Iterative Learning Modelling and Control of Batch Fermentation Processes

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Abstract: In this paper a novel method for batch-to-batch modelling and optimization, Iterative Learning Partial Least Squares Optimization (IL-PLSO) is proposed. This method uses a recursive technique to update a multi-way PLS model so that it is able to track the varying dynamics from one batch to the next. Based on the model obtained at the end of one batch, a Quadratic Programme (QP) is used to identify the required trajectory for the primary manipulated variable in the subsequent batch to ensure that the target end-point quality is met. This target quality can be gradually increased to optimise the productivity, or yield of the process. The capabilities of the proposed IL-PLSO method are illustrated through its application to optimise the end-point product quality of a benchmark simulation of a fermentation process. In this application, the proposed algorithm is able to identify an optimal trajectory for the manipulated variable after approximately 10 batches. The results are shown to compare very favourably with alternative approaches.

Keywords: Iterative methods, Partial Least Squares, Optimal control, Adaptive control, Batch control, Quadratic programming.

1. INTRODUCTION

Almost all processes in nature work through cycles and as most industrial processes are based on natural systems, they too tend to be cyclic. Iterative Learning Control (ILC) is a technique, first applied in robotic systems, that was designed to deal with the control of systems such as this. In ILC, information collected from previous cycles of the system is used to obtain an *optimal* Manipulated Variable Trajectory (MVT) in subsequent cycles. The optimal MVT is typically obtained by minimizing a function related to the difference between the actual and desired outputs of the system (Owens & Hätönen 2005). ILC and similar techniques, such as Repetitive Control and Run–to-Run Control have been successfully applied in many control applications (Wang et al. 2009).

The focus of the work described in this paper is optimising fermentation processes, where the control requirement is typically to identify an appropriate trajectory, or feeding law, for substrate addition, which ensures that product quality or yield is maximised. The use of optimization procedures to improve yield and product quality is crucial in fed-batch processes, such as fermentation systems, as there are intense pressures on manufactures to improve quality and profitability of these processes (Zhang & Nguyan 2008). Unfortunately, the optimization and control of batch processes is complicated by the nature of the dynamics, which tend to contain nonlinearities, have slow response times and contain large numbers of variables that affect the outputs of the system (Lei et al. 2001).

As a result of the difficulties in controlling batch processes, many such processes in industry operate in open-loop, which is far from ideal. To regulate such processes, several techniques have recently been proposed in academia. One approach is to design a control system that is based on a mechanistic understanding of the dynamics within the process (Jobé et al. 2003; Picó-Marco et al. 2005; Valentinotti et al. 2003). A major drawback with this approach is that the knowledge required to develop such a control system is typically unavailable. As a result, alternative approaches have been proposed that utilise data-driven or empirical models to estimate the optimal feeding law (Fu & Barford 1992; Mezghani et al. 2001; Lee & Lee 2003; Francois et al. 2003; Camacho et al. 2007; Busch et al. 2007; Zhang & Nguyan 2008).

Several approaches have been proposed for modelling the dynamics of batch and fed-batch processes. These include non-linear techniques, such as neural networks (Lennox et al, 2001b) and multi-way extensions to multivariate statistical methods, such as Partial Least Squares (PLS) (Nomikos and MacGregor, 1995). The simplicity and ease with which PLS models can be identified has made them particularly popular in batch applications. PLS models are identified for a process by reducing the dimensionality of the measured variables by projecting them on to a new *Latent Variable* space (Wold et al, 1984).

Whilst multi-way PLS models have traditionally been used in fault detection studies (Lennox et al, 2001a), in recent work their application to regulate batch processes has been proposed. For example, in Flores-Cerrillo & MacGregor (2004) and Flores-Cerrillo & MacGregor (2005), the authors use latent variable models to define a cost function, which is solved to identify an optimal manipulated variable trajectory. Wan et al. (2012) later extended this technique to enable it to provide improved disturbance rejection capabilities. These PLS based control techniques have until now been based on PLS models with fixed parameters, that don't explicitly consider the iterative nature of the batch process. Improved process operation can be obtained by adapting these models to the local conditions of the process. For example, Camacho & Pico (2007) presented a Batch to Batch gradient-based optimization method that utilised adaptive PLS models. Their technique gathered data from the process and then used these data to update the PLS model at the end of each batch. Their results showed significant improvement in end-point quality compared to those presented in Pham & Larsson (1998) and Lei et al (2001). However the gradient based approach that was applied in this study required data from approximately 20 batches before the process could begin to be optimised and then took a further 60+ batches before the process was optimised. Operating such large numbers of batches can in many cases be impractical or financially prohibitive.

This article presents an alternative approach to batch-to-batch optimization that defines a cost function for batch performance, which takes in account the change in the manipulated variables, and that is based on a multiway adaptive PLS model. This cost function is then solved using a QP to identify a suitable Manipulated Variable Trajectory (MVT) that can be applied to optimise the process.

The paper is organized as follows: Section 2 presents the mathematical tools used in the proposed IL-PLSO technique. Section 3 presents the methodology employed in the adaptive optimization scheme. Section 4 deals with the case study and compares the results with those obtained in other research studies. Finally, in section 5 the conclusions from this work are presented.

2. MATHEMATICAL PRELIMINARIES

2.1 Partial Least Squares modelling

PLS regression (Wold et al, 1984) is a popular technique used in batch modelling. It reduces the dimensionality of the variables included in the model by projecting them on to a Latent Variable (LV) space and then performing the regression in this space using only a limited number, n, of these LVs. The technique is described by equations 1 and 2.

$$X = TP^{T} + E$$
(1)
$$Y = TC^{T} + F$$
(2)

The PLS model describes the correlation between the output quality variables Y, and the input variables X. The loading matrices P and C describe the relationships between the X and Y matrices to the scores for each LV respectively. The T matrix is referred as the scores of the LVs and E and F are the residual matrices, which are obtained when some of the LVs are discarded.

PLS can be applied to the three-dimensional datasets obtained in batch processes by unfolding the data contained in the X and Y matrices, as presented in Nomikos and MacGregor (1995). This can be achieved by extending the variables (J) and the time intervals (K) of the data in the batch (I) direction (batch-wise unfolding). Equation 3 shows the 3D to 2D transformation of the X matrix.

$$\boldsymbol{X}(I,J,K) \Rightarrow \boldsymbol{X}(I,JK) \tag{3}$$

2.2 Adaptive PLS model

Batch to batch modelling requires the use of adaptive techniques to enable the developed model to gradually adjust itself to better approximate the local conditions of the process as they change from one batch to the next. Batch processes tend to be highly non-linear, but over limited operating spaces, linear models, such as multi-way PLS techniques have been shown to provide a reasonable approximation of the process dynamics (Nomikos and MacGregor, 1995). The adaptive optimisation technique proposed in this article gradually adjusts the operating point of the process, by manipulating the MVT from batch to batch. The optimal MVT is determined by using an optimisation function to minimise the difference between the estimated end-point quality of the batch and its target. The estimated end-point quality is provided by a multi-way PLS model that adapts to the current conditions of the batch.

It is important, at least in the case studies investigated in this paper, that the model adapts such that it gives greater weighting to the most recent batches and forgets older batches. The reason for this is that as the operating conditions change from batch to batch, so too will the process dynamics and it is important that the model captures the most recently encountered dynamics.

A computationally efficient method for adapting PLS models was proposed by Qin (1998). This approach incorporates a forgetting factor, λ , which enables the model to *remember* only the most recently collected data. Using Qin's approach, a new PLS model is identified when data from a new batch, xand y becomes available. New X and Y matrices are formulated as follows:

$$\boldsymbol{X} = \begin{bmatrix} \lambda \boldsymbol{P}^T \\ \boldsymbol{x}^T \end{bmatrix}$$
(4)

$$\boldsymbol{Y} = \begin{bmatrix} \boldsymbol{\lambda} \boldsymbol{C}^T \\ \boldsymbol{y}^T \end{bmatrix}$$
(5)

Where P and C are obtained from the previously identified PLS model.

The number of batches of data, N, that are used in the adaptation phase is related to the forgetting factor, λ , in the following way (Dayal & MacGregor 1997):

$$N = \frac{1}{1 - \lambda}$$
(6)

$$0 < \lambda \le 1$$

2.3 Quadratic Programming Optimization

where

To identify the MVT that is required to satisfy a performance criteria, such as a specific target end-point quality, a cost function, related to this must be determined and solved.

In the work reported in (Flores-Cerrillo & MacGregor 2004), the authors used an optimisation algorithm to identify the MVT that minimised a function that described the quadratic difference between the target for a quality measurement and its estimated value. The cost function used in that work is provided in equation [7]. In this expression, constraints in the latent variable space are introduced to ensure that the process does not move too far away from the original operating conditions.

$$\min_{\Delta t} \quad \left(\hat{y} - y_{sp}\right)^T Q_1 (\hat{y} - y_{sp}) + \Delta t^T Q_2 \Delta t \tag{7}$$
where
$$\hat{y}^T = (\Delta t + \hat{t})^T C^T$$
st
$$\Delta t_{min} \le \Delta t \le \Delta t_{max}$$

Where \hat{y} is an estimate of the final quality; y_{sp} is the target end-point, or set-point; \hat{t} is the score vector for the current batch; Δt is the change in the score vector which is to be optimized; Q_1 and Q_2 are diagonal weighting matrices. In the research published in (Zhang et al. 2010), the authors use a similar approach using the score directly in the cost function.

The use of constraints in the latent variable space is not ideal as the real constraints are imposed on the raw measured variables. Equation 8 transforms the cost function in to the the space of the manipulated variables, u:

$$\min_{\Delta u} (\hat{y} - y_{sp})^T Q_1 (\hat{y} - y_{sp}) + \Delta u^T Q_2 \Delta u$$
s.t. $\hat{y}^T = score_{batch}^T C^T$

$$lb \le \hat{u} \le ub$$
(8)

Where *lb* and *ub* are vectors containing the lower and upper bounds; the score vector for the current batch $score_{batch}^{T}$ can be decomposed into the input variable vector x and the projection weights matrix W^* as defined in equations 9 and 10.

$$score_{batch}^{T} = x^{T} W^{*}$$
(9)

$$\boldsymbol{W}^* = \boldsymbol{W} \left(\boldsymbol{P}^T \boldsymbol{W} \right)^{-1} \tag{10}$$

In order for the optimisation to consider changes in the initial conditions of the batch, the vector of input variables is defined as in equation 11 (Flores-Cerrillo & MacGregor, 2004). This vector divides the measured data in to the previous process measurements, $\mathbf{x}_{measured}^T$; values for the previously implemented manipulated variable changes, $\mathbf{u}_{implemented}^T$; future changes to the manipulated variable, $\Delta \mathbf{u} + \mathbf{u}_{future}^T$ and future estimated values for the process measurements (which are determined using missing data techniques that utilise the identified PLS model), \mathbf{x}_{future}^T .

$$\boldsymbol{x}^{T} = \begin{bmatrix} \boldsymbol{x}_{measured}^{T} & \boldsymbol{u}_{implemented}^{T} & \Delta \boldsymbol{u} + \boldsymbol{u}_{future}^{T} & \boldsymbol{x}_{future}^{T} \end{bmatrix}$$
 (11)

Using equation 11, equation 8 can be reformulated as a QP problem defined by equation 12.

$$\min_{\Delta u(i)} \frac{1}{2} \Delta u^T H \Delta u + f^T \Delta u$$
(12)
where
$$H = W^*_{Ufuture} C^T Q_1 C W^{*T}_{Ufuture} + Q_2$$

$$f^T = [C(W^{*T}x) - y_{sp}] Q_1 C W^{*T}_{Ufuture}$$

$$\Delta u = \hat{u} - u_{future}$$
s.t.
$$lb - u_{future} \leq \Delta u \leq ub - u_{future}$$

The diagonal matrices Q_1 and Q_2 are the weights that describe the relative importance of the difference between the target and predicted quality and the changes that need to be made to the trajectory of the manipulated variable. In this work, Q_1 was set to be the identity matrix and Q_2 was adjusted until an acceptable response was obtained.

3. METHODOLOGY

The proposed IL-PLSO algorithm is applied in 6 relatively straightforward steps.

Step1: Collect data from open-loop batches

A suitable initial trajectory is identified for the manipulated variable. This could be the MVT for a *golden batch*, an initial estimate of a suitable trajectory, or as was applied in the case study in Section 4, a vector of zeros. A small PRBS is applied to this nominal MVT and then data is collected from m batches.

In most manufacturing processes, the cost of running batches to identify the system is prohibitive as it requires process excitation and hence there is an incentive to use the minimum amount of initial testing. In the case study investigated in this work, it was found that 3 test batches were sufficient to identify the initial model, which is consistent with the results of Flores-Cerrillo & MacGregor (2005).

Step 2: Identify Initial PLS model

A PLS model is identified using the data collected from the m initial batches. To determine the number of latent variables required in the model, leave-one-out cross validation utilising the mean squared prediction error (MSEP) was used.

Step 3: Estimate the future values of \mathbf{x} based on initial conditions

The initial conditions for the current batch are collected and the PLS model is used to make a prediction of the end-point quality, y. When making the prediction, the future values of the manipulated variables are set to nominal conditions and the Projection to the Modal Plane (Arteaga & Ferrer 2002) algorithm is used to obtain the future values of the process variables in the x^{T} vector. This algorithm is defined in equation 13.

$$\boldsymbol{x}_{A:N}^{T} = (\boldsymbol{P}_{1:A}^{T} \boldsymbol{P}_{1:A})^{-1} \boldsymbol{P}_{1:A}^{T} \boldsymbol{x}_{1:A}^{T} \boldsymbol{P}_{A:N}^{T}$$
(13)

Where: $P_{1:A}$ is a matrix which consist of the values of P for the measured and implemented values x from the start point to the interval A where the control is applied $(x_{1:A})$ and $P_{A:N}$ is a matrix with the values of P which corresponds to the estimated future values of $x(x_{A:N})$.

Step 4: Calculate optimal MVT

The objective in the case study investigated in this paper was to increase end-point yield, which was the chosen measure of quality for this particular process. Hence, the target measure, y_{sp} was increased from batch to batch and the quadratic optimization function, defined by equation 12 was then solved to find a suitable vector for the MVT. The precise amount by which the target end-point quality can be

manipulated from one batch to the next will be problem dependent, but the case study in Section 4 provides some suggestions as to how the end-point quality can be increased from batch to batch.

For the PLS model to adapt to the new conditions, it is necessary to apply continuous excitation to the MVT. This excitation need not be large and in the study described in Section 4, a low amplitude PRBS was added to the newly acquired MVT. Finally, the MVT is passed through a low pass filter to reduce the changes made from one sample point to the next, transforming the MVT into a time correlated vector (Camacho et al. 2007). Smoothing the MVT was found to improve the results significantly.

Step 5: Run the batch and collect data

The batch is run with the computed MVT and data is collected. At the end of the batch a check is made that the output quality has improved. If it has not then the previous MVT, with newly computed PRBS should be applied to the next batch and the target for the output should remain unchanged. If however, quality is improved then the output target should be increased slightly for the next batch.

Step 6: Model Adaptation

With data collected from the most recent batch, two different options are available for adapting the model for use in the next batch. If the number of batches of data available is less than LV+1, then the model cannot be identified using the maximum number of LVs. Therefore equations 13 and 14 should be employed to increase the size of the X and Y matrices. If the number of batches exceeds LV+1 then equations 4 and 5 should be used.

$$X_{new} = \begin{bmatrix} \lambda x_{previous \ batches}^T \\ x^T \end{bmatrix}$$
(14)

$$\boldsymbol{Y} = \begin{bmatrix} \lambda \boldsymbol{y}_{previous \ batches}^T \\ \boldsymbol{y}^T \end{bmatrix}$$
(15)

4. CASE STUDY

4.1 Saccharomyces cerevisiae production

The proposed IL-PLSO was applied to the simulated fermentation process described in (Lei et al. 2001). This is a simulation of a *Saccharomyces cerevisiae* fed-batch production process. The proposed algorithm has been demonstrated on several fermentation simulations. However, because of space limitations, only the results obtained from the Saccharomyces simulation are presented here. The results for this system were consistent with those obtained from other simulations.

The objective of the case study was to maximize the endpoint biomass concentration by iteratively optimising the trajectory of the highly concentrated glucose feed (100g/l). The total time for each batch is 10 hours, which is divided in to 100 sample points. To simulate the effects of sensor noise, Gaussian noise with a signal to noise ratio of 0.01 was added to the output quality measurement and $\pm 5\%$ variability in the amplitude of the initial conditions in order to simulate realistic process changes. The amplitude of the PRBS added to the MVT was set to 3% of the nominal amplitude, which is consistent with the work published in (Camacho et al. 2007).

The simulation model includes 11 model reactions and 9 mass balance dynamic equations. The variables for the equations and initial conditions are shown in table 1.

Table 1 Variables of the dynamic equations

Variable or state	Initial condition
Glucose concentration	0 (g/l)
Pyruvate concentration	0 (g/l)
Acetaldehyde concentration	0 (g/l)
Acetate concentration	0 (g/l)
Ethanol concentration	0 (g/l)
Biomass concentration	1 (g/l)
Active cell material	0.3
Acetaldehyde dehydrogenase	0.0075
Volume	7 (I)

The initial conditions in this study were consistent with those used in other research studies that have used this simulation (Lei et al. 2001; Camacho et al. 2007). One exception to this is the initial value for the active cell material. This was reported to be 0.1 in Camacho & Pico, 2007. However, consultation with the authors of this work suggests that the value used was actually 0.3.

The process is subject to a volume constraint of 9 litres in the reactor, and therefore the feeding law must be set such that this volume is not exceeded. This volume constraint is defined in equation 16.

$$\sum_{i=initial}^{totaltime} u_{i nominal} + \sum_{i=initial}^{totaltime} \Delta u_i \le vol_{max} - vol_{ini}$$
(16)

Equation 16 is equivalent to equation 17, which takes account of the fact that the initial volume in the reactor was 7 litres.

$$\sum_{i=initial}^{totaltime} \Delta u_i \le 2 - \sum_{i=initial}^{totaltime} u_{nominal}$$
(17)

Equation 17 represents a simple inequality constraint for volume. However, care must be taken with it as the normalisation within the PLS model must be considered, as shown in equation 18.

$$a * \Delta u' \leq 2 - b * (u_{nom}' * std_{unom} + mean_{unom}')$$
(18)
Where $a = timeinterval * std_{unom}$
 $b = timeinterval * [1 \ 1 \ 1 \dots 1]_{size \ u_{nom}}$

Equation 18 scales the mean centred variables from the PLS model and tries to restrict the volume to 9l. As the model adapts, the mean of each of the variables may not be zero, which implies that the optimized values of Δu won't be exactly zero centred. In the case study reported in this paper, this didn't cause any problems. However, future work will

focus on ensuring that volume constraints can be better handled within the optimisation routine.

Figure 1 shows the final volume for 100 batches, produced in the case study. This figure shows that the 91 constraint was not exceeded during any of the batches.



Figure 1 Final volume for 100 batches

4.2 Results from the application of IL-PLSO

The initial PLS model obtained in step 1 was identified using data collected from 3 batches with 5% variability in the biomass concentration, the active cell material and the acetaldehyde dehydrogenase.

It should be noted that one of the objectives in this study was to develop an optimisation approach that required the minimum number of initial test batches. Using more batches to identify the initial PLS model was not found to provide significant benefits. The value of λ for the model adaptive modelling was set to 0.8 which corresponds to the relevant information of 5 batch data sets, similar results were obtained from 3 to 10 batches used for the adaptive modelling. For this simulation, the number of LV used was automatically adjusted from batch to batch up to 7 LV, from that point on the number of LV was kept fixed.

To try to increase biomass production from batch to batch, the target, or set-point, for the end-point biomass concentration was initially set to a final value of 2g/l and then increased by 1g/l whenever the target was reached. The biomass target reached a value of 11g/l, which was not exceeded. The initial value of 2g/l was considered appropriate through analysis of the variation in biomass concentration in the three initial batches. By imposing only a gradual increase in the end-point target, this allowed the model to slowly adapt to changing conditions in the simulation.

Figure 2 compares the results obtained when a fixed target of 11g/l was applied to the process (solid line) and when a gradually increasing target (dotted line) was applied over 30 batches. The trends on this graph were the averages obtained from 100 repeated tests. These show that although the fixed target led to a faster increase in biomass concentration, it also produced greater variability in this concentration and as a consequence a gradually increasing target was used in subsequent tests. Upper and lower limits are also plotted on this graph. These limits were set at +/- 3 x the standard deviation of biomass production over the 100 test runs.



Figure 2 Comparison of the constant and variable set points.

To ensure only smooth changes in substrate were applied, upper and lower constraints of 0 l/h and 0.6 l/h respectively where applied to Δu .

Figure 3 shows the final biomass concentration that was obtained for 100 batches when IL-PLSO was applied to the simulation. Also displayed on this figure are the approximate results obtained using the technique proposed by (Camacho et al. 2007). This figure shows that the proposed algorithm converges to its optimal point after approximately 15 batches and that the final biomass concentration for both techniques is very similar. The first 3 batches for IL-PLSO and the first 20 batches for the Camacho & Pico technique relate to the batches used to identify the initial PLS model.



Figure 3 Final Biomass concentration average for 100 tests.

The mean of the Biomass concentration for the IL-PLSO result was 10.98 g/l with a standard deviation of 0.27 g/l. In comparison, the results obtained by Camacho and Pico (2007) were a final average biomass concentration of 10.74 g/l with a standard deviation of 0.16 g/l. This indicates that the consistency of the approach proposed by Camacho and Pico (2007) exceeds that of IL-PLSO. However, IL-PLSO

converges significantly faster and requires fewer initial batches.

The MVT evolution of the feeding law of a test with 100 batches is shown in figure 5. The final MVT shows a smooth, low frequency response, which is consistent with what would be required on a real process.



Figure 4 Optimal MVT for 100 batches

5. CONCLUSIONS

A novel batch to batch optimization technique termed IL-PLSO was proposed and its performance compared with results presented elsewhere. This comparison showed that although IL-PLSO produced results with slightly lower consistency, the speed of convergence was considerably faster than alternative techniques.

For the proposed technique to be applied to the simulated process investigated in this study, only 3 initial batches of data were required. These batches required PRBS sequences to be applied to the primary manipulated variable and using these data an initial model of the process could be identified. Following this, only a further 12 batches were required before the algorithm converged to an optimal MVT.

The IL-PLSO method is well suited for high cost – low quantity production in batch multivariate processes, and can be used to improve even further the MVT obtained from an understanding of the process dynamics, a *golden batch* trajectory or even an initial guess at the optimal MVT.

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