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Integrated condition monitoring and control of fed-batch fermentation processes

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Abstract

This paper investigates the benefits that the partial least squares (PLS) modelling approach offers engineers involved in the operation of fed-batch fermentation processes. It is shown that models developed using PLS can be used to provide accurate inference of quality variables that are difficult to measure on-line, such as biomass concentration. It is further shown that this model can be used to provide fault detection and isolation capabilities and that it can be integrated within a standard model predictive control framework to regulate the growth of biomass within the fermenter. This model predictive controller is shown to provide its own monitoring capabilities that can be used to identify faults within the process and also within the controller itself. Finally it is demonstrated that the performance of the controller can be maintained in the presence of fault conditions within the process.

Keywords: Partial least squares; Model predictive control; Fault detection

1. Introduction

Industrial fed-batch fermentation systems present a very difficult challenge to systems engineers. The lack of robust on-line sensors for key fermentation variables, such as biomass concentration has proved to be a significant obstacle for the implementation of advanced control and optimisation solutions [1]. The sensors which do exist for measuring these key variables, such as optical density measuring devices, high-resolution liquid chromatographs, nuclear magnetic resonance meters and biosensors [2] are unfortunately both expensive and have been shown to be unreliable when applied to large-scale systems [3].

As a consequence the majority of industrial fermentation control systems are based upon infrequent off-line assays and process operator supervision [4]. Low sampling frequencies and long delays in obtaining the results from off-line assays means that this approach to process supervision results in an inevitable compromise in the resulting quality of control.

To improve the quality of information that operations staff are presented with and to hence improve the quality of the resulting control, indirect measurement of biomass concentration, through the use of *soft-sensors*, has received considerable interest in recent years. Several techniques have been proposed for on-line estimation of conditions within fed-batch fermentation reactors. These techniques, which appear to be very promising, include mechanistic and data-based modelling techniques, such as neural networks [2]. A comprehensive review of these techniques is provided by [3].

In addition to providing operations staff with useful information regarding the progress of a batch, it is possible to integrate the soft-sensor within a variety of automatic control structures. The algorithms which have been proposed for controlling biomass growth in fed-batch fermentation systems tend to fall into three categories; optimal control, feedback control and hybrid control. The optimal control strategies typically adjust substrate feed rates by means of an optimal profile that is either determined online or offline [5,6]. The objective functions for the optimal controllers are usually formulated in order to maximise operating profits or productivity. In feedback control strategies, the regulation of the feed rate can be determined by

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standard control methods, such as PID controllers or more advanced model-based adaptive schemes [7]. Hybrid control strategies typically involve both optimal and feedback controllers with the former serving as the primary controller and the latter the compensator [8]. To enable the controller to deal with the non-linear features that are present within fed-batch fermentation processes, recent work has focused on the integration of neural network soft-sensors into non-linear model predictive control structures [9].

A further issue in the successful operation of fed-batch fermentation processes is the early and accurate detection of fault conditions, such as sensor failures or drifts, that may occur. The early detection of fault conditions is of great benefit in fed-batch fermentation processes since the earlier that a fault can be detected and acted upon, the lower its impact will be on the process. In some situations this can be critical, for example, a drift on a pH sensor could have catastrophic results on biomass growth if this measurement is used within a feedback control scheme.

In recent years condition monitoring tools have been developed and successfully applied to industrial fermentation processes. A particularly promising approach is the application of multivariate statistical process control techniques, such as Principal Component Analysis (PCA) and Partial Least Squares (PLS). The benefits of using these approaches, rather than more traditional methods, such as Statistical Process Control have been demonstrated through their application to fed-batch fermentation systems. These applications have exploited PCA and PLS to accurately detect and isolate several fault conditions, including a pH sensor drift in an industrial fermentation process [10] and contamination by foreign micro-organisms [11].

In previous studies monitoring and controlling of fed-batch fermentation processes have been viewed as independent problems. In this paper, however, these problems are considered together and an integrated fault detection and process control scheme is developed. This scheme relies heavily on the successful development of a PLS model to provide soft-sensing capabilities in a fed-batch fermentation processes. It is demonstrated that this PLS model can subsequently be used, not only in a predictive control framework to regulate the growth of biomass within the fermenter, but to also provide fault detection and isolation capabilities. It is further shown that the integration of the predictive controller and fault detection capabilities provides a useful diagnostic tool for the control system.

An overview of the basic PLS algorithm is provided in the following section along with a description of how this linear modelling approach can be extended to identify characteristics within a highly non-linear fed-batch fermentation process. It is then demonstrated how a PLS model can be integrated within a predictive control algorithm and applied to the benchmark fed-batch fermentation simulation developed by Birol et al. (2001). Finally, the conclusions from this work are discussed.

2. Partial least squares

2.1. Basic algorithm

Partial least squares (PLS) is a regression tool that is ideally suited for situations where high levels of correlation exist between cause variables. The algorithm has been applied extensively to industrial processes and its ability to generate accurate regression models in the presence of high levels of correlation is well documented (Piovoso and Kosanovich, 1997). Due to space limitations, the PLS algorithm is not reproduced here. However, for those that are interested the tutorial paper by Geladi [12] provides an excellent overview of the algorithm.

In addition to providing a mechanism for developing regression models, PLS may also be used as a method for detecting and isolating fault conditions. The approach for achieving this is very similar to that adopted when using Principal Component Analysis (PCA) [13]. Rather than attempting to detect the presence of any fault condition by monitoring each process variable independently, two statistics, referred to as the SPE and T^2 statistics, are monitored. Control limits can be placed around these statistics, which if violated indicate deviations from the process conditions that were recorded in the data used to develop the PLS model. More information regarding the application of PLS in the area of fault detection and isolation can be found in Nomikos and MacGregor [14].

3. PLS for model based predictive control

3.1. Model predictive control

Several authors, including [10] and Lakshminarayanan et al. [15] have suggested controlling the score space that is calculated within the PCA and PLS models, rather than the quality process variables themselves. This method of control is very much in its infancy and in this work a much more traditional approach to model predictive control (MPC) is employed. The PLS model that has been identified in this work uses a standard time-series, finite impulse response model which can be integrated with ease into a relatively standard MPC strategy to regulate the growth of biomass during the batch.

MPC has generated widespread interest in academia over the past three decades and its acceptance in industry is illustrated in a survey conducted by Qin and

Badgwell [16] which reported over 4600 industrial applications of MPC technology world-wide. Although there have been a variety of MPC algorithms developed, such as Dynamic Matrix Control (DMC) [15] and Generalised Predictive Control (GPC) [17] the concept of each of them is similar. This concept is to use a model of the system to predict future process outputs and thereby determine suitable future control moves. By placing appropriate limits on the length of the prediction horizon and the values of future control moves, a robust controller results that is capable of handling process constraints. A number of references exist to the development of predictive control, for example Clarke et al. [17]. As an example, for a linear GPC system, the model is used to predict the output trajectory between minimum and maximum horizons, N_1 and N_2 respectively, based upon control moves up to a horizon N_u in the future. A typical performance criteria (J) that the controller is developed to minimise is provided in Eq. (1).

$$J = \sum_{k=N_1}^{N_2} [w_{t+k} - \hat{y}_{t+k}]^2 + \sum_{k=1}^{N_u} \lambda_k \Delta u_{t+k-1}^2 \quad (1)$$

where Δu represents a series of changes that are made to the manipulated variable up to the horizon N_u. Only the first of these control moves is implemented and the calculations are repeated at the next time step. w is the set point, λ is a control action weighting chosen to prevent excessive control moves, $\hat{y}$ is the value of the output, as predicted by the model and t is the current sample time.

For application to batch processes there is a clear problem with the cost function in Eq. (1) which is that the prediction horizon reaches a maximum, which will be the end-point of the batch. In this work, therefore, the cost function is changed to the following:

$$\begin{aligned} J &= \sum_{k=t}^{t+N} [\hat{y}_k - w_k]^2 + \lambda \Delta u_k^2 \qquad \text{for} \quad t + N < t_{\text{end}} \\ J &= \sum_{k=t}^{t_{end}} [\hat{y}_k - w_k]^2 + \lambda \Delta u_k^2 \qquad \text{for} \quad t + N \geqslant t_{\text{end}} \end{aligned} \quad (2)$$

where: t is the current sample time of the batch; N is the length of the prediction horizon; w_k is the desired biomass concentration at sample time, k; $\hat{y}_k$ is the biomass concentration that is predicted by the PLS model at sample time k; Δu_k is the change in the manipulated variable (the substrate feed) made at sample time, k; λ is a tuning parameter. In this work, N and λ were manipulated in a structured manner to maximise the resulting performance of the controller. Eq. (2) also indicates that the value of N_u has been set to 1. A value of 1 for N_u and 10 for N were found to provide acceptable control performance in this application.

3.2. Application of PLS controller to the benchmark plant

To investigate the application of this control system, a benchmark simulation was used. This simulator, called Pensim, is based upon a series of detailed mechanistic models that describe a penicillin fed-batch fermentation process. For further details of this simulation see Birol et al. [18].

The first stage in the development of the control system for the Pensim simulation is to construct a soft-sensor, using the MPLS technique, to estimate biomass concentration. To generate the data necessary for the development of this model, data from 30 batches was collected. The standard pensim simulator applies a pseudo-random binary signal (PRBS) to several process variables, including aeration rate and agitator power. Since it was the intention to use the substrate federate as the manipulated variable in the developed control system, a further pseudo-random signal (PRS) was applied to this variable during each of the batches. 20 of these batches were used to train the PLS model (training batches) with the remainder used to validate the model (validating batches). Fig. 1 provides an example of the data that was collected during one of these batches. The sampling interval used in this work was 1 h.

A PLS model, containing 3 latent variables, was developed using the training batches. In this model the following measurements were used as input, or cause, variables: substrate feed rate aeration rate, agitator power, substrate feed temperature, substrate concentration, dissolved oxygen concentration, culture volume, pH, fermenter temperature and generated heat. In keeping with typical practices in industry it was assumed that it was not possible to use the biomass concentration measurements in either the model or the controller that is described later in this paper.

The accuracy of this model is illustrated in Fig. 2 which compares the actual biomass concentration with that predicted by the PLS model for five of the validation batches. This figure shows that the model provides a good estimate of biomass concentration within the fermenter.

Following the development of this PLS model it was subsequently integrated within a MPC control scheme for the simulator. The performance of the developed PLS model based control system when applied to the benchmark simulator is illustrated in Fig. 3. Fig. 3 demonstrates the ability of the MPC control scheme to regulate the biomass concentration within the reactor to several pre-specified trajectories. In these examples the trajectory was determined off-line and is based upon the open-loop response of the process.

Fig. 3 demonstrates that the controller achieves tight control when the end-point biomass concentration is set between 11 and 15. However, the performance is poor when the end-point biomass concentration is set to 9 or 17.

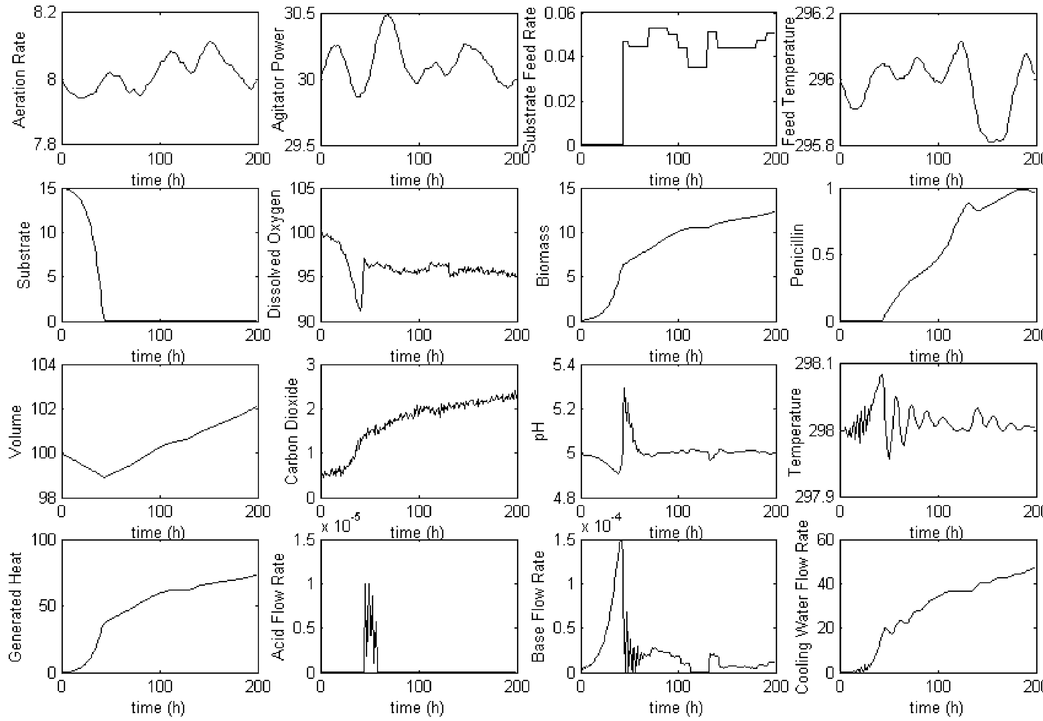

Fig. 1. Pensim training data.

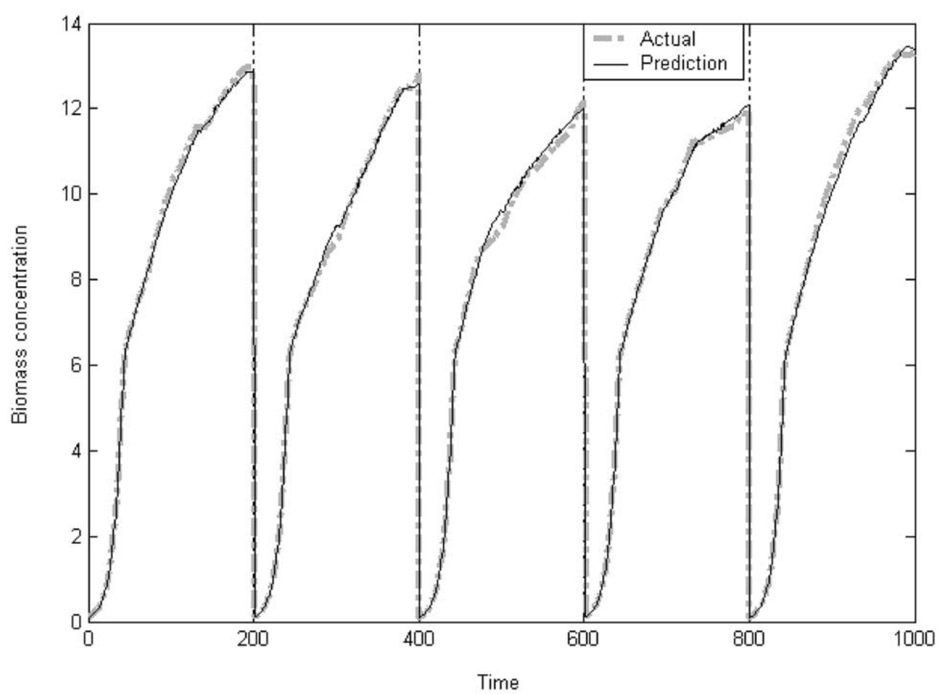

Fig. 2. PLS model prediction.

The reason why the performance of the controller is good when the end-point concentration is set between 11 and 15 is because the conditions necessary to achieve such end-point concentrations are well represented in the training batches. However, the conditions necessary to achieve end-point concentrations of 9 or 17 are not present in the training batches. The non-linearities that are present in the system have the effect that the model that is developed using the training batches is not valid for operating conditions that stray far beyond the conditions represented in the training batches. Since the MPC controller is only as good as the model that is used

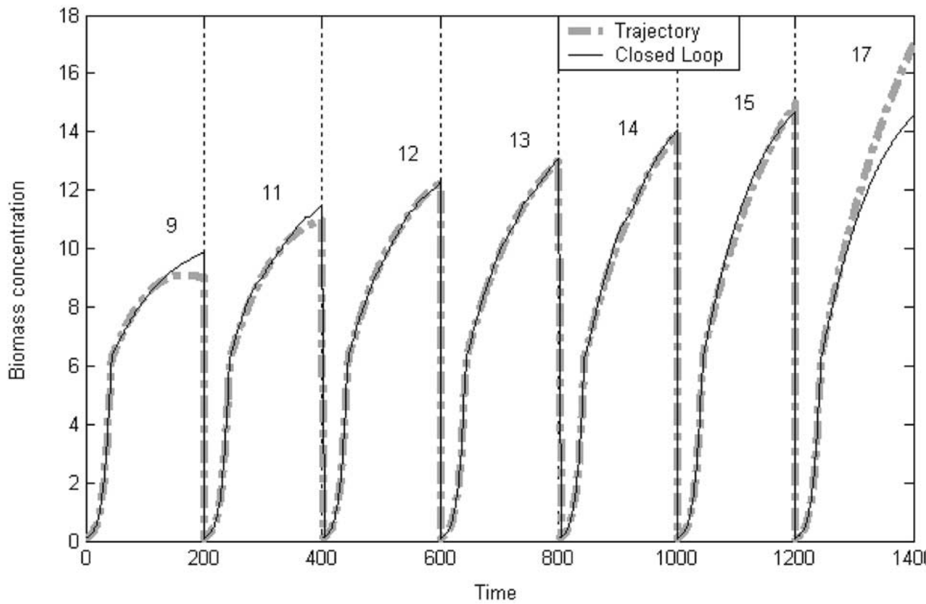

Fig. 3. Closed loop control performance.

within it then the performance of the control system will degrade as the operating conditions move away from the conditions that the model was trained on.

The complex, multivariable nature of the fermentation process means that it is not possible to simply state that the developed controller is valid within a certain set of conditions. For example, if the aeration rate increased beyond the values that were present in the training batches does this mean that the PLS model is no longer valid and the predictive controller should be switched off. The following section demonstrates how by using a PLS model within the predictive control system it is possible for such questions to be answered.

3.3. Controller monitoring

Monitoring the performance and suitability of control systems has received significant interest in both academia and industry in recent years. This interest was initiated by the work of Astrom [19] and Harris [20] who showed that it was possible to compare the performance of a particular control loop with that which could be achieved through the use of minimum variance control. This comparison was shown to provide a statistic which could be used to monitor the performance of single input, single output systems. The technique has since been extended to multivariable systems [21] and to time-varying processes [22]. Unfortunately, the approach involves the analysis of on-line measurements of manipulated and controlled variables. As stated earlier in this paper such data is not available in typical fed-batch fermentation systems. Consequently, the approaches that are based upon a comparison with minimum variance control are not appropriate for typical fed-batch fermentation processes.

An advantage, however, that the use of a PLS model within the control system has is that it is able to provide some diagnostic information regarding the status of the control system. This ability is illustrated in Fig. 4. This figure shows the SPE and T^2 charts that were produced for the PLS model in the earlier control results. These charts show that the SPE statistic continuously violates its control limits when the end-point biomass concentration is set to 9 and 17 and that the T^2 chart violates its control limit when the end-point biomass concentration is set to 9, 11, 15 and 17.

The SPE and T^2 charts can be interpreted as follows:

- The SPE chart provides an indication of the quality of the PLS model, i.e. its ability to predict the biomass concentration during the batch. A high SPE value would indicate that the relationships between the variables have changed to such a degree that the accuracy of the model is likely to be significantly degraded.
- The T^2 chart provides a measure of where the fermenter is operating, with respect to the conditions that were recorded in the batches used to develop the PLS model. A high T^2 value would indicate that the conditions within the fermenter are significantly different from those present in the training batches.

This analysis of the SPE and T^2 statistics allows the following observations to be made regarding the results presented in Figs. 3 and 4. When the end-point biomass concentration is set to 12, 13 or 14, the operating conditions are consistent with those of the training batches and the accuracy of the PLS model remains good. This is indicated by the fact that the T^2 and SPE values, respectively, remain below their limits throughout these batches. Consequently, as demonstrated in Fig. 5, the performance of the MPC controller remains good.

When the end-point biomass concentration is set to 11 or 15 the operating conditions within the fermenter begin to deviate from those present in the training data (this is indicated by the violation of the T^2 chart for this data), however the quality of the model remains good (the SPE value remains, with some exceptions, below the control limit). The MPC controller should therefore still perform reasonably well, however, its occasional violation of the control limit indicates that the performance will be reduced from what is achieved for the

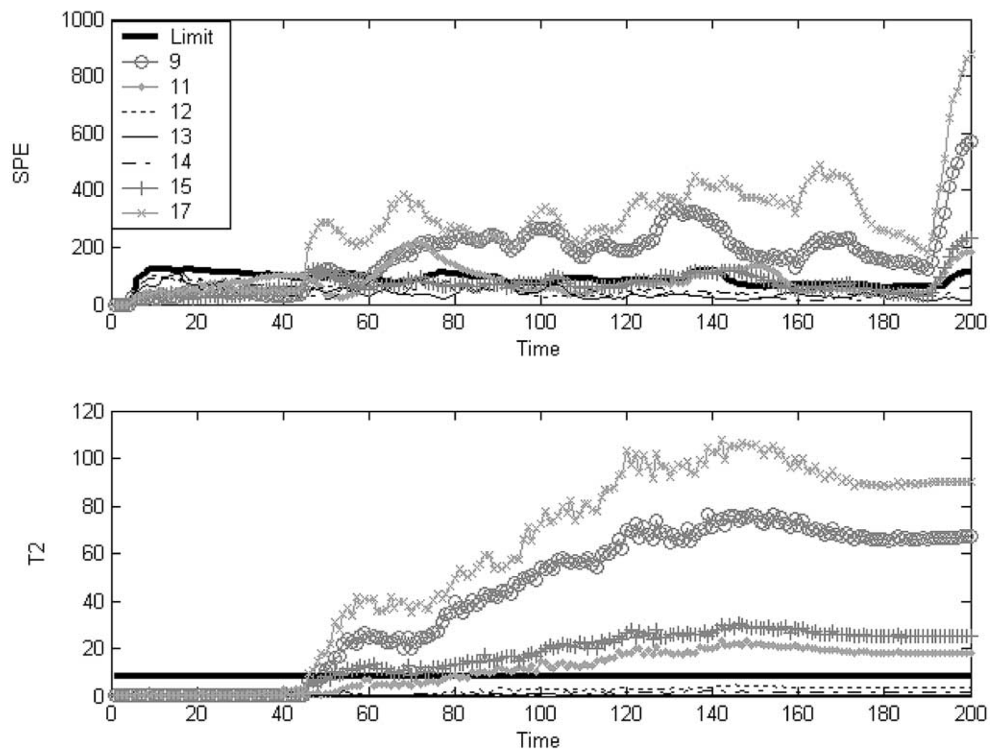

Fig. 4. SPE and T^2 charts for closed loop data.

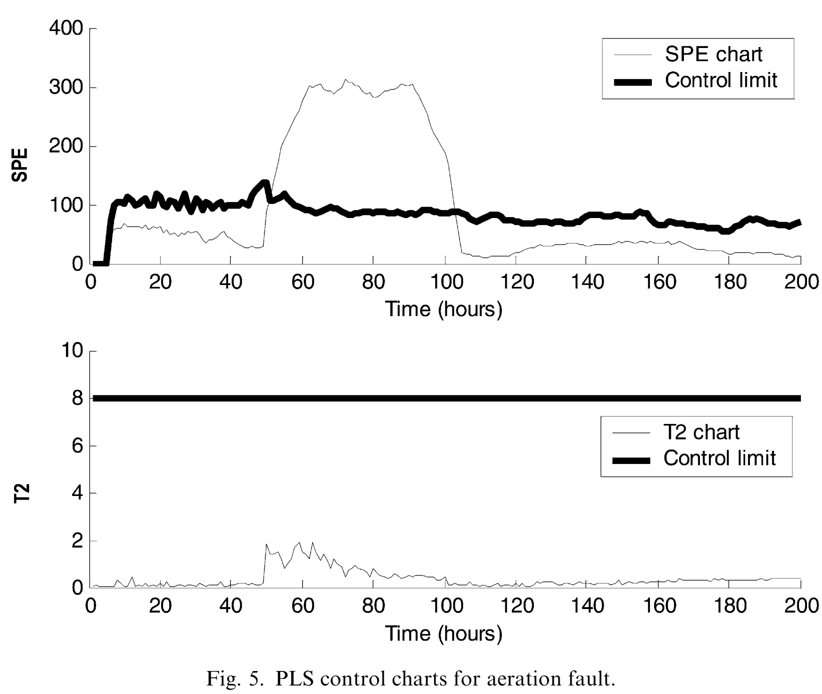

Fig. 5. PLS control charts for aeration fault.

end-points of 12, 13 and 14. This is confirmed in Fig. 3, which shows that although the performance of the controller is not as good for the end-point concentrations of 12, 13 or 14, it is still reasonable.

When the end-point biomass concentration is set to 9 and 17 it is seen that both the *SPE* and T^2 charts violate their control limits. This indicates that the conditions within the reactor are significantly different to those present in the training data and the accuracy of the model has deteriorated significantly. The deterioration of the accuracy of the model would suggest that the performance of the controller would be compromised, which is confirmed in Fig. 3 which shows a significant deterioration in performance of the controller for these end-points.

3.4. Integrated process control and fault detection

In addition to providing control capabilities, the PLS model that is used within the MPC controller can also be used to detect faults on the process. To test the ability of the PLS model to detect and isolate fault conditions within the fermenter, a series of faults were introduced into the process, while it was under closed loop control. The faults that were introduced were those that were suggested and analysed by the authors of the simulation [23].

Fig. 5 illustrates the ability of the PLS model to correctly detect and isolate one process fault, a step fault of 5% applied to the aeration measurement between 50 and 100 h. Fig. 5 shows that the *SPE* chart violates its control limit immediately after the fault condition occurs, while the T^2 chart remains well below its limit. The inability of the T^2 chart to detect this fault condition is consistent with the results of Goulding et al. [24] who demonstrated that the *SPE* chart is much more sensitive to the detection of faults than the T^2 chart.

Fig. 6 shows the SPE contribution chart that was produced immediately after the *SPE* limit was violated. This chart, indicates correctly that variable 1, which is the aeration measurement, is the likely cause of the fault condition.

In further tests it was found that the PLS model was able to detect and isolate all the faults that were investigated by Undey et al. [23].

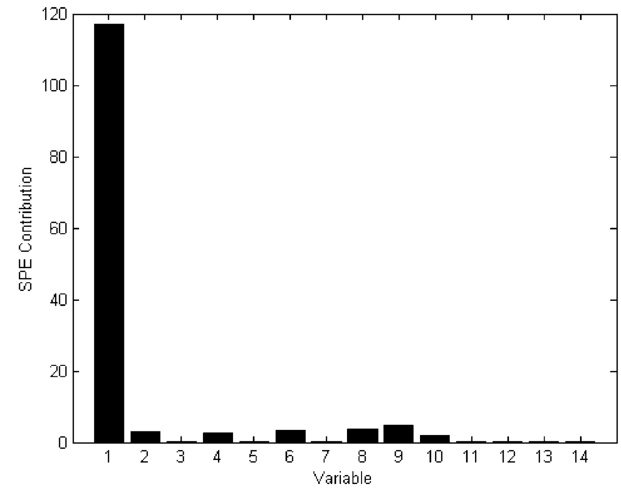

Fig. 6. Contribution chart for aeration fault.

3.5. Intelligent process control

A weakness of most process control and fault detection schemes is that following the detection of a fault condition, such as a drift on a sensor, then the scheme is rendered useless until the particular fault is resolved. This is a problem if there is likely to be a delay before any fault, such as a sensor failure, is dealt with, because the process controller and condition monitor may be unavailable for a significant length of time.

This problem is highlighted in the following example, where a step increase of 0.5 is applied to the pH sensor measurement (this increase means that if the actual value of the pH within the reactor is 5.0, then the pH sensor will read a value of 5.5). This fault creates a major disturbance to the process as the pH measurement is used in two automatic control loops. The pH measurement is firstly used in a single loop feedback control scheme that regulates the pH in the fermenter to 5. Since there is a drift of 0.5 on the pH sensor then this controller will actually maintain the pH within the reactor at 4.5 (this is because at this value of the actual pH, the sensor will read 5.0), which could result in an adverse response by the bio-organisms inside the fermenter. In addition the pH measurement is used by the PLS model to predict the biomass concentration. Since the pH measurement is incorrect then so too will be the biomass prediction made by the model. As a consequence the predictive controller will operate poorly and the productivity of the batch may be affected. It is therefore important that such a fault can be quickly detected and isolated and a mechanism put in place so that the predictive controller and fault detection scheme can function normally in spite of this fault. Fig. 7 displays the control charts produced by the PLS model during this fault. The charts clearly show that the fault has been detected following its introduction after 100 h.

One method that is available for enabling the controller and condition monitor to function during this fault it is to use the capabilities of the PLS model to infer the pH measurement, rather than use the actual pH measurement itself. The ability of PLS to infer unavailable and inaccurate process variables is discussed in detail in Nelson et al. [25]. In this paper three methods are proposed for estimating the values of any missing process variables. Of the three methods proposed it has been found in previous studies [10], that the method referred to as single component projection is an appropriate technique to use. This approach is described by

Nelson et al. [25] as being equivalent to *replacing the missing values by their minimum distance projections onto the current estimate of the loading or score vector at each iteration*.

Fig. 7 shows that both the *SPE* and T^2 values exceed their control limits immediately after the fault enters the system at 100 h. The PLS model correctly identifies this violation as a fault with the pH sensor and after 5 consistent violations of the *SPE* control limit are recorded then the PLS model is used to infer the pH measurement, using the single component projection method. The reason that the algorithm waits for 5 continuous violations of the *SPE* chart before acting is to be sure that the violation of the *SPE* control limit is actually a result of a fault condition and is not a false alarm.

Fig. 8 compares the actual pH measurement with that recorded by the sensor and that inferred by the PLS model. This figure shows that the pH value inferred by

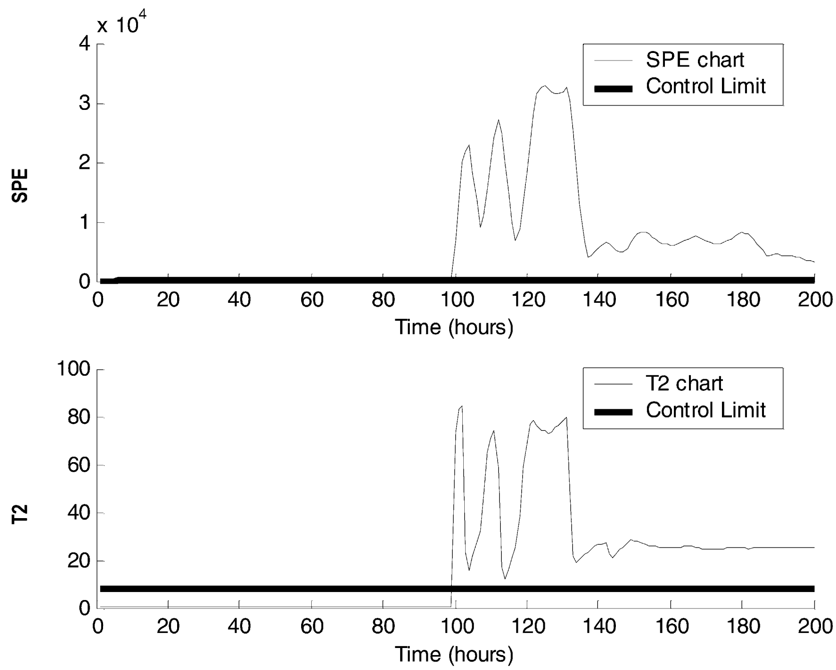

Fig. 7. PLS control charts during pH fault.

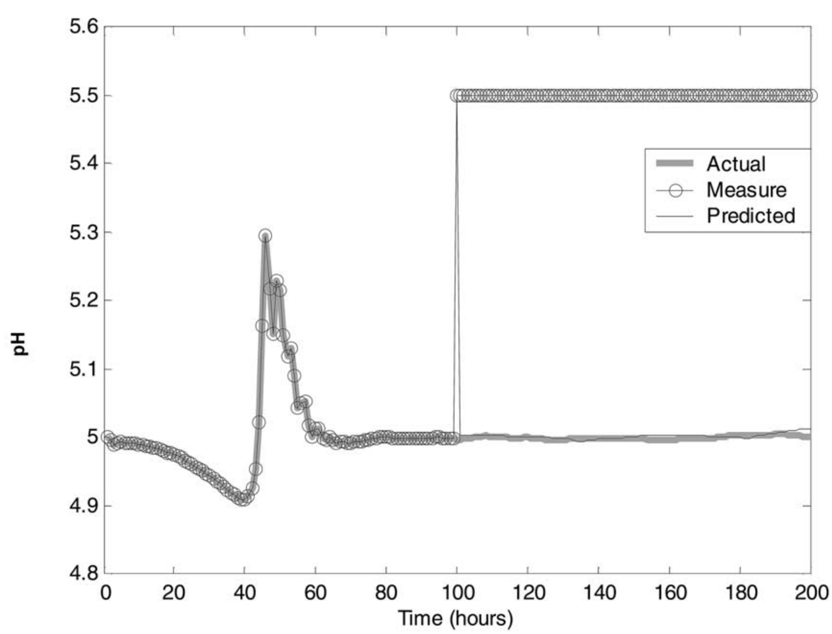

Fig. 8. pH measurement.

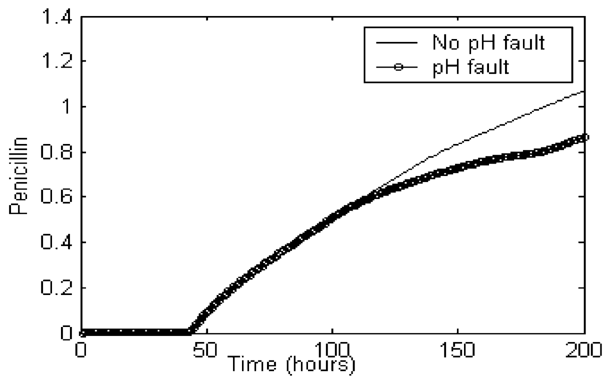

Fig. 9. Penicillin production.

the PLS model is very consistent with the actual pH within the reactor. A result of this accurate inference of the pH measurement is that the performance of the controller is largely unaffected. This is reflected in Fig. 9 which shows that if the MPC controller uses the raw pH measurement, the penicillin production reduces significantly. However, when the PLS model is used to infer this measurement the penicillin production is seen to remain very similar to that which would result if there were no pH sensor fault.

4. Conclusions

This paper has demonstrated the benefits that the PLS modelling technique offers in improving the operation of fed-batch fermentation systems. It is shown, through application to a benchmark simulation of a fed-batch fermentation process that mutli-way PLS can provide accurate inference of quality variables, such as biomass concentration, that are often difficult to measure using on-line sensors. It is also demonstrated that the same PLS model can be used to provide early detection and isolation of fault conditions within the fermenter.

A further advantage of using a model developed using the PLS algorithm is that it can be integrated within a fairly standard model predictive control strategy and used to regulate the growth of biomass in the fermenter. The structure of the PLS model then enables charts to be constructed that are able to monitor the status of the predictive controller. This monitoring provides a measure of how consistent current operating conditions are with the data used to develop the model and also an indication of how accurate the PLS model is likely to be in these conditions.

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References

[1] S. James, R. Legge, H. Budman, Comparative study of black-box and hybrid estimation methods in fed-batch fermentation, Journal of Process Control 12 (1) (2002) 113–121.
[2] I. Golobic, H. Gjerkes, I. Bajsic, J. Malensek, Software sensor for biomass concentration monitoring during industrial fermentation, Instrumentation Science and Technology 28 (4) (2000) 323–334.
[3] G.A. Montague, Monitoring and Control of Fermenters, Institution of Chemical Engineers, 1998.
[4] P. Dacosta, C. Kordich, D. Williams, J.B. Gomm, Estimation of inaccessible fermentation states with variable inoculum sizes, Artificial Intelligence in Engineering 11 (4) (1997) 383–392.
[5] S. Park, W.F. Ramirez, Optimal regulatory control of bioreactor nutrient concentration incorporating system identification, Chemical Engineering Science 45 (12) (1990) 3467–3481.
[6] J.A.D. Rodrigues, R.M. Filho, Optimal feed rates strategies with operating constraints for the penicillin production process, Chemical Engineering Science 51 (11) (1996) 2859–2864.
[7] C.B. Youssef, V. Guillou, et al., Modelling and adaptive control strategy in a lactic fermentation process, Control Engineering Practice 8 (11) (2000) 1297–1307.
[8] J.-P. Chiou, F.S. Wang, Hybrid method of evolutionary algorithms for static and dynamic optimization problems with application to a fed-batch fermentation process, Computers and Chemical Engineering 23 (9) (1999) 1277–1291.
[9] D. Hodge, M.N. Karim, Nonlinear MPC for optimization of recombinant Zymomonas mobilis fed-batch fermentation, Proceedings of the American Control Conference 4 (2002) 2879–2884.
[10] B. Lennox, G.A. Montague, H.G. Hiden, G. Kornfeld, P.R. Goulding, Process monitoring of an industrial fed-batch fermentation, Biotechnology and Bioengineering 74 (2) (2001) 125–135.
[11] S. Lakshminarayanan, R.D. Gudi, S.L. Shah, K. Nandakumar, Monitoring batch proceses using multivariate statistical tools: extensions and practical issues, in Proceeding of IFAC World Congress, San Francisco, (1996) pp. 241–246.
[12] P. Geladi, B.R. Kowalski, Partial least squares regression: a tutorial, Anal. Chim. Acta 185 (1986) 1–17.
[13] B.M. Wise, N.B. Gallagher, The process chemometrics approach to process monitoring and fault detection, J. Proc. Cont. 6 (6) (1996) 329–348.
[14] P. Nomikos, J.F. MacGregor, Multi-way partial least squares in monitoring batch processes, Chemometrics and Intelligent Laboratory Systems 30 (1995) 97–108.
[15] S. Lakshminarayanan, S.L. Shah, K. Nandakumar, Modeling and control of multivariable processes: a dynamic PLS approach, AIChE J. 43 (1997) 2307–2322.
[16] S.J. Qin, T.A. Badgwell A survey of model predictive control technology, Control Engineering Practice, in press.
[17] D.W. Clarke, C. Mohtadi, P.S. Tuffs, Generalised predictive control. Part 1: the basic algorithm and part 2: extensions and interpretations, Automatica 23 (2) (1987) 137–160.
[18] G. Birol, C. Undey, A. Cinar, A modular simulation package for fed-batch fermentation: penicillin production, Computers and Chemical Engineering 26 (11) (2002) 1553–1565.

[19] Astrom, Computer control of a paper machine—an application of linear stochastic control theory, IBM J. Res. Dev. 11 (1967) 389–405.
[20] T.J. Harris, Assessment of control loop performance, The Canadian Journal of Chemical Engineering 67 (1989) 856–861.
[21] T.J. Harris, F. Boudreau, J.F. MacGregor, Performance assessment of multivariable feedback controllers, Automatica 32 (11) (1996) 1505–1518.
[22] B. Huang, Minimum variance control and performance assessment of time-variant processes, Journal of Process Control 12 (6) (2002) 707–719.
[23] C. Undey, E. Tatara, B. A. Williams, G. Birol, A. Cinar, A hybrid supervisory knowledge-based system for monitoring penicillin fermentation, in Proceedings of the American Control Conference, Chicago, 2000, pp. 3944–3948.
[24] P.R. Goulding, B. Lennox, D.J. Sandoz, K. Smith, O. Marjanovic, Fault detection in continuous processes using multivariate statistical methods, International Journal of Systems Science 31 (11) (2000) 1459–1471.
[25] P.R.C. Nelson, P.A. Taylor, J.F. MacGregor, Missing data methods in PCA and PLS: score calculations with incomplete observations, Chemometrics and Intelligent Laboratory Systems 35 (1996) 45–65.