MODELING AND CONTROL OF A CONTINUOUS BIOREACTOR WITH CROSS-FLOW FILTRATION

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Abstract This work is based on an industrial application of a continuous bioreactor with cross-flow filtration. In this paper the general features of this application are studied. The control objective for this biochemical process is to maintain cell concentration at a desired high concentration in order to maximize the production of cell mass. In this work a controller-independent controllability measure, the partial disturbance gain (PDG), is used for control structure selection and controllability analysis with respect to disturbance rejection, and we study the possibility of partial control of this bioreactor.

keywords: Continuous bioreactor; controllability analysis; disturbance rejection; partial control.

1 Introduction

The studied biochemical process is the propionibacteria fermentation process. Dairy propionibacteria are commercially important in the production of "eyes" and typical flavors in Swiss-type cheeses as they ferment lactic acid with the production of propionic acid and carbon dioxide. Thus there is a strong interest in food industry to continuously obtain the propionibacteria with high concentration at the maximum production rate. To attain this, the development of efficient on-line computer control system is essential.

A schematic overview of this continuous fermentation process is shown in Fig. 1.

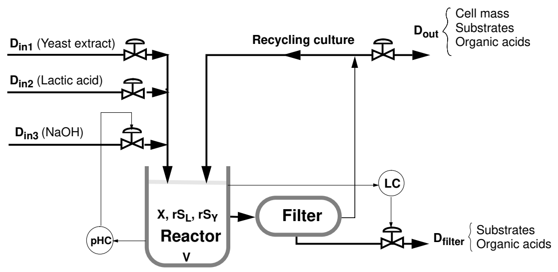

Figure 1: A continuous bioreactor with cross-flow filtration.

The operation objective of this process is to get high concentration cultivation of propionibacteria in this bioreactor with cross-flow filtration. There are three feed streams into this continuous bioreactor: Yeast extract (YE) acts as nitrogen source for incorporation into cell mass synthesis (D_{in1}), lactic acid (LA) acts as both energy source for cell growth and carbon source for incorporation into cell mass synthesis (D_{in2}), and the base solution (D_{in3}) is used for compensating pH changes in the bioreactor. The reactor effluent is fed to a filter which is used for increasing the cell concentration by bleeding off some used media at flow rate D_{filter}, and a part of the remaining stream including cell mass, organic acids and media is recycled to the bioreactor. D_{out} denotes the product stream flow rate. All flow rates F are normalized with respect to the bioreactor volume V, i.e., $D = F/V$.

In the paper simple frequency-dependent tools are used for control structure selection and controllability analysis with respect to disturbance rejection. In particular, by using a frequency-dependent tool: the partial disturbance gain (Skogestad and Wolff, 1992, and Zhao and Skogestad, 1994), the possibility of partial control of this continuous bioreactor is studied, which is the main consideration in this paper.

2 Dynamic Model of Process and Its Characteristics

The following assumptions are made.

1. The concentrations of cell mass and substrates are uniform respectively in the whole fermenter-filter system.

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2. The bioreactor volume is constant.

Material balances yield:

$$\frac{dX}{dt} = (\mu - D_{out})\,X \tag{1}$$

$$\frac{drS_L}{dt} = -\frac{\mu\, X}{K_L} - (D_{filter} + D_{out})\, rS_L + D_{in2} \tag{2}$$

$$\frac{drS_Y}{dt} = -\frac{\mu\, X}{K_Y} - (D_{filter} + D_{out})\, rS_Y + D_{in1} \tag{3}$$

where

X— Cell concentration

$rS_L = S_L/S_{fL}$— Normalized LA concentration with respect to its feed concentration S_{fL}.

$rS_Y = S_Y/S_{fY}$— Normalized YE concentration with respect to its feed concentration S_{fY}.

$K_L = Y_{X/L}S_{fL}$— Product of cell yield coefficient on LA and LA feed concentration.

$K_Y = Y_{X/Y}S_{fY}$— Product of cell yield coefficient on YE and YE feed concentration.

μ— the specific cell growth rate.

In this fermentation process YE acts as growth-limiting substrate, and it is assumed that the Monod model is used for describing this fermentation process kinetics.

$$\mu = \mu_m \frac{rS_Y}{rK_s + rS_Y}$$

where μ_m represents the maximum specific cell growth rate and $rK_s = K_s/S_{fY}$ is the normalized saturation constant with respect to YE feed concentration.

2.1 Steady state behavior

From eqs. (1-3), the steady state values of cell and substrate concentrations can be calculated:

$$\frac{dX}{dt} = 0 \Rightarrow \mu = D_{out} \Rightarrow rS_Y = \frac{rK_s\, D_{out}}{\mu_m - D_{out}} \tag{4}$$

$$\frac{drS_L}{dt} = 0 \Rightarrow rS_L = \frac{D_{in2} - \frac{D_{out}X}{K_L}}{D_{filter} + D_{out}} \tag{5}$$

$$\frac{drS_Y}{dt} = 0 \Rightarrow X = \frac{D_{in1} - (D_{filter} + D_{out})\, rS_Y}{D_{out}} K_Y \tag{6}$$

The nominal model parameter values and steady-state data are given in Table 1.

Table 1: Steady State Data

Flow rates	D_{in1}	D_{in2}	D_{filter}	D_{out}
$[1/h]$	0.21	5.60	5.72	0.11
Concentrations	X	rS_L	rS_Y	
	29.43 $[g/l]$	0.017	0.000667	
parameters	rK_s	K_L	K_Y	μ_m
	0.000172	0.6 $[g/l]$	16 $[g/l]$	0.141 $[1/h]$

(1.) The steady state relationship between the cell concentration (X) and the cell production rate (D_{out}) is shown in Fig. 2.

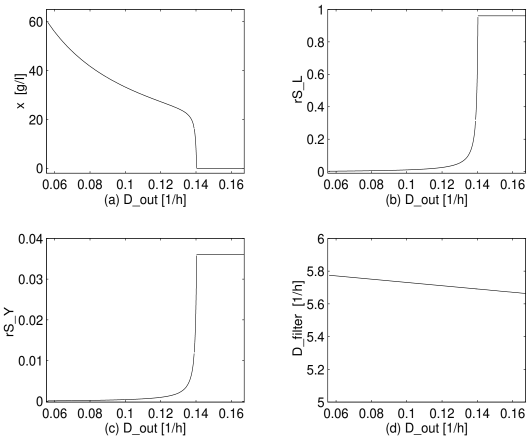

Figure 2: Steady state values of X, rS_L and rS_Y as functions of D_{out} with other flow rates at constant except adjusting D_{filter} to keep V constant

When D_{out} increases, X decreases and substrate concentrations rS_Y and rS_L increase. If D_{out} reaches to a critical value $D_{out_{max}}$ which can be calculated from eq. (6), the cell can not grow fast enough to keep up with its outflow, and the culture is washed out of the reactor and then rS_L and rS_Y rise to their maximum values respectively.

(2.) The steady state relationship between X and the growth-limiting substrate YE feed flow rate (D_{in1}) is shown in Fig. 3.

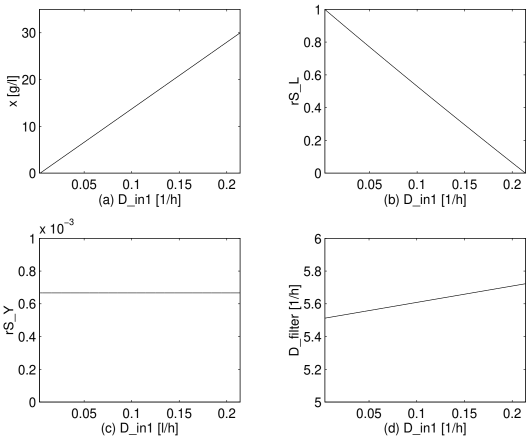

Figure 3: Steady state values of X, rS_L and rS_Y as functions of D_{in1} with other flow rates at constant except adjusting D_{filter} to keep V constant

In this case, X is proportional to D_{in1} while rS_Y does not vary with D_{in1}. rS_L decreases with increasing D_{in1} and then this gives a upper bound to D_{in1} (see Fig. 3b), i.e., D_{in1} should be below $D_{in1_{max}}$, otherwise $rS_L = 0$. On the other hand, D_{in1} should be above a critical value $D_{in1_{min}}$ (see

Fig. 3a), otherwise at very low YE feed flow rate, a large fraction of cells may die from starvation since the limiting substrate is not being added fast enough to permit maintenance of cell growth.

In addition, the LA feed flow rate D_{in2} does not have much effect except on rS_L.

In conclusion, in this continuous bioreactor with multiple substrate streams the cell concentration is sensitive to changes in D_{out}, which is different from a general biochemical CSTR with single substrate stream where the cell concentration almost remains constant throughout most of the range of the dilution rates (except close to the $D_{washout}$). The growth-limiting substrate concentration rS_Y only depends on the cell production rate D_{out} as in a general CSTR. In addition, X is also sensitive to changes in D_{in1} but rather insensitive to the changes in D_{in2}, and rS_L is sensitive to changes in feed flow rates D_{in1} and D_{in2} but almost remains constant throughout most of the range of D_{out}.

2.2 Dynamic behavior

The main control objective is to keep cell concentration X at a given high concentration. We have three output variables X, rS_L and rS_Y, and five manipulated inputs as shown in Fig. 1. Since pH is already controlled by the base addition rate D_{in3} and the reactor volume is assumed constant such that $D_{in1} + D_{in2} + D_{in3} = D_{filter} + D_{out}$, three independent manipulated variables D_{in1}, D_{in2} (or D_{filter}) and D_{out} remain. Since large flow rates are preferred to control reactor volume (level), and this leaves two alternative manipulated inputs D_{in2} and D_{filter} for reactor volume control. However biotechnologically it is preferred to use D_{filter} because for a given organism the ratio D_{in1}/D_{in2} should be nearly constant.

In the following we will use a plant description of the form

$$y(s) = G(s)u(s) + G_d(s)d(s) \tag{7}$$

where G and G_d denote the process and disturbance model, and

$$y = \begin{bmatrix} X \\ rS_L \\ rS_Y \end{bmatrix}; \quad u = \begin{bmatrix} D_{in1} \\ D_{in2} \\ D_{out} \end{bmatrix}; \quad d = \begin{bmatrix} D_{in1_d} \\ D_{in2_d} \\ D_{out_d} \\ K_Y \\ rK_s \\ \mu_m \end{bmatrix}$$

The variables are scalled as follows:
The allowed maximum output changes are

$$\bar{\Delta} X = 10\%\,\bar{X}; \quad \bar{\Delta} rS_L = 30\%\,\bar{rS}_L; \quad \bar{\Delta} rS_Y = 20\%\,\bar{rS}_Y$$

The allowed maximum input changes are 50% changes in D_{in1}, D_{in2} and D_{out} respectively.
The expected maximum disturbance changes in inputs are 5% changes in D_{in1}, D_{in2} and D_{out} respectively. Here we have also included disturbances in the model parameters K_Y, rK_s and μ_m which are sensitive to variations in the environment conditions such as temperature, pH and aeration rate etc. The expected maximum disturbance changes are

$$\bar{\Delta} K_Y = 10\%\,\bar{K}_Y; \quad \bar{\Delta} rK_s = 10\%\,\bar{rK}_s; \quad \bar{\Delta} \mu_m = 10\%\,\bar{\mu}_m$$

In the following the overbar ($\bar{}$) used to denote steady-state values will be deleted to simplify notation.

The plant has no poles or transmission zeros in the RHP, and thus there are no fundamental problems related with instability, inverse responses or inherent bandwidth limitations.

The steady-state elements of the open-loop disturbance matrix G_d (appropriately scaled) are

$$G_d(0) = \begin{bmatrix} 0.51 & -0.01 & -0.55 & 1.00 & -0.02 & 0.09 \\ -9.31 & 9.31 & 0.84 & -18.29 & 0.34 & -1.68 \\ 0.00 & 0.00 & 1.22 & 0.00 & 0.50 & -2.44 \end{bmatrix}$$

The steady-state open-loop gain matrix in terms of scaled variables is

$$G(0) = \begin{bmatrix} 5.09 & -0.09 & -5.46 \\ -93.15 & 93.15 & 8.42 \\ 0.00 & 0.00 & 12.21 \end{bmatrix}$$

Their frequency-dependent plots are shown in Fig 4. We see that feedback control is necessary to reject disturbances; the output X is sensitive to D_{in1} and D_{out} but rather insensitive to D_{in2}; D_{in1} and D_{in2} have large effect on rS_L; at steady state rS_Y only depends on D_{out}.

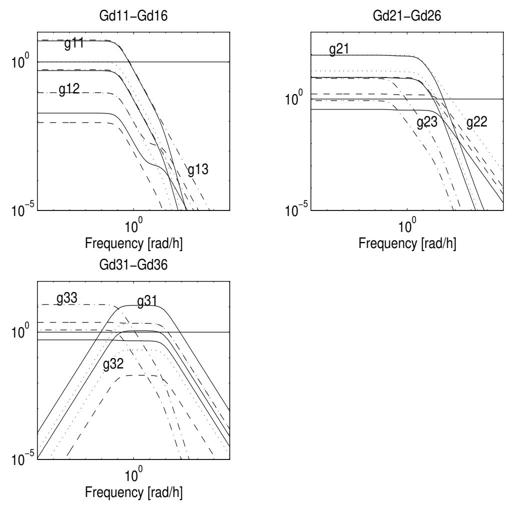

Figure 4: Frequency-dependent plots of G and G_d

3 × 3 control

The steady-state elements of relative gain array (RGA) and the closed loop disturbance gain (CLDG) which is the appropriate measure when we use decentralized control (Hovd and Skogestad, 1992) are given as following,

$$RGA(0) = \begin{bmatrix} 1.02 & -0.02 & 0.00 \\ -0.02 & 1.02 & 0.00 \\ 0.00 & 0.00 & 1.00 \end{bmatrix}$$

$$CLDG(0) = \begin{bmatrix} 0.51 & 0.00 & 0.00 & 1.00 & 0.21 & -1.02 \\ 0.00 & 9.31 & 0.00 & 0.01 & 3.81 & -18.63 \\ 0.00 & 0.00 & 1.22 & 0.00 & 0.50 & -2.44 \end{bmatrix}$$

The CLDG show that for all three outputs, the most difficult disturbance to reject is changes in the parameter μ_m. An objective is to control this plant by using the decentralized control, and we see that there is one possible set of pairings $D_{in1} - X$, $D_{in2} - rS_L$ and $D_{out} - rS_Y$ corresponding to the positive steady-state RGA values and without input constraints problem as all $|g_{ii}| > |[CLDG]_{ik}|$ for $i = 1, 2, 3$ and $k = 1, ..., 6$. However implementation of a 3×3 control system of bioreactor is expensive and difficult. Therefore the main consideration in this paper is on whether one may achieve acceptable control performances of all three outputs by controlling only one or two of them, i.e., the plant is partially controlled.

3 Controllability Analysis and Control Structure Selection

3.1 Measures for evaluating controllability

We now close only one loop (1×1 control) or two loops (2×2 control) and define $y = [y_c \quad y_u]^T$ and $u = [u_c \quad u_u]^T$, where

y_c— controlled outputs

y_u— uncontrolled outputs

u_c— manipulated inputs used to control y_c

u_u— unused inputs

The problem is to select the controlled outputs (y_c), and the unused inputs (u_u) such that :

1. Use of u_c to control y_c should yield satisfactory control performance.
2. With these control loops closed the uncontrolled outputs y_u should be relatively insensitive to disturbances.

To evaluate both these issues a controllability analysis of the alternative structures needs to be performed. A useful tool when considering issue 2 is the partial disturbance gain (PDG) which is the effect of a disturbance on uncontrolled outputs when the plant is under partial control.

For a square plant with only one output y_j perfectly controlled (1×1 control), the sensitivity of the uncontrolled outputs y_i to a disturbance d_k is derived (see appendix):

$$PDG_{1\times 1} = \left(\frac{\partial y_i}{\partial d_k}\right)_{y_j, u_{l\neq j}} = [G_d]_{ik} - [G(\hat{G})^{-1}]_{ij}[G_d]_{jk} \quad (8)$$

where $u_{l\neq j}$ are unused inputs, $\hat{G}$ is the matrix consisting of only the diagonal elements of G, i.e., $\hat{G} = diag\{g_{ii}\}$.

Next consider two outputs $y_{l\neq i}$ perfectly controlled (2×2 control). Since we have a 3×3 control system this is the same as having 1 input u_j "unused" and the sensitivity of the uncontrolled output y_i to a disturbance d_k is given by Skogestad and Wolff in 1992:

$$PDG_{2\times 2} = \left(\frac{\partial y_i}{\partial d_k}\right)_{u_j, y_{l\neq i}} = [G^{-1}G_d]_{jk}/[G^{-1}]_{ji} \quad (9)$$

For simultaneous disturbances d_k, $k = 1, 2, ...$, the worst overall effect may be evaluated by taking the sum of element magnitudes for each "pairing". This gives rise to a combined PDG-matrix, denoted C_{PDG}, with elements

$$[C_{PDG}]_{ij} = \sum_k |[PDG]|$$

The objective of the controllability analysis in this paper is to find the best partial control scheme so that we can get the acceptable disturbance sensitivity for the uncontrolled outputs even under simultaneous disturbances. To attain this, we prefer pairings corresponding to C_{PDG} - elements less than 1 at all frequencies.

3.2 Case study

1 × 1 control

The effect of disturbances on the uncontrolled outputs are given by the PDG. The steady-state combined PDG (C_{PDG}) is listed in Table 2. From this and the frequency response of C_{PDG} (not shown in the paper), the best partial control scheme is the $D_{in1} \rightarrow rS_L$ – scheme No. 2. It yields $C_{PDG} = 1$ for X and $C_{PDG} = 4.16$ for rS_Y. Practical implementation of this partial control system is possible since on-line measurement of lactic acid concentration is easier than cell mass or yeast extract concentration (Yeast extract is a complex medium and its composition is chemically undefined and may vary as the fermentation process is in progress).

Table 2: The combined partial disturbance gain

Controlled paring			C_{PDG}		
No.	u_c	y_c	$\Sigma_k \frac{\partial X}{\partial d_k}$	$\Sigma_k \frac{\partial rS_L}{\partial d_k}$	$\Sigma_k \frac{\partial rS_Y}{\partial d_k}$
1	D_{in1}	X		18.31	4.16
2	D_{in1}	rS_L	1.00		4.16
3	D_{in1}	rS_Y	∞	∞	
4	D_{in2}	X		2.20	4.16
5	D_{in2}	rS_L	2.14		4.16
6	D_{in2}	rS_Y	∞	∞	
7	D_{out}	X		36.43	6.09
8	D_{out}	rS_L	23.64		53.57
9	D_{out}	rS_Y	2.72	36.91	

Schemes No. 3 and 6 with rS_Y controlled by D_{in1} or D_{in2} are not feasible since disturbance sensitivities of uncontrolled outputs X and rS_L are infinite because rS_Y only depends on D_{out}. Schemes No. 1 and No. 7–9 are unacceptable with large sensitivities of uncontrolled outputs to disturbances.

2×2 control

In this case the effect of disturbances on the controlled output are evaluated by eq. (9) and the steady-state C_{PDG} values are given in Table 3. The best 2×2 control system is No. 6 with $u_c = [D_{in1}\, D_{out}]^T$ and $y_c = [rS_L\, rS_Y]^T$. It gives almost acceptable sensitivity of the uncontrolled X to disturbances. However comparing with the case by 1×1 control, we see that cell concentration X is more sensitive to disturbances than the scheme No. 2 in Table 2.

Table 3: The combined partial disturbance gain

Controlled paring			C_{PDG}		
No.	u_c	y_c	$\Sigma_k \frac{\partial X}{\partial d_k}$	$\Sigma_k \frac{\partial rS_L}{\partial d_k}$	$\Sigma_k \frac{\partial rS_Y}{\partial d_k}$
1.	$\begin{bmatrix} D_{in1} \\ D_{in2} \end{bmatrix}$	$\begin{bmatrix} X \\ rS_L \end{bmatrix}$			4.16
2.	$\begin{bmatrix} D_{in1} \\ D_{in2} \end{bmatrix}$	$\begin{bmatrix} X \\ rS_Y \end{bmatrix}$		∞	
3.	$\begin{bmatrix} D_{in1} \\ D_{in2} \end{bmatrix}$	$\begin{bmatrix} rS_L \\ rS_Y \end{bmatrix}$	∞		
4.	$\begin{bmatrix} D_{in1} \\ D_{out} \end{bmatrix}$	$\begin{bmatrix} X \\ rS_L \end{bmatrix}$			4.17
5.	$\begin{bmatrix} D_{in1} \\ D_{out} \end{bmatrix}$	$\begin{bmatrix} X \\ rS_Y \end{bmatrix}$		31.2	
6.	$\begin{bmatrix} D_{in1} \\ D_{out} \end{bmatrix}$	$\begin{bmatrix} rS_L \\ rS_Y \end{bmatrix}$	1.71		
7.	$\begin{bmatrix} D_{in2} \\ D_{out} \end{bmatrix}$	$\begin{bmatrix} X \\ rS_L \end{bmatrix}$			6.02
8.	$\begin{bmatrix} D_{in2} \\ D_{out} \end{bmatrix}$	$\begin{bmatrix} X \\ rS_Y \end{bmatrix}$		2765.8	
9.	$\begin{bmatrix} D_{in2} \\ D_{out} \end{bmatrix}$	$\begin{bmatrix} rS_L \\ rS_Y \end{bmatrix}$	2.68		

3.3 Dynamical simulation results

In this section we present nonlinear simulation results to compare with the controllability analysis results presented in the previous section. In all simulations simple PI controllers are used for the controlled outputs and we consider the step responses to the combined disturbances in parameters K_Y, rK_s and μ_m as shown in Fig. 5(d).

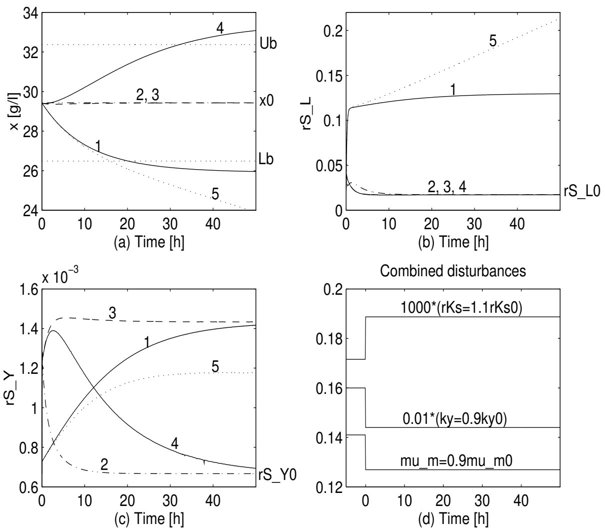

Figure 5: Time responses for the combined step disturbances in parameters K_Y, rK_s and μ_m. 1: uncontrolled. 2: 3×3 control. 3: 1×1 control $D_{in1} \rightarrow rS_L$. 4: 2×2 control. 5: 1×1 control $D_{in1} \rightarrow rS_Y$.

From simulation results we find:
The system can not be left uncontrolled, otherwise after long time (for example during the weekend) as shown in Fig. 5 (curves 1) the cell concentration X will decrease and below its lower bound (Lb); and the substrate concentration, especially rS_L, will be much high and then result loosing more substrate.

As shown in Fig. 5 (curves 2), if all outputs X, rS_L and rS_Y were on-line measurable, then the 3×3 control system (X is controlled by D_{in1}, rS_L is controlled by D_{in2} and rS_Y is controlled by D_{out}) could work well against the combined disturbances in parameters as all three outputs remain at their desired steady states without violating the input constraints.

With 1×1 partial control scheme $D_{in1} \rightarrow rS_L$ shown in Fig. 5 (curves 3), rS_L is perfectly controlled without violating the input constraint of D_{in1}; the uncontrolled X almost goes back its desired value after several hours so that the main operation objective of this fermentation process has been achieved. The deviation of uncontrolled rS_Y from its desired value is large but tolerable.

With 2×2 partial control system $u_c = [D_{in1}\, D_{out}]^T$ and $y_c = [rS_L\, rS_Y]^T$ shown in Fig. 5 (curves 4), we find no improvement compared to the 1×1 scheme $D_{in1} \rightarrow rS_L$ except the rS_L returns quicker to its desired value, and after long transition process rS_Y may be controlled at its desired value. However the uncontrolled X exceeds its upper bound (Ub).

The partial control scheme D_{in1} (or D_{in2})$\rightarrow rS_Y$ with D_{out} left in manual should be avoided, otherwise as shown in Fig 5 (curves 5) the uncontrolled X decreases quickly and eventually down to zero and then the reaction will stop: D_{in1} has to be continuously lowered in order to try to keep rS_Y constant, however, it is not possible to keep rS_Y constant in the long run while D_{out} is unchanged because rS_Y is independent of D_{in1} at steady state, and finally D_{in1} will reach 0 and results in a failure of the reactor.

4 Conclusions

Based on both linear controllability analysis and simulation results, we suggest that to control this continuous bioreactor with cross-flow filtration is by using a 1×1 partial control scheme ($D_{in1} \rightarrow rS_L$) where the YE feed flow rate D_{in1} is used to control lactic acid concentration rS_L which furthermore is relatively easy to implement practically.

In this paper we have generalized the partial disturbance gain which was proposed by Skogestad in 1992 to the case that a plant is under 1×1 partial control. A careful comparison shows that the simulation results are consistent with the linear controllability analysis. This indicates that the partial disturbance gain (PDG) is an effective tool for controllability analysis without considering the controller design.

Acknowledgment. Thanks to Ivar Storrø for fruitful discussions.

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APPENDIX

Derivation of PDG when only one output y_j of the plant is perfectly controlled with inputs $u_{l\neq n}$ left in manual.

For the uncontrolled outputs $y_{i\neq i}$, set $u_{l\neq n} = 0$ and the eq. (7) yields

$$y_i = g_{in}u_n + [G_d]_{ik}d_k \tag{10}$$

$$y_j = g_{jn}u_n + [G_d]_{jk}d_k \tag{11}$$

$$y_j = 0 \Rightarrow u_n = -(g_{jn})^{-1}[G_d]_{jk}d_k \tag{12}$$

By substituting eq. (12) into eq. (10) and thus

$$y_i = -g_{in}(g_{jn})^{-1}[G_d]_{jk}d_k + [G_d]_{ik}d_k \tag{13}$$

By taking the partial derivative of y_i w.r.t d_k, we derive

$$PDG_{1\times1} = \left(\frac{\partial y_i}{\partial d_k}\right)_{y_j, u_{l\neq n}} = [G_d]_{ik} - g_{in}(g_{jn})^{-1}[G_d]_{jk} \tag{14}$$

When $j = n$, we have

$$PDG_{1\times1} = \left(\frac{\partial y_i}{\partial d_k}\right)_{y_j, u_{l\neq j}} = [G_d]_{ik} - [G(\hat{G})^{-1}]_{ij}[G_d]_{jk} \tag{15}$$