\widetilde{x}_{j.}^{(B)})(\widetilde{x}_{j.}^{(B)} - \mu_i^{(s+1)})(\widetilde{x}_{j.}^{(B)} - \mu_i^{(s+1)})^T}{\sum_{j=1}^{I^{(B)}L^{(B)}} P^{(s)}(\theta_i|\widetilde{x}_{j.}^{(B)})} \tag{9}$$

$$\omega_i^{(s+1)} = \frac{\max\left\{0, \left(\sum_{j=1}^{I^{(B)}K^{(B)}} P^{(s)}(\theta_i|\widetilde{x}_{j.}^{(B)})\right) - \frac{V}{2}\right\}}{\sum_{i=1}^{C} \max\left\{0, \left(\sum_{j=1}^{I^{(B)}L^{(B)}} P^{(s)}(\theta_i|\widetilde{x}_{j.}^{(B)})\right) - \frac{V}{2}\right\}} \tag{10}$$

where s is the serial number of E-M iterations, V represents the total number of scalar parameters specifying each Gaussian component, and $P^{(s)}(\theta_i|\widetilde{x}_{j.}^{(B)})$ denotes the posterior probability of the j-th training sampling within the i-th Gaussian component at the s-th iteration. After the different Gaussian components are identified from the above E-M procedure, the different batches at the same sampling point first need to be re-aligned to the same operation phase and then the outlier clusters should be merged into the most probable neighboring phase [19].

3. MGMM BASED ADAPTIVE KERNEL PLS METHOD

The process and quality variables in batch processes are often characterized by significantly nonlinear relationship. Therefore, the regular PLS model may not be effective to capture the local nonlinearity within different operating phases identified by MGMM. In this study, the nonlinear kernel PLS model is adopted for the local operating phases and the kernel function based mapping is employed to project the unfolded input matrix $\widetilde{X}^{(B)}$ from the original measurement space onto the high-dimensional feature space for further PLS regression. Then the Bayesian inference based posterior probabilities are estimated with respect to different phases and used to adaptively select the corresponding KPLS model from the multiple localized models for online quality variable predictions.

Let $\phi : R^{I^{(B)}L^{(B)}} \rightarrow F$ be a nonlinear mapping function, where F represents the high-dimensional feature space. Thus the projected measurement sample of batch process can be expressed as $\phi(\widetilde{x}_{j.}^{(B)})$. Due to the curse of dimensionality, it is not feasible to calculate the nonlinear mapping of each unfolded sample from batch processes and then conduct the PLS regression in the feature space. To tackle this issue, a nonlinear kernel function K can be defined as the inner product of two mapped samples

$$K_{ij} = K(\widetilde{x}_{i.}^{(B)}, \widetilde{x}_{j.}^{(B)}) = \left\langle \phi(\widetilde{x}_{i.}^{(B)}), \phi(\widetilde{x}_{j.}^{(B)}) \right\rangle \tag{11}$$

Before nonlinear kernel projection, the mean centering is conducted on the above kernel matrix as follows

$$\overline{K} = K - L_{I^{(B)}L^{(B)}}K - KL_{I^{(B)}L^{(B)}} + L_{I^{(B)}L^{(B)}}KL_{I^{(B)}L^{(B)}} \tag{12}$$

where $L_{I^{(B)}L^{(B)}}$ is a $I^{(B)}L^{(B)} \times I^{(B)}L^{(B)}$ matrix with each element being equal to $1/I^{(B)}L^{(B)}$. In this study, the following radial basis function (RBF) is selected as the kernel function

$$K(\widetilde{x}_{i.}^{(B)}, \widetilde{x}_{j.}^{(B)}) = \exp(-\frac{||\widetilde{x}_{i.}^{(B)} - \widetilde{x}_{j.}^{(B)}||^2}{2\sigma^2}) \tag{13}$$

with σ representing the width of RBF kernel and its value is set to 1.0 in this work.

For the regression model in the kernel feature space

$$Y = \phi(X)\widetilde{\Gamma} + \widetilde{\Gamma}_0 \tag{14}$$

the corresponding regression coefficient matrix is expressed as

$$\widetilde{\Gamma} = \phi^T W(P_X^T \bar{K} W)^{-1} P_Y^T Y \tag{15}$$

Thus the KPLS based predictions for test points X_t are given by

$$\widehat{Y}_t = K_t W(P_X^T \bar{K} W)^{-1} P_Y^T Y \tag{16}$$

where K_t is the kernel matrix between the training and test points [20].

After the Gaussian mixture model is estimated from the Bayesian inference based E-M algorithm with different operating phases being identified as $\{P_1, P_2, \ldots, P_C\}$, the unfolded input and output data matrices from training set can be split into C blocks corresponding to the different operating phases as follows

$$\widetilde{X}^{(B)} = \left[\widetilde{X}^{(1)^T}\ \widetilde{X}^{(2)^T} \ldots \widetilde{X}^{(C)^T}\right]^T \tag{17}$$

and

$$\widetilde{Y}^{(B)} = \left[\widetilde{Y}^{(1)^T}\ \widetilde{Y}^{(2)^T} \ldots \widetilde{Y}^{(C)^T}\right]^T \tag{18}$$

With each pair of input and output block matrices $\{\widetilde{X}^{(i)^T}, \widetilde{Y}^{(i)^T}\}$, the following C localized KPLS model can be built

$$\{\mathrm{KPLS}_1, \mathrm{KPLS}_2, \ldots, \mathrm{KPLS}_C\} \tag{19}$$

For the i-th measurement sample $\widetilde{x}_i^{(t)}$ of a test batch, its posterior probabilities with respect to different phases can be computed as follows

$$P(\theta_j|\widetilde{x}_i^{(t)}) = \frac{P_j p(\widetilde{x}_i^{(t)}|\mu_j, \Sigma_j)}{\sum_{l=1}^{C} P_l p(\widetilde{x}_i^{(t)}|\mu_l, \Sigma_l)} \tag{20}$$

Then this measurement point is classified into the $c(\widetilde{x}_i^{(t)})$-th Gaussian component as

$$c(\widetilde{x}_i^{(t)}) = \arg\max_j P(\theta_j|\widetilde{x}_i^{(t)}) \tag{21}$$

For this test sample, the $c(\widetilde{x}_i^{(t)})$-th KPLS model is automatically adopted to estimate the quality attribute value as

$$\widetilde{Y}_i^{(t)} = \{K_t W(P_X^T \bar{K} W)^{-1} P_Y^T Y\}_{c(\widetilde{x}_i^{(t)})} \tag{22}$$

The schematic diagram of the proposed MGMM-AKPLS approach is shown in Fig. 2.

4. CASE STUDY

In this section, the MGMM based adaptive kernel PLS method is compared to the conventional kernel PLS model on a simulated fed-batch penicillin fermentation process [21] and the accuracy of the soft sensor predictions is evaluated. The fermentation process is used to produce antibiotic that is the secondary metabolite of microbial cell culture. As the formation of the product penicillin is not associated with cell growth, the bioreactor operation is initiated with a short period of batch operation to grow the microorganism and then followed by penicillin production in fed-batch operation mode. The process flow sheet is shown in Fig. 3. The simulator is based on the mechanistic model [22] and the process has two cascade controllers to maintain the fermentor pH and temperature by manipulating the acid/base and cold/hot water flow ratios, respectively. The substrate and air are fed into the fermentor to provide glucose and oxygen for cell growth and penicillin formation, though both parameters are operated under open-loop conditions. The selected process input variables include substrate feed rate, agitation power, aeration rate, substrate feed temperature, fermentor temperature, pH, dissolved oxygen concentration, CO_2 concentration, culture volume and generated heat. On the other hand, three quality related variables (penicillin concentration, substrate concentration and biomass concentration) are selected

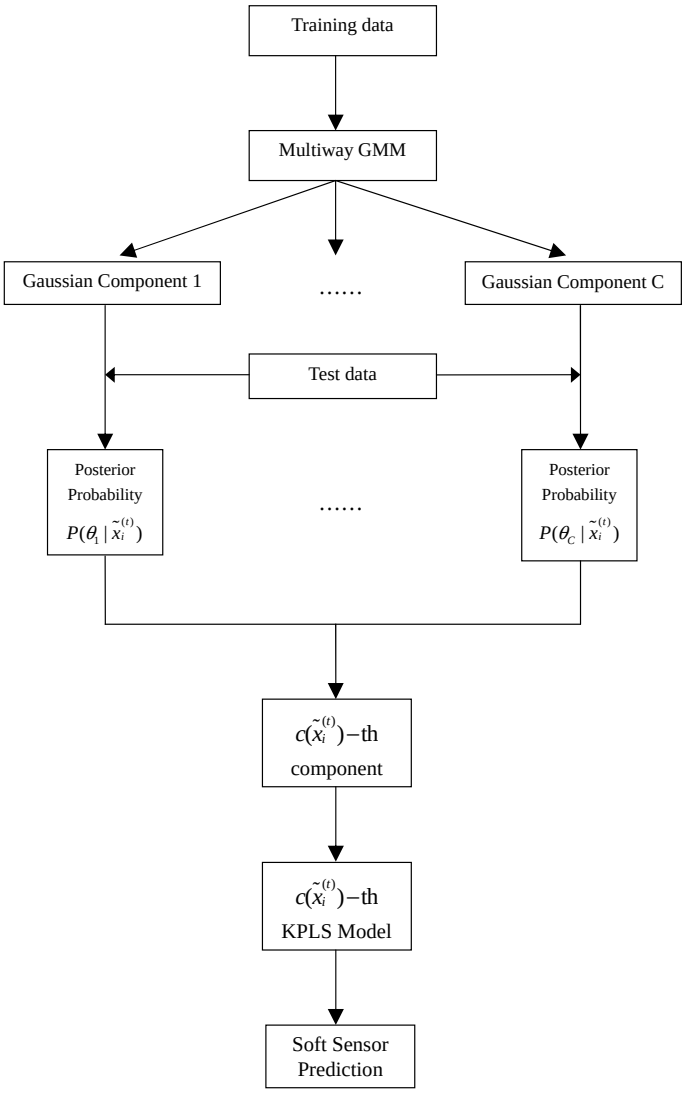

Fig. 2. Schematic diagram of the proposed MGMM-AKPLS approach

as output variables for soft sensor modeling. Both the input and output variables are summarized in Table 1. Total 30 batches are collected for soft sensor model learning and then additional 10 batches are used to test the model accuracy and reliability. The entire batch duration is 400 hours and the sampling period is 0.5 hour. Each of the training batches include pseudo random binary signals (PRBS) to ensure the adequate signal excitation for soft sensor modeling. The following root mean square square error (RMSE) index is used to evaluate the performance of the built soft sensors.

$$\mathrm{RMSE}(j) = \sqrt{\frac{\sum_{i=1}^{I^{(t)}} \sum_{l=1}^{L^{(t)}} (\hat{y}_{ijl}^{(t)} - y_{ijl}^{(t)})^2}{I^{(t)} L^{(t)}}} \qquad (23)$$

Table 1. Input and output variables of soft sensors in the fed-batch penicillin fermentation process

No.	Input Variable	No.	Output Variable
1	Substrate feed rate	1	Penicillin concentration
2	Agitator power	2	Substrate concentration
3	Aeration rate	3	Biomass concentration
4	Substrate feed temperature		
5	Fermentor temperature		
6	pH		
7	Dissolved oxygen		
8	CO_2 concentration		
9	Culture volume		
10	Generated heat		

where $I^{(t)}$ and $L^{(t)}$ denote the number of batches and number of sampling instants in the test set, and $y_{ij}^{(l)}$ and $\hat{y}_{ij}^{(l)}$ are the actual and predicted measurements of the j-th output variable, respectively.

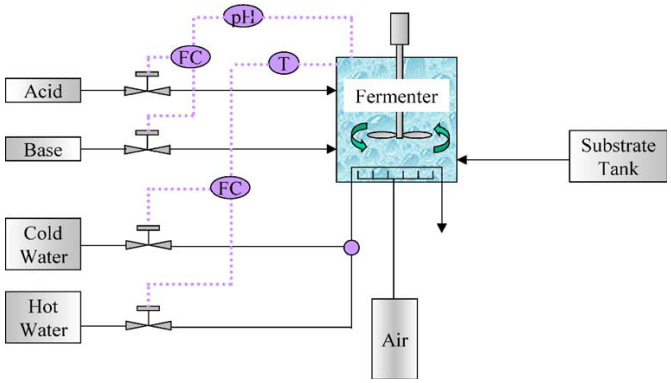

Fig. 3. Flow sheet of fed-batch penicillin fermentation process

With the multiway GMM estimation in the projected kernel subspace, the entire process operation is identified with three distinct phases that correspond to the cell growth, penicillin production and saturation stages. Then three localized PLS models can be built in the kernel feature space and the quality variable predictions are adaptively estimated for sampling instants from different operation phases. The trend plots of output predictions using single KPLS model and MGMM-AKPLS method are shown in Figs. 4, 5 and 6. As seen in Fig. 4, the single KPLS model results in fairly poor predictions on penicillin concentration. The predicted trend has significant pattern changes among the three different operation phases so that the innovation errors are inflated. The inferior accuracy and reliability of KPLS prediction is mainly due to the underlying relationship changes between process and quality variables among different operation stages, which causes the estimations to substantially deviate from the actual values. In contrast, the prediction accuracy on penicillin concentration is dramatically improved by adopting MGMM-AKPLS approach because the multiple KPLS models are adaptively switched among different phases to account for the shifting variable relationship. The

MGMM method has led to a relatively precise phase identification and then the Bayesian inference driven adaptive KPLS models can be automatically applied to the sample points from different operation stages. Therefore, the MGMM-AKPLS predictions coincide well with the actual values of penicillin concentration with very minimal innovation errors. The RMSE values of KPLS and MGMM-AKPLS based quality predictions are calculated and compared in Table 2. The RMSE value of KPLS model for penicillin concentration is as large as 0.195 while the MGMM-AKPLS model has reduced it by 80.5%. Likewise, the MGMM-AKPLS predictions on substrate and biomass concentrations are also far superior to those of single KPLS method. It can readily observed from Figs. 5 and 6 that the predicted values of KPLS model are drifting either significantly above or below the actual values during different operation phases. It is evident that the inherent multi-phase feature of fermentation process makes the single-model approach ill-suited. However, the proposed adaptive multi-model strategy integrates different local models corresponding to various operation stages and provides more reliable inferential predictions

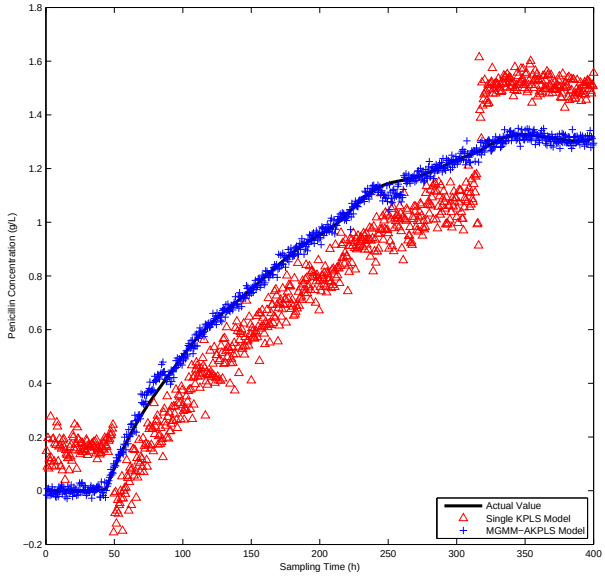

Fig. 4. Trend plots of penicillin concentration predictions using KPLS and MGMM-AKPLS methods

Table 2. Comparison of soft sensor predictions using single KPLS and MGMM-AKPLS methods

Quality Variable	KPLS	MGMM-AKPLS
Penicillin concentration	0.195	0.038
Substrate concentration	0.541	0.073
Biomass concentration	0.897	0.092

5. CONCLUSIONS

In this article, a multi-model based adaptive soft sensor approach has been developed for multi-phase batch or fed-batch

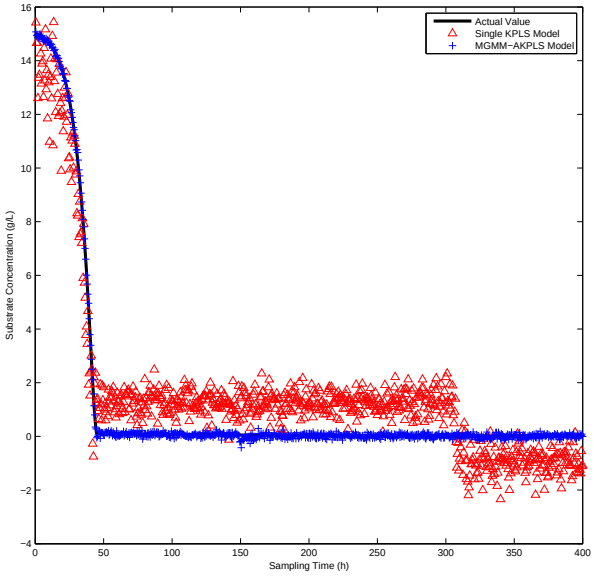

Fig. 5. Trend plots of substrate concentration predictions using KPLS and MGMM-AKPLS methods

processes to accurately predict the key quality variables. The presented MGMM-AKPLS approach has the attractive merits of automatic operating phase identification and adaptive selection of localized kernel PLS models using the Bayesian inference strategy. The application to the fed-batch penicillin fermentation progress has demonstrated that the new MGMM-AKPLS method is of much higher prediction accuracy and reliability than those of the conventional single KPLS method. The new soft sensor technique can be implemented on-line in batch or semi-batch processes to provide real-time measurements of essential quality variables and effectively save the cost of hardware sensors and maintenance.

REFERENCES

[1] B. Lennox and G.A. Montague and H.G. Hiden and G. Kornfeld and P.R. Goulding, Process Monitoring of An Industrial Fed-batch Fermentation, *Biotechnol. Bioeng.*, vol. 74, 2001, pp 125-135.

[2] Ündey and S. Ertunç and A. Çinar, Intelligent real-time performance monitoring and quality prediction for batch/fed-batch cultivations, *J. Biotech.*, vol. 108, 2004, pp 61-77.

[3] J. Yu, Nonlinear Bioprocess Monitoring using Multiway Kernel Localized Fisher Discriminant Analysis, *Ind. Eng. Chem. Res.*, vol. 50, 2011, pp 3390-3402.

[4] P. Kadlec and B. Gabrys and S. Strandt, Data driven soft sensor in the process industry, *Comput. Chem. Eng.*, vol. 33, 2009, pp 795-814.

[5] L. Fortuna and S. Graziani and A. Rizzo and M.G. Xibilia, *Soft Sensors for Monitoring and Control of Industrial Processes*, Springer, London, United Kingdom; 2007.

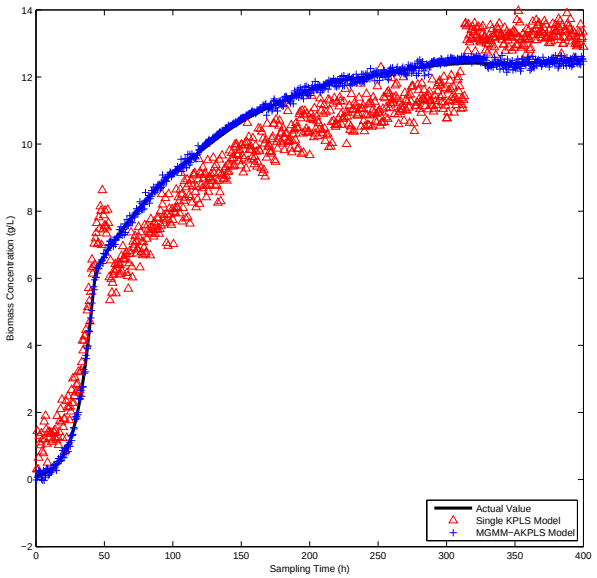

Fig. 6. Trend plots of biomass concentration predictions using KPLS and MGMM-AKPLS methods

[6] K. Desai and Y. Badhe and S.S. Tambe and B.D. Kulkarni, Soft-sensor development for fed-batch bioreactors using support vector regression, *Biochem. Eng. J.*, vol. 27, 2006, pp 225-239.

[7] D. Wang and R. Srinivasan and J. Liu and P.N.S. Guru and K.M. Leong, "Data-driven Soft Sensor Approach For Quality Prediction in a Refinery Process", *in IEEE International Conference on Industrial Informatics*, Singapore, 2006, pp. 230.

[8] J. Yu, Localized Fisher Discriminant Analysis Based Complex Process Monitoring, *AIChE J.*, vol. 57, 2011, pp 1817-1828.

[9] E. Zamprogna and M. Barolo and D.E. Seborg, Optimal selection of soft sensor inputs for batch distillation columns using principal component analysis, *J. Proc. Cont.*, vol. 15, 2005, pp 39-52.

[10] P. Facco and F. Doplicher and F. Bezzo and M. Barolo, Moving average PLS soft sensor for online product quality estimation in an industrial batch polymerization process, *J. Proc. Cont.*, vol. 19, 2009, pp 520-529.

[11] Q.P. He and S.J. Qin and J. Wang, A new fault diagnosis method using fault directions in Fisher discriminant analysis, *AIChE J.*, vol. 51, 2005, pp 555-571.

[12] H. Kaneko and M. Arakawa and K. Funatsu, Development of a new soft sensor method using independent component analysis and partial least squares, *AIChE J.*, vol. 55, 2009, pp 87-98.

[13] M.M. Rashid and J. Yu, Hidden Markov model based adaptive independent component analysis approach for complex chemical process monitoring and fault detection, *Ind. Eng. Chem. Res.*, vol. 51, 2012, pp 5506-5514.

[14] R. Jain and R. Rahman and B.D. Kulkarni, Development of a Soft Sensor for a Batch Distillation Column Using Support Vector Regression Techniques, *Chem. Eng. Res. Des.*, vol. 85, 2007, pp 283-287.

[15] J. Yu, A Bayesian inference based two-stage support vector regression framework for soft sensor development in batch bioprocesses, *Comput. Chem. Eng.*, vol. 41, 2012, pp 134-144.

[16] P. Geladi and B.R. Kowalski, Partial Least-Squares Regresion: A Tutorial, *Anal. Chim. Acta*, vol. 185, 1986, pp 1-17.

[17] J. Yu and S.J. Qin, Multimode process monitoring with Bayesian inference-based finite Gaussian mixture models, *AIChE J.*, vol. 54, 2008, pp 1811-1829.

[18] J. Yu and S.J. Qin, Multiway Gaussian mixture model based multiphase batch process monitoring, *Ind. Eng. Chem. Res.*, vol. 48, 2009, pp 8585-8594.

[19] M.A.F. Figueiredo and A.K. Jain, Unsupervised learning of finite mixture models, *IEEE Trans. Pattern Anal. Mach. Intell.*, vol. 24, 2002, pp 381-396.

[20] R. Rosipal and L.J. Trejo, Kernel partial least squares regression in reproducing kernel hilbert space, *J. Machine Learning Res.*, vol. 2, 2001, pp 97-123.

[21] I. Birol and C. Ündey and G. Birol and E. Tatara and A. Çinar, A web-based simulator for penicillin fermentation, *Int. J. Eng. Sim.*, vol. 2, 2001, pp 24-30.

[22] R.K. Bajpai and M. Reuss Çinar, A Mechanistic Model for Penicillin Production, *J. Chem. Technol. Biotechnol.*, vol. 30, 1980, pp332-344.