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Multivariate batch to batch optimisation of fermentation processes incorporating validity constraints

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ABSTRACT

This paper presents an innovative optimisation technique, which utilises an adaptive Multiway Partial Least Squares (MPLS) model to track the dynamics of a batch process from one batch to the next. Utilising this model, an optimisation algorithm solves a quadratic cost function that identifies operating conditions for the subsequent batch that should increase yield. Hard constraints are shown to be required when solving the cost function to ensure that batch conditions do not vary too greatly from one batch to the next. Furthermore, validity constraints are imposed to prevent the PLS model from extrapolating significantly when determining new operating conditions. The capabilities of the proposed technique are illustrated through its application to two benchmark fermentation simulations, where its performance is shown to compare favourably with alternative batch-to-batch optimisation techniques.

1. Introduction

Batch processes, and fermentation systems in particular, tend to exhibit highly non-linear characteristics. These non-linearities can be introduced by changes that affect the process from one batch to the next, for example changes in raw material properties or equipment changes or may be a result of the complex dynamics of the chemical or biological materials [1]. These changes to the process are typically ignored by recipe-based systems in use on the majority of industrial fermentation plants and as a consequence there can be considerable variation in product quality from batch-to-batch. As regulatory authorities, such as the Food and Drugs Agency (FDA) introduce more stringent requirements, it is crucial that control systems are introduced that ensure product consistency despite variations in process characteristics [2]. Model based control systems are now used routinely to regulate continuous processes in the presence of process variability. However, as a consequence of the difficulties in obtaining a model that adequately describes the process dynamics, the application of such technology to batch processes is rare [3].

A variety of modelling techniques have been proposed to describe the dynamics of batch processes. These include mechanistic techniques [4] and linear and non-linear empirical techniques. Empirical models are typically easier to develop and more accurate for large-scale systems, where there is an incomplete understanding of the fundamental dynamics of the process. For batch processes, the most frequently applied empirical techniques are based on Multiway Partial Least Squares (MPLS). MPLS was originally designed to detect and locate abnormal conditions, such as sensor faults, within batch processes [5–8] and it is particularly well suited to modelling batch processes where product quality measurements are only available at the end of the batch. Such processes are the subject of this work.

In recent years there have been several studies that have integrated multivariate statistical models, such as MPLS, within control systems to regulate product quality and improve yield. Flores-Cerrillo and MacGregor [6] for example, integrated an MPLS model within a Model Predictive Control (MPC) strategy to regulate operating conditions within an emulsion polymerisation process to improve product consistency in the presence of disturbances. Wan et al. [7] extended this approach and demonstrated that if a disturbance model was used within the controller then control performance could be improved significantly. A similar approach was used in Ref. [8], where a constrained control strategy was applied to reduce product quality variation resulting from unmeasured disturbances in an exothermic chemical batch reactor.

Further studies in to the use of multivariate statistical models to regulate batch processes have been conducted by several research groups, including [9–13]. Whilst this work has been demonstrated to be successful, multivariate techniques are not without their limitations. For example, many multivariate methods assume fixed

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batch lengths, which can introduce problems. Whilst there exist many processes where batch lengths vary considerably the case studies considered in this work are fermentation processes where it is common for batch lengths to be fixed. The extension of multivariate statistical techniques to processes with variable batch lengths is an area of considerable interest; see for example [14], which involved the successful application of MPLS to an industrial process where batch length varied between 8 and 24 h and [15] which proposed the use of dynamic time warping to allow MSPC techniques to be applied a polymerisation process.

In the studies described above, the control systems were applied to regulate end-point product quality by adjusting the manipulated variables in the process. In such systems, the conditions within the process should not differ considerably from one batch to the next and hence linear models are often sufficient to model the process dynamics. However, the focus of the present work was to maximise product quality or yield from one batch to the next, in a process known as *batch-to-batch optimisation*.

In batch-to-batch optimisation, a model of the process is used at the start of the batch to compute the trajectory of the manipulated variable (or Manipulated Variable Trajectory−MVT) over the full batch length that it is expected will ensure that the end-point product quality meets its target. This target may change from batch-to-batch to, for example, continuously increase yield. To maximise product quality, it is likely that the conditions within the batch process, and as a consequence the dynamics of the system, will change considerably. Linear techniques, such as MPLS will have difficulties in tracking the non-linear characteristics of the process under such conditions and hence alternative techniques have been investigated for batch-to-batch optimisation. Lee [16,17], for example proposed a MPC technique which used characteristics of Iterative Learning Control (ILC) to achieve batch to batch optimisation. Their results showed a clear increase in yield from one batch to the next when applied to a jacketed semi-batch reactor. Similarly, in Ref. [18] an ILC strategy was formulated to ensure a tracking performance was achieved in a semi-batch chemical reactor. This strategy used a dynamic model based on energy balance equations and an MPC based optimization strategy. Another example [19] consisted of using a sliding mode control scheme to increase the growth rate in a fermentation process. The primary distinction with this approach was that it required minimum knowledge of the online process parameters by relying on a partial state feedback law derived from a reference model. The sliding mode scheme was then used to overcome model uncertainties.

Despite its limitations attempts have been made to incorporate MPLS within batch to batch optimisation schemes. In Ref. [20], for example, the authors proposed and successfully implemented a batch to batch optimisation technique that used a hybrid model to predict the final particle size distribution (PSD) in a cobalt oxalate synthesis process. The hybrid model was a combination of a simplified first principle model and an MPLS model; the latter being used to correct errors in the mechanistic model. An alternative approach, proposed by Camacho [21], involved using an evolutionary optimisation technique that identified MVTs that would improve product yield in the forthcoming batch. The MVTs were determined by consideration of the gradient identified from an MPLS model that described the dynamic characteristics of the batch. The MPLS model was adapted from one batch to the next. The proposed technique led to a significant increase in yield when applied to a simulated fermentation process and compared very favourably with knowledge based techniques.

An important advantage of the MPLS based optimisation approach proposed in Ref. [21] is its low computational complexity. However, a limitation with the approach is that the technique does not consider that the model is only valid around the operating conditions used to calibrate the model. In the technique proposed in this paper, the validity of the MPLS model is considered as the new MVT is determined. This ensures that the identified MVT will not upset the process considerably from one batch to the next, ensuring a gradual and more robust change to process conditions from one batch to the next.

A number of techniques have been suggested for ensuring the validity of PLS models. These techniques have typically been formulated to provide confidence limits on the predictions made by the models. For example, in Ref. [22] a method was proposed for determining confidence limits for PLS estimates that used a combination of the Mean Squared Error (MSE) of the PLS model and the value of Hotelling's T^2 statistic. The limits were combined with Squared Prediction Error (SPE) charts in Ref. [6] to produce an integrated technique for quality prediction, fault diagnosis and monitoring of batch processes.

Confidence intervals were also used in Ref. [23], where an innovative Latent Variable Model Predictive Control (LVMPC) strategy for continuous processes was presented. The authors included the use of normalized restrictions in the cost function to avoid the tuning of a weighting factor used in Ref. [6]. In addition, a quadratic error term for the model, frequently employed in monitoring and fault diagnosis, was included in the cost function to ensure the model remained valid. This work was extended in Ref. [24] where the validity of the model, measured using both the T^2 and Square Prediction Error (*SPE*) statistics were introduced as a hard constraint within the control system.

The work in this article formulates an alternative batch-to batch optimisation approach that presents a QP problem that is solved in the MVT space. This is in contrast to alternative formulations found in the literature which solve the QP problem in the Latent Variable (LV) space [6,7,9,24]. The drawback of the LV approach is that once the optimised points are found, it is necessary to compute the real MVT by inverting the PLS model, which can cause actuation changes that are detrimental to the yield if the PLS model is not sufficiently constrained. In addition, the proposed design uses validity restrictions inside the MVT optimization to limit the solution of the QP problem to the region within which there is confidence in the predictions made by the PLS model. Similar validity restrictions have been used before for MPC in the literature [11,23], but not to batch-to-batch optimization.

The work presented in this paper firstly proposes a novel batch-to-batch optimisation technique, which adapts a MPLS model from one batch to the next so that it is able to track the conditions within the process. This model is then used within a control system that iteratively adjusts the MVT to increase yield of the batch process. The benefits of introducing validity constraints within the control system are then demonstrated through its application to two benchmark simulation studies.

Section 2 of this paper formulates the mathematical theory and control methodology that is used in the proposed approach. Section 3 then describes the two benchmark batch fermentation simulations that the proposed batch-to-batch control technique is applied to. The results obtained using these simulations are then discussed and compared with those obtained using previously proposed techniques. Finally, the conclusions from the work are presented in Section 4.

2. Methodology

This section provides a brief overview of MPLS modelling and the approach by which an MPLS model can be integrated within a batch-to-batch optimisation strategy. The nomenclature used in this section is summarised in Appendix A. Further details of PLS and MPLS can be found in Refs. [3,22] respectively.