Multi-scale Analysis and Control Structure Design for Biotechnological Processes

Jobrun Nandong[1], Yudi Samyudia[1] and Moses O. Tadé[2]
[1]Department of Chemical Engineering, Curtin University of Technology Sarawak Malaysia;
[2]Department of Chemical Engineering, Curtin University of Technology, Perth WA, Australia

Abstract

In this paper, a novel methodology of multi-scale analysis and control structure design is proposed for typical multi-scale biotechnological processes. This methodology combines the concepts of factorial design, multiprojection analysis and control relevant metric. The effectiveness of this methodology in handling multi-scale variables including micro-scale phenomena is demonstrated using two examples, which are two-stage distributed feed (TSDF) extractive alcoholic fermentation and recycled micro-aerobic fermentation processes. In both examples, the control structure designs resulting from the proposed methodology shows superior robustness/performance than the arbitrarily chosen control structures.

Keywords: multi-scale, fermentation, PCA, v-gap, control structure design

1. INTRODUCTION

Most of the fundamentally important processes are multi-scale in nature where one of the most striking examples which have served the humanity since prebiblical time is biotechnological process (Knorr & Sinskey, 1985). Recent progress in biotechnological field has created tremendous amount of disparate data and information about many biological systems of interests. This disparate data and information are multi-scale in nature spanning across different time and length scales. Despite this progress, the realization of the potential benefits from this multi-scale data particularly in practical aspects remains a daunting task. This provides the challenges and opportunities which have become the subject of intensive research especially in the last few years. A unified framework which is capable to integrate all this data and information across different time and length scales is a vital aspect towards producing new insights and meaningful knowledge which then, could subsequently be used to improve bioreactor performance – the heart of biotechnological processes (Cooney, 1983). In this respect, one of the key enabling tools which could serve as platform for integrating this disparate data and knowledge is multi-scale modeling where recently, its application to complex biological processes has shown significant progress (Ayton et al., 2007).

Although the applications of multi-scale modeling and analysis have recently shown some progress in the performance improvement of biochemical processes, for examples (Teixeira et al. 2007; Bideaux et al., 2006; Galaktionov et al., 2002; Charbon & Swaminarayan, 1998; Schwarzer & Peukert, 2005), the most prevalence approach currently adopted in the bioprocess improvement remains relying on the macroscopic models. These models are generally based on the unstructured kinetics i.e. *formal* macro-scale approach. In view of the recently growing competition in biochemical industry worldwide, the development of efficient process monitoring and control are considered as one of the key aspects in bioprocess improvement (Henson, 2006; Alford, 2006; Schügerl, 2001). Not withstanding this significance,

the applications of advanced control methods which have been practiced extensively in chemical industries are still scarcely implemented in biological processes (Komives & Parker, 2003).

Moreover, the extension of the advanced controller techniques to bioprocesses might not be straight forward owing to the different natures between chemical and biotechnological processes. One of the key differences between chemical and biochemical processes is that the former consists of large numbers of functionally diverse, and frequently multifunctional, sets of elements that interact selectively and nonlinearly, which produce coherent rather than complex behaviours as in the later (Kitano, 2002). In other words biological systems are finely tuned across multiple resolutions e.g. from genomic to metabolic resolution. Another important aspect in bioprocess control adopted so far is that, most of the research efforts have only been dedicated in the development of controller algorithms and only scarce reports are available on the control structure design (Nandong et al., 2008a).

In chemical industries, the choice of control structure design has been recognized as a factor that has far more important impact than the choice of controller algorithms on the plant dynamic performance (Arbel et al., 1996; Hovd & Skogestad, 1993; Morari et al., 1980). The tasks of designing control structure or strategy involve the selection of and pairings of suitable manipulated and measured variables. To date in bioprocess control design, the choice of controlled outputs and manipulated variables are generally predetermined from process knowledge and experience, for examples, substrate and dissolved oxygen concentrations are normally controlled owing to their well-known influences on the cellular metabolisms. The reason why this approach works well in bioprocess could be due to the relatively small number of available inputs and outputs (e.g. frequently only one bioreactor involved) as compared with the traditional chemical processes. Additionally, in bioprocess the control system is normally focused on bioreactor.

But credible studies indicate that many of the bioprocess improvements including the finding of innovative operations could be achieved by using multiple bioreactors rather than single large bioreactor (Dourado et al. 1987; Bayrock & Ingledew, 2001; Chaabane et al., 2006; Xiu et al., 2002). Although increasing the number of bioreactors would not increase dramatically the number of inputs, the number of total bioreactors outputs generally multiplied by the number of bioreactors i.e. two bioreactors could have twice the number of outputs as single bioreactor. Thus, whenever multiple bioreactors are used, the engineers would then have to face more challenges in term of selecting the most suitable controlled outputs. Furthermore, an interesting result from recent studies (Nandong et al., 2007a; Nandong et al., 2008a) show that the implementation of appropriate control structure based on multi-scale analysis could enable the control of nonlinear system using only the traditional linear PID-type controllers. Thus, this reveals that by adopting an appropriate control structure design based on multi-scale concept could lead to an interesting, and yet yields practical alternative to applying complex advanced control strategies. Additionally, application of simple PID controllers is advantageous over that of complex advanced controller algorithms owing to its robustness and ease of maintenance and operations.

Presently, there is no control structure design methodology which has been reported in literature which is suitable for the multi-scale processes that include micro-scale phenomena i.e. most of the control structure methodologies presented to date are suitable for the macro-scale variables. In this paper, the key aim is to present a proposed methodology of multi-scale analysis and control structure design for multi-scale biotechnological processes (see Nandong et al., 2008a). The effectiveness of this proposed methodology is demonstrated on two examples, which are (1) two-stage distributed feed (TSDF) continuous extractive alcoholic

fermentation, and (2) recycled micro-aerobic fermentation system. It would be shown that based on the proposed methodology, one could find a control strategy that could be efficiently used to control a nonlinear multi-scale system using only simple linear PID controllers. Furthermore, the simulation study shows that the control structure design based on the proposed methodology has superior robustness and performance than that of the arbitrary one.

2. METHDOLOGY

Due to the space limitation, only brief description of the proposed methodology is presented. The details about this methodology are presented in Nandong et al. (2008a). The key idea underlying the proposed methodology is to identify the *critical* variables which are strongly correlated with the specified plant performance measures. The foremost performance measure which is to be achieved by the resulting control structure design is to minimize the nonlinear excitation in the face of external disturbance occurrence. If the nonlinear excitation is small then this should justify the use of simple linear PID-type controller. And of course other important performance measures such as yield and productivity must also be achieved or at least be maintained closed at the desired values. But, it is expected that to be able to control a system such that steady-sate performance measures (i.e. yield and productivity) could be maintained closed at desired values (or minimized variability), it is crucial that the system is easily control (i.e. has favorable dynamic operability). Thus this is the reason why finding the control structure which could minimize the nonlinear excitation when external disturbance occurs is the foremost objective to be fulfilled (i.e. dynamic performance measure) before meeting steady-state performance measures.

Figure 1 shows the mapping concept from the key or *critical* variables to the performance measures. One way to do this mapping is by adopting the technique of multiprojection analysis e.g. Principal Component Analysis (PCA). In the PCA, the objective is to reduce the large number of interacting variables in a dataset into smaller group of key variables i.e. dimensional reduction. As applied to the control structure analysis as illustrated by Figure 1 below, the PCA analysis is used to identify the *critical* variables that strongly correlate with the performance measures. This mapping could lead to three general cases as:

1. **Single Variable - Single Performance (SVSP) Mapping** – One variable/parameter is strongly correlated with a certain performance measure.
2. **Single Variable-Multiple Performances (SVMP) Mapping** – One variable/parameter is strongly correlated with more than one performance measures.
3. **Multiple Variables-Multiple Performance (MVMP) Mapping** – Multiple variables/parameters are strongly correlated with multiple performance measures – cross mapping exists.

The complexity of the control structure design problem depends on the cases above, for example, if the mapping results in case 1, then the control structure problem is expected to be relatively simple as compared with case 2 or 3. But in most practical applications, case 2 and 3 are expected to be common. Additionally, in view that the control structure also depends on the operating level, thus it is possible that there is no proper control structure exists at all i.e. there is no critical variables that map strongly to the specified performance measures as reported in Nandong et al. (2007b). The methodology for finding the operating conditions with

favorable dynamic operability could be found in this paper. The interested readers could refer to Kourti and MacGregor (1995) for background on PCA and Vinnicombe (2001) for v-gap metric concept used in this methodology.

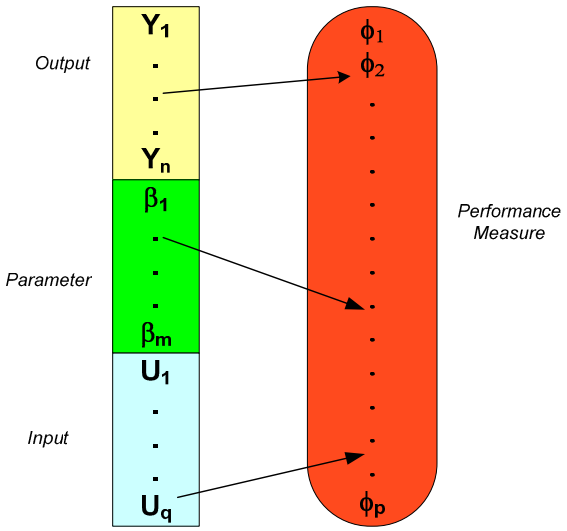

Figure 1 - Schematic of mapping from critical variables to performance measures

Algorithm

The proposed control structure design methodology in this paper could be summarized as following:

Step 1 – Generation of Operating Regimes: Select a set of nominal operating levels, and for each operating level apply step inputs perturbations using a factorial design concept.

Step 2 – Generation of Linear Model Sets: Linearize the nonlinear process model at each nominal operating level and at the corresponding perturbed levels.

Step 3 – Generation of Quality Variables: Determine the performance measures, for examples, productivity, yield, etc at nominal and perturbed operating levels. Also, compute the nonlinearity excitation as measured by *v-gap* value between the nominal and perturbed levels.

Step 4 – Mapping of Critical Variables to Performance Measures: Gather and combine all the generated data on the process parameters, input-output variables and the computed performance measures (or quality variables) in **Step 3** to form a dataset, which is to be used in the PCA (multiprojection) analysis.

Step 5 – Control Structure Design: There are three main tasks involved which are the selection of controlled variables, manipulated variables and controller pairings.

3. RESULTS AND DISCUSSIONS

The application of the proposed methodology to multi-scale biotechnological processes is demonstrated using two fermentation examples. The first example which is on TSDF alcoholic fermentation process is taken from the work reported in Nandong et al. (2008a). Meanwhile the multi-scale model describing the recycled micro-aerobic fermentation process is taken from Nandong et al. (2008b).

Also note that, in these examples only linear PI controllers are used. As for the case of multi-scale control strategy, the micro-scale controller is not specified but it is assumed that this controller could maintain the micro-scale output within certain range.

3.1 Example 1: Two-stage Distributed Feed (TSDF) Alcoholic Fermentation Process

Figure 2 shows the schematic of TSDF continuous alcoholic fermentation processes. The key feature of this design is that the fresh feed is distributed between the two bioreactors that are in series (R1 and R2) according to ratio SR (fraction of fresh feed that enters the R1). The details about this process could be found in Nandong et al. (2008). Table 1 shows the variables forming the dataset. Note that there are 16 perturbed levels (P1, P2…P16) around the nominal level P0 based on the four inputs (r, R, SR and So).

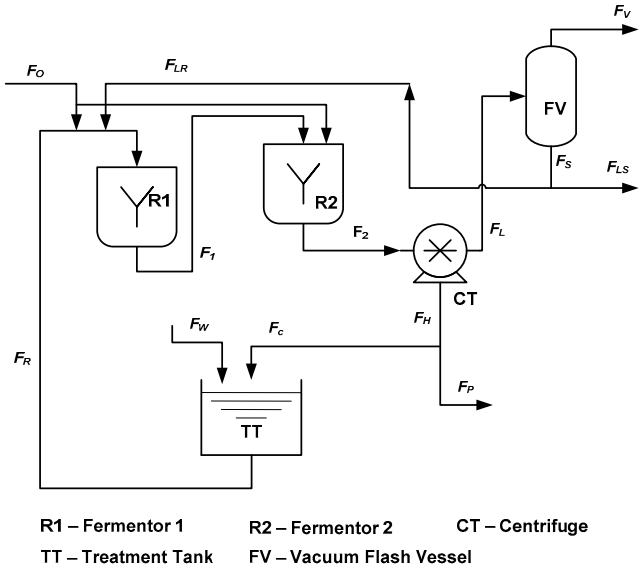

Figure 2 – Schematic of TSDF continuous alcoholic fermentation process

Table 1 – Variables forming the dataset for PCA analysis

Variable	Description	Variable	Description
Yield	*Ethanol yield*	S_1	*Substrate concentration in R1*
Prod	*Ethanol productivity*	S_2	*Substrate concentration in R2*
Conv	*Substrate conversion*	T_1	*Temperature in R1*
r	*Flash recycle ratio*	T_2	*Temperature in R2*
R	*Cell recycle ratio*	P_1	*Ethanol concentration in R1*
SR	*Split feed ratio*	P_2	*Ethanol concentration in R2*
So	*Fresh substrate concentration*	Xv_1	*Viable cell concentration in R1*
L_1	*Liquid level in R1*	Xv_2	*Viable cell concentration in R2*
L_2	*Liquid level in R2*	$v\text{-}gap_1$	*v-gap of R1*
Rp_1	*Rate ethanol production in R1*	$v\text{-}gap_2$	*v-gap of combined R1 and R2*
Rp_2	*Rate ethanol production in R2*	Rx_1	*Rate cell production in R1*
Rs_1	*Rate substrate consumption in R1*	Rx_2	*Rate cell production in R2*
Rs_2	*Rate substrate consumption in R2*		

There are 26 variables in total which are considered in the PCA analysis as following:

$$\phi = [v-gap_1 \quad v-gap_2 \quad Yield \quad Prod \quad Conv]^T$$
$$U = [r \quad R \quad SR \quad So]^T$$
$$Y = [L_1 \quad L_2 \quad S_1 \quad S_2 \quad T_1 \quad T_2 \quad P_1 \quad P_2 \quad Xv_1 \quad Xv_2]^T \qquad (1)$$
$$\beta = [Rp_1 \quad Rp_2 \quad Rs_1 \quad R_2 \quad Rx_1 \quad Rx_2]^T$$

In this case, there are 5 performance measures, 4 macro-scale inputs, 10 macro-scale outputs and 6 macro-scale parameters. These parameters could be viewed as the outputs of micro-scale inputs *(see Nandong et al., 2007a)*. Thus in the dataset there is no direct micro-scale variables being considered i.e. only indirectly via the parameters. Table 2 shows some of the selected values from the original dataset for few observations. Notice that for observation #3 at P2, the value of v-gap$_2$ is the largest. Thus it is interesting to know whether this will lead to outlier or not in the PCA analysis latter. And if this becomes outlier, then the question is whether v-gap$_2$ has any contribution to this outlier.

Table 2 – Selected values from the complete dataset

No	Level	v-gap$_2$	S_1 (kg/m^3)	S_2 (kg/m^3)	Yield (%)	Prod (kg/m^3.hr)	Conv (%)
1	P0	0	17.35	1.60	89.90	14.83	98.49
2	P1	0.980	43.18	20.31	75.09	18.51	79.39
3	**P2**	**0.995**	**99.17**	**79.58**	**45.42**	**16.73**	**45.87**
5	P4	0.980	73.85	38.85	67.41	21.15	75.44

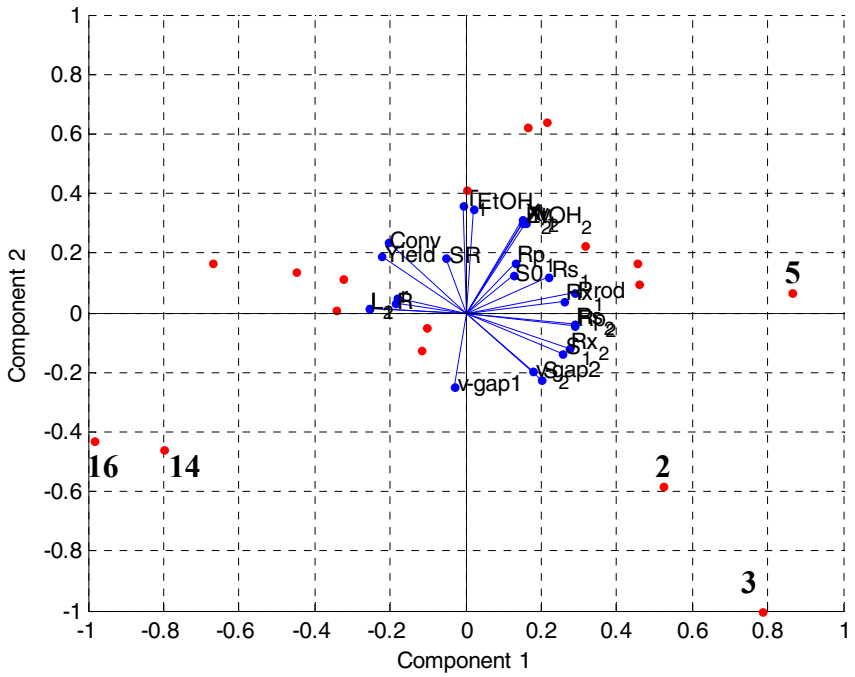

Figure 3- Plot of PC for two principal components PC1 and PC2 of the complete dataset

From Figure 3, the outliers #2 and #3 (at P1 and P2 respectively) could be due to 14 variables which are *v-gap*$_2$, T_1, L_1, L_2, *r*, *R*, *SR*, *Yield*, *Conv*, S_1, S_2, R_{x2}, R_{p2}, R_{s2} (i.e. these variables occupy 2nd and 4th quadrants. Other variables which occupy 1st and 3rd quadrants could be responsible for other outliers i.e. outlier #14, #15 and #16. Since the main objective in this example is to obtain the critical variables that strongly correlate with nonlinear excitation (i.e. v-gap), thus further analysis will be focused on the variables that responsible for outlier #3 where v-gap$_2$ could be one of the contributor to this outlier. Therefore, to identify which variables that really have strong correlation with the outlier #3, the original dataset is reduced to 14 variables and another PCA analysis is performed on this first reduced dataset.

The PCA analysis performed on this first reduced dataset indicates that there are 7 variables that may have strong correlations with outlier #3, which are *v-gap*$_2$, S_1, S_2, *SR*, T_1, *Yield* and *Conv*. However, it is still rather unclear at this stage which variable/s actually has dominant contribution to the outlier #3. More importantly, could it be that v-gap$_2$ has strong correlation with this outlier. Thus, the dataset is further reduced to only 7 variables (*v-gap*$_2$, S_1, S_2, *SR*, T_1, *Yield* and *Conv*). Another PCA analysis is performed on this second reduced dataset.

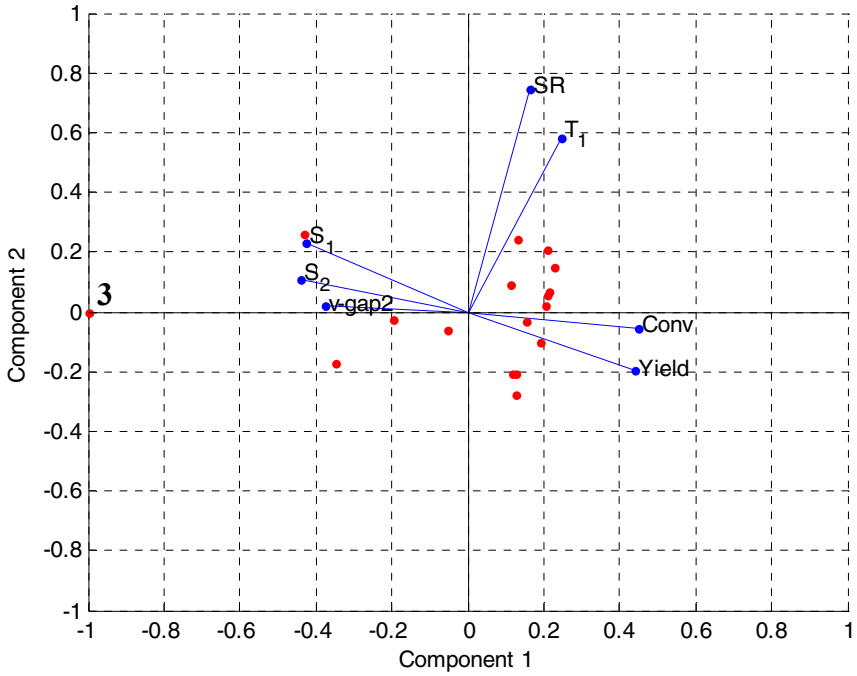

Figure 4 - Plot of PC score and loading for PC1 and PC2 of the second reduced dataset

Figure 4 shows the plot of two principal components from this second reduced dataset. This plot indicates that the outlier #3 is positively correlated with *S$_1$, S$_2$* and *v-gap*$_2$ and is negatively correlated with *Conv* and *Yield*. Moreover, this mapping analysis reveals two critical variables which are S_1 and S_2 that strongly correlate with the performance measures, which are v-gap$_2$, Yield and Conv. Because S_1 and S_2 are positively correlated with v-gap$_2$ (in the same quadrant), thus to reduce the nonlinear excitation (i.e. as measure by v-gap) the values

of S_1 and S_2 must be reduced. Also in this example the mapping results in case 3 i.e. Multiple Variables-Multiple Performance (MVMP).

Now the next question is whether it is necessary to control both S_1 and S_2? Because they are positively correlated, this implies that if one of these variables is controlled then this would indirectly control another variable. So in this case S_2 is selected as the controlled variable. Another variable to be controlled is liquid level in bioreactor 2 (i.e. L_2). Two inputs which are chosen as manipulated variables are r and R because these inputs have strong *cause*-and-*effect* relationship with the outputs i.e. high process gains. This control structure is called S-L structure. As a benchmark, another arbitrary control structure uses viable cell concentration in bioreactor 2 (Xv_2) and ethanol concentration in bioreactor 2 (P_2) as the controlled variables. In this control structure, r and R are also used as manipulated variables. This arbitrary control structure is called Xv-P structure. Note that in both structures, only PI controllers are used and tunings are based on linearized model at nominal operating level (P0) using Ziegler-Nichols formula.

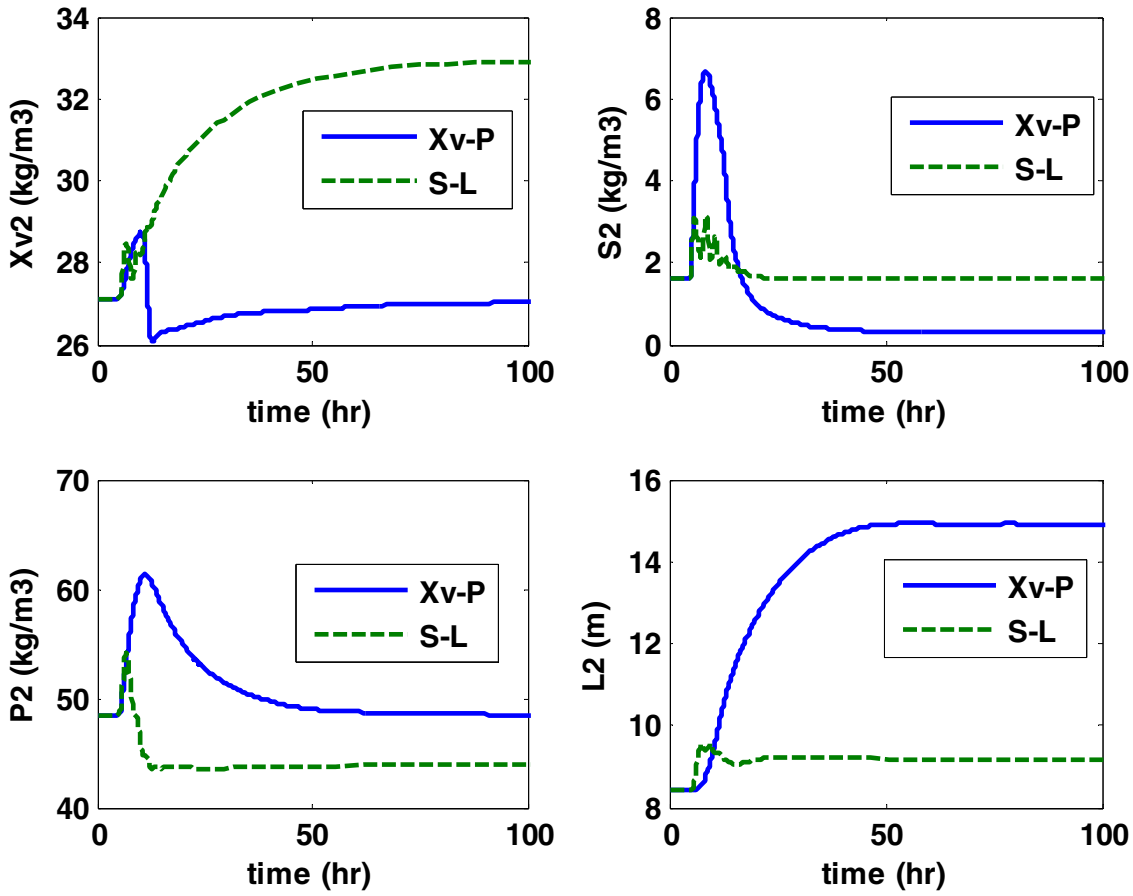

Figure 5 – Response to step change ΔS_o = 60 kg/m^3: nominal S_o = 170 kg/m^3

Figure 5 shows the closed-loop responses of the two control structures when subject to step disturbance in fresh substrate concentration (So) of 60 kg/m^3. For the S-L control structure, note that the uncontrolled Xv_2 and P_2 show significant deviations from the nominal

value and yet the closed-loop responses in S_2 and L_2 are still stable and faster than that of arbitrary Xv-P control structure. It is interesting to note that the Xv-P strategy is unstable when subject to step decrease in So by 60 kg/m^3. However S-L strategy remains stable. For Xv-P structure, under this disturbance it seems that S_2 increases sharply (result not shown). Because S_2 is positively correlated with v-gap$_2$, sharp increase in S_2 would lead to increase in nonlinear excitation thereby causing severe performance degradation to the linear control system – hence leading to instability. Meanwhile, under S-L control strategy the value of S_2 is prevented from drifting from the nominal value. Consequently this prevents the severe nonlinear excitation.

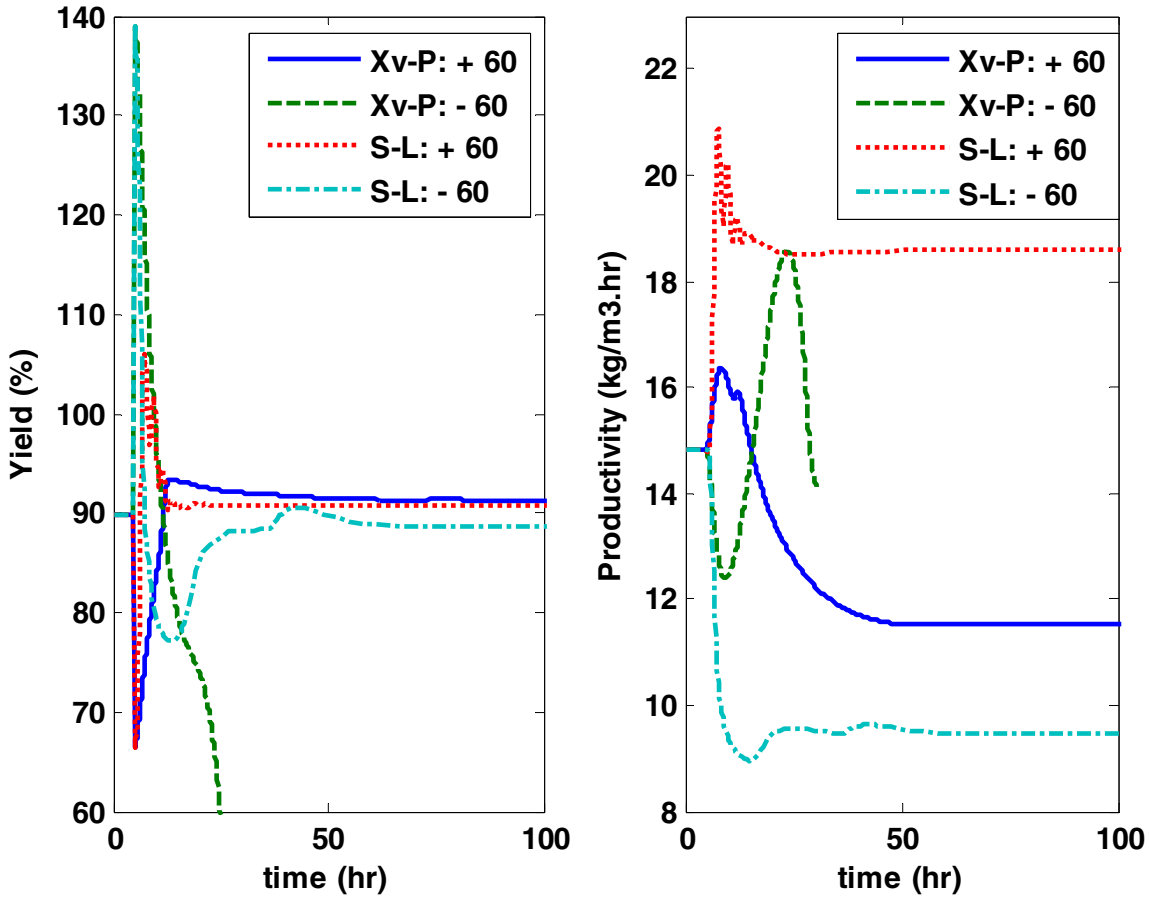

Figure 6 – Impact of ΔS_o = ±60 kg/m^3 on yield and productivity: nominal S_o = 170 kg/m^3

Figure 6 displays the impact of step disturbance in So of ±60 kg/m^3 on the steady state performances (yield and productivity). Notice that the S-L control strategy is able to maintain the yield closed to the nominal value (small steady-state offset). On the other hand, Xv-P strategy fails to remains stable when subject to -60kg/m^3 in So. For S-L strategy the ability of the control structure to have good impact on yield is expected since the S_2 is negatively correlated with this performance measure. Thus controlling S_2 is not only essential to prevent severe nonlinear excitation but also necessary to keep yield at nominal value. However, there is no clear advantage of S-L structure (other than it is stable) over Xv-P strategy for the

productivity i.e. large offset of yield for S-L structure. Again this could be expected because neither S_2 nor L_2 is strongly correlated with productivity. So, to control this productivity measure, one needs to find other critical variable/s that correlates well with this performance but this is not done in this work.

3.2 Example 2 – Recycled Micro-aerobic Fermentation System

The multi-scale model of the recycled micro-aerobic fermentation system used in this example is taken from Nandong et al. (2008b). Table 3 shows the variables forming the dataset used in the PCA analysis. There are 20 variables in total which are considered in this PCA analysis as following:

$$\phi = Magap$$
$$U = \begin{bmatrix} So & ADP & ATP & NADH \end{bmatrix}^T \quad (2)$$
$$Y = \begin{bmatrix} GlcE & Gly & Ace & EtOH & Cx & Xa & Glc & G6P & F6P & FBP & DHAP & GAP & PEP & PYR & ALDE \end{bmatrix}^T$$

Note that U and Y are multi-scale in nature i.e. GlcE is macro-scale output while G6P, PYR and ALDE are micro-scale outputs or intracellular metabolite concentrations. It is important to point out in this dataset there is no parameter i.e. both macro- and micro-scale variables are treated explicitly. Of course, one could also include the parameters such as specific growth and product formation rates but these parameters are calculated directly by the micro-scale system.

Table 3 – Variables forming the dataset used in PCA analysis

Variable	Description	Variable	Description
Ma gap	*v-gap metric*	Xa	*Fraction of active cells*
So	*Inlet glucose concentration*	GlcC	*Intracellular glucose concentration*
ADP	*Adenosine diphosphate*	G6P	*Glucose-6-phosphate*
ATP	*Adenosine triphosphate*	F6P	*Fructose-6-phosphate*
NADH	*Nicotinamide adenine dinucleotide*	FBP	*Fructose-1,6-phosphate*
GlcE	*Extracellular glucose concentration*	DHAP	*Dihydroxyacetone phosphate*
Gly	*Extracellular glycerol concentration*	GAP	*Glyceraldehyde-3-phosphate*
Ace	*Extracellular acetate concentration*	PEP	*Phosphoenol pyruvate*
EtOH	*Extracellular ethanol concentration*	PYR	*Pyruvate*
Cx	*Total cells concentration*	ALDE	*Acetaldehyde*

Table 4 – Selected values from complete dataset

No	Level	Ma gap	Ace (g/m^3)	G6P (mM)	F6P (mM)	PYR (mM)	ALDE (mM)
1	P0	0	85.62	3.6883	0.6949	6.5833	0.0358
11	P10	0.0002	87.69	3.5608	0.6680	8.7191	0.0369
14	**P13**	**0.7072**	**104.93**	**3.5907**	**0.6744**	**8.4752**	**0.0473**
15	P14	0.0002	87.20	3.8174	0.7220	5.1704	0.0367

Table 4 displays selected values from the complete dataset for 4 observations only. An interesting observation is that at P13 the value of v-gap (Ma gap) is abnormally large equals to 0.707 compared with at other perturbed levels (very small). PCA analysis is performed and the

analysis shows that there are 9 variables which could significantly correlate with the outlier #14 (at P13) that are Glc, PYR, Ace, ALDE, Ma gap, G6P, F6P, ATP and PEP. To clearly identify the key variables, the original dataset is reduced to these 9 variables and second PCA analysis is performed. The plot of the two principal components which describe about 90% of the total variances in the reduced dataset is shown in Figure 7. From this plot, one can conclude that there are two critical variables which positively correlate with Ma gap which are Ace and ALDE.

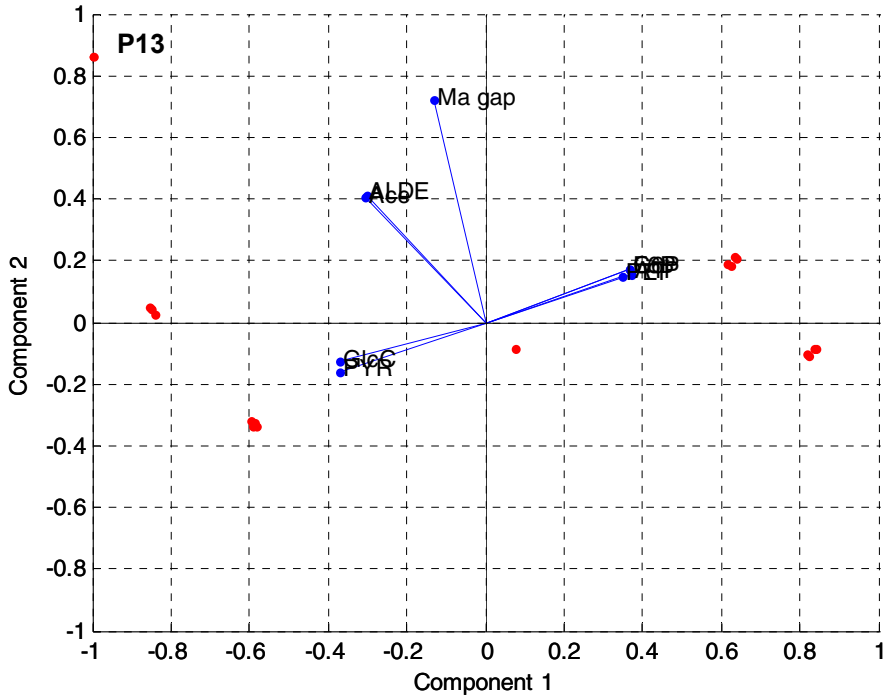

Figure 7 - PCA plot of reduced dataset for two major principal components

Both variables positively correlate with Ace and ALDE. So, the implication to control structure design is that whether both of these critical variables need to be controlled or not in order to prevent large nonlinear excitation in the face of disturbance occurrence. Recall in the previous example, if two critical variables are positively correlated then only one need to be controlled because this also lead to indirectly control another critical variable. But this strategy seems to work if both critical variables are of similar scale i.e. previously both variables are macro-scale. The question now, does this strategy works if the critical variables are of different scales as in this example.

To evaluate the effectiveness of applying the strategy which is adopted in example 1, two MIMO control structures would be proposed:

Single-scale Control (SSC) Strategy 1 – Only Ace is controlled while the micro-scale variable ALDE is left uncontrolled. In addition the EtOH is selected as another controlled variable.

Multi-scale Control (MSC) Strategy – Both of the critical variables are controlled in addition to controlling the EtOH.

Another macro-scale control structure which adopts GlcE and EtOH as controlled variables is proposed as a benchmark – called *SSC strategy 2*. Also, note that all macro-scale controllers are PI-type where the tuning is based on the linearized model at the nominal

operating level using the Ziegler-Nichols open-loop formula. For the MSC strategy, the micro-scale controller is simply assumed to be able to keep the ALDE within ±0.0002 mM. The performance is assessed based on the EtOH closed-loop response when subject to unit step disturbance in cellular ATP concentration.

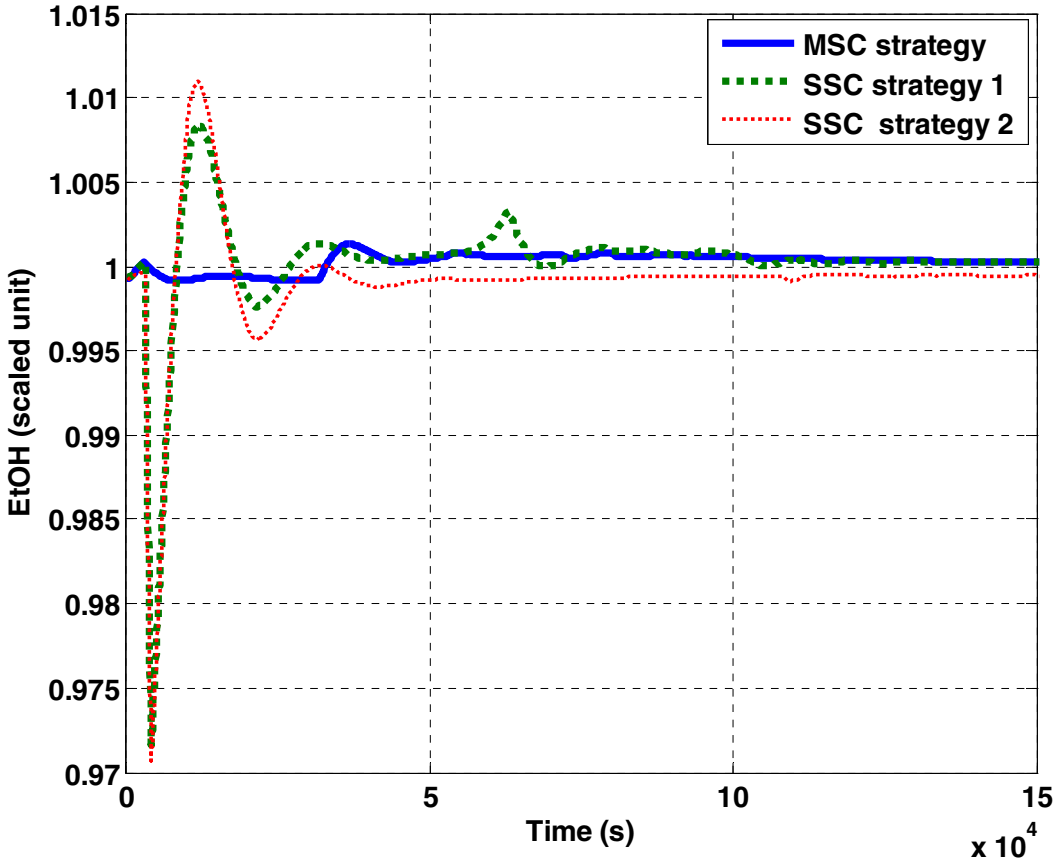

Figure 8 – Closed loop response of EtOH to pulse disturbance in ATP at time 2000s (duration 1000s, amplitude 1) for three different control strategies

From Figure 8, it shows that multi-scale control (MSC) strategy outperforms the two macro-scale (or single-scale) strategies i.e. much smaller overshoot and faster settling time. For the case of single-scale control (SSC) strategy 1, it seems that the advantage to control Ace (i.e. one of the critical variables) is small as compared to the arbitrary control structure that controls GlcE and EtOH (SSC strategy 2).

Thus in contrary to the previous example, it is important to control both *critical* variables which are actually multi-scale in terms of length and time resolution i.e. multi-scale control strategy required in this example to have significance improvement in control performance. Note that, the offset in MSC strategy and SSC strategy 1 could be due to the lack of integral action and no controller retuning has been considered in this example.

CONCLUSIONS

The effectiveness of proposed methodology in handling multi-scale processes has been confirmed using extractive fermentation and recycled micro-aerobic fermentation systems. The key novelty in this approach is its ability to find which variables among the multi-scale outputs which directly or strongly correlated with the specified performance measures and must be controlled. Essential to this methodology is to find which variables that have strong impacts on the nonlinear excitation i.e. v-gap metric. Controlling these variables is vital to ensure good dynamic operability so that it can justify the use of simple linear PID-type controllers for strongly nonlinear system. If two critical variables exist for certain performance measure/s, then only one of these variables need to be controlled if they are both positively correlated and if both are also of similar macro-scale type. On the other hand, if two critical variables are multi-scale than both variables must be controlled i.e. as shown in the example 2. Thus this would lead to full multi-scale control (MSC) strategy.

The key limitation of adopting MSC strategy is the lack of suitable micro-scale manipulated variables that could be used to control the micro-scale outputs directly. Additionally, the lack of currently suitable sensors to measure the micro-scale outputs online is another major hindrance in the adoption of MSC strategy. However, these obstacles would soon be resolved by the rapid advances in (1) cellular design methodology (see Kaznessis, 2006), (2) measurement and sampling technologies, and (3) multi-scale modeling and computation.

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