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Trajectory Tracking Controller for a Nonlinear Fed-batch Bioprocess.

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ABSTRACT/ ***RESUMEN***

This paper aims to develop a simple but efficient control technique based on a linear algebra approach for tracking optimal profiles of a nonlinear multivariable fed-batch bioprocess. The methodology proposed allows, knowing the desired states, to find the values for the control actions by solving a system of linear equations. Its main advantage is that the condition for the tracking error tends to zero. The efficiency of the proposed controller is tested through several simulations. The optimal controller parameters are selected through Montecarlo Randomized Algorithm in order to minimize a cost index.

Keywords: Multivariable control, trajectory tracking, nonlinear systems, algebraic approaches, optimal trajectories.

El objetivo de este trabajo es desarrollar una técnica de control simple pero eficiente, basada en un enfoque del algebra lineal para el seguimiento de perfiles óptimos de un bioproceso fed-batch, multivariable y no lineal. La metodología propuesta permite, conociendo los estados deseados, encontrar las acciones de control adecuadas mediante la resolución de un sistema de ecuaciones lineales. La principal ventaja es que el error de seguimiento tiende a cero. La eficiencia del controlador propuesto es verificada a través de varias simulaciones. Los parámetros óptimos del controlador se seleccionan mediante un algoritmo de Montecarlo bajo la condición de minimizar un cierto índice de costo.

Palabras Claves: Control multivariable, seguimiento de trayectoria, sistemas no lineales, enfoque algebraico, trayectorias óptimas.

Controlador de Seguimiento de Trayectoria para un Bioproceso Fed-batch no Lineal.

1. -INTRODUCTION

Fed-batch processes are widely used in the biotechnological industry, which is demanding for more efficient, reliable and safer processes to optimize production and improve power quality [1]. In a fed-batch operation, one or more nutrients are gradually supplied to the bioreactor, but no product is withdrawn until the process is finished. Its main advantages are the avoidance of substrate overfeeding which can inhibit the growth of microorganisms and catabolite repression. On the other hand, from the control engineer's viewpoint, the fed-batch fermentation is characterized for a large number of obstacles: complex dynamic behavior of microorganisms, the process model usually contains strongly time-varying parameters, changes in initial conditions, input saturation, external disturbances and the stiffness and nonlinearity of the model equations [2-6].

Several control techniques are studied today associated with optimization and control of bioprocess, such as: bio-inspired algorithms [7], genetic algorithms [8, 9], robust control [4, 10], nonlinear fuzzy control [11],evolutionary algorithms [12], model predictive control (MPC) [13] and nonlinear MPC [14, 15], adaptive stochastic algorithms [16], neural network model [17, 18], etc. Most of the control literature for fed-batch cultures focuses on open-loop operation owing to the highly nonlinear and inherently difficult dynamic behavior [19]. These methods have good results in biological processes; however, they have limitations regarding the need for advanced specific knowledge, the difficulty of mathematical processing (especially in nonlinear systems), trouble with real-time implementation and the need for a complicated database of the processes [20]. Besides that, in the open-loop control strategies, the main disadvantage is that no compensation is made for modeling mismatch or random disturbances during the process operation [5, 21-23]. It is therefore important to design a controller to track the optimal policy considering disturbance compensation for the closed-loop control problem.

The aim of this work is to solve the problem of tracking optimal profiles of an important biological system, which has a complex dynamics and a strong nonlinearity. The proposed methodology to achieve the stated objective is based on solving a system of linear equations. One of the key features of this technique is its simple approach, which suggests that knowing the value of the desired state, analyzing the conditions for a system to have an exact solution and then solving the system of linear equations; it can find the values for the control actions, which forces the system to move from its current state to the desired one.

The main advantages of this method are its simplicity, versatility and accuracy even under parametric uncertainty. The methodology for the controller design is very simple, nonlinear model is used; thus, its performance is independent of the operating point, and has an excellent performance against the set point changes. The optimal controller parameters are selected through Montecarlo Experiments in order to minimize a proposed cost index. The computing power required to perform the mathematical operations is low. Furthermore, the developed algorithm is easier to implement in a real system because the use of discrete equations allows direct adaptation to any computer system or programmable device. Moreover, because its simplicity and the mathematical tools that it use, this methodology is applicable to many systems, not only to bioprocesses.

The case study proposed for control is the Lee-Ramirez fed-batch bioreactor [24], developing a mathematical model for the induced foreign protein production by recombinant bacteria in a fed-batch bioreactor. The advantage of using this system is that it has been already used by a number of researchers using different techniques, so the available data can be used to assess other methods.

The controller efficiency is tested through simulations using Matlab® software. The assays include a simulation in normal operation conditions and then, the control system under parametric uncertainty is analyzed through a Montecarlo randomized algorithm.

The paper is organized as follows. In Section 2, the mathematical model of the proposed system is presented and the optimal profiles are defined. Then, the controller design is considered in Section 3. The results of the simulation tests to demonstrate the efficiency of the controller are shown in Section 4. Finally, Section 5 outlines the conclusions of the work.

2.- MATHEMATICAL MODEL

The mathematical model used is taken of Balsa Canto et al. [25]. Although simple, it can effectively describe the dynamics of the bioprocess.

The original model was developed by Lee and Ramirez [24], who described the dynamics for the process of induced foreign protein production by recombinant bacteria. Then, they used it to obtain an optimal control policy to maximize the foreign protein production with a nutrient and inducer feeding strategy [26]. The same problem was studied by Tholudur and Ramirez [18] using neural network parameter function models. Carrazco and Banga [16] used adaptive stochastic algorithms to obtain better results. Since the performance index exhibits a very low sensitivity with respect to the controls, Tholudur and Ramirez [27] constructed a modified parameter function set to increase the sensitivity to the controls. Balsa-Canto also used the same parameter function set [25]. A genetic algorithm to optimize the same system considering multiple control variables was presented in [9].

The operation of the fed-batch bioreactor considering two control variables (u_1 and u_2, nutrient and inducer feed rates) is described by seven differential equations (1).

The state variables are the reactor volume x_1 *(L)*, the cell density x_2 *(g/L)*, the nutrient concentration x_3 *(g/L)*, the foreign protein concentration x_4 *(g/L)*, the inducer concentration x_5 *(g/L)*, the inducer shock factor on the cell growth rate x_6, and the inducer recovery factor on the cell growth rate x_7 (both dimensionless).

The model parameters were described by Tholudur and Ramirez [27]. The concentration of nutrient feed stream is N, I is the concentration of inducer in the inducer feed stream, and Y is the growth yield coefficient. In addition, g is the specific growth rate, R is the foreign protein production rate, p is a Monod-type constant and K_1, K_2 are the shock and recovery parameters respectively.

$$\left.\begin{aligned}
\dot{x}_1 &= u_1 + u_2 \\
\dot{x}_2 &= x_2 g - \frac{u_1 + u_2}{x_1} x_2 \\
\dot{x}_3 &= \frac{u_1 N}{x_1} - \frac{u_1 + u_2}{x_1} x_3 - \frac{g}{Y} x_2 \\
\dot{x}_4 &= x_2 R - \frac{u_1 + u_2}{x_1} x_4 \\
\dot{x}_5 &= \frac{u_2 I}{x_1} - \frac{u_1 + u_2}{x_1} x_5 \\
\dot{x}_6 &= -K_1 x_6 \\
\dot{x}_7 &= K_2 (1 - x_7)
\end{aligned}\right\} \tag{1}$$

Where,

$$g = \left(\frac{\mu_{\max} x_3}{K_{CN} + x_3 \left(1 + \frac{x_3}{111.5} \right)} \right) \left(x_6 + \frac{x_7 K_{CI}}{K_{CI} + x_5} \right) \tag{2}$$

$$R = \left(\frac{f_{\max} x_3}{K_{CN} + x_3 \left(1 + \frac{x_3}{111.5} \right)} \right) \left(\frac{f_I + x_5}{K_I + x_5} \right) \tag{3}$$

$$K_1 = K_2 = \frac{x_5 p}{K_{IX} + x_5} \tag{4}$$

The two control variables are the glucose feeding rate, u_1 *(L/h)*, and inducer feeding rate u_2 *(L/h)* to the fed-batch bioreactor. The desired output variables to follow are the reactor volume x_1, the cell density x_2, and the foreign protein concentration x_4.

It may be noted that the desired trajectories to track are directly the optimal profiles of controlled variables (x_1, x_2, and x_4). These trajectories were obtained by an open-loop simulation of the bioprocess using the optimal feeding policies achieved by Balsa Canto et al. [25].

3.- CONTROLLER DESIGN

The proposed controller methodology is based on approximating the differential equations of the mathematical model (1) through the Euler method. Hence, the control problem for tracking optimum profiles of volume (x_1), cell density (x_2), and protein concentration (x_4) is reduced to the resolution of a system of linear equations.

To achieve the control goal, the feed flow rate of nutrient (u_1) and inducer (u_2) are available to be used as control actions. Therefore, the goal is to find the values of u_1 and u_2 such that the variables x_1, x_2 and x_4 follow paths desired with minimal tracking error.

3.1.- METHODOLOGY

The first step for this technique, is rearrange the system of equations (1) in matrix form as $A\boldsymbol{u}=b$. The matrix $\boldsymbol{u}$ is composed of the control variables, for this model, u_1 and u_2:

$$\overbrace{\begin{pmatrix} 1 & 1 \\ -1 & -1 \\ (N-x_3) & -x_3 \\ -1 & -1 \\ -1 & (I-x_5) \end{pmatrix}}^{A} \overbrace{\begin{pmatrix} u_1 \\ u_2 \end{pmatrix}}^{u} = \overbrace{\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \frac{x_1}{x_2} - x_1 g \\ \dot{x}_3 x_1 + \frac{g}{Y} x_2 x_1 \\ \frac{\dot{x}_4 x_1}{x_4} - \frac{R x_2 x_1}{x_4} \\ \dot{x}_5 x_1 \end{pmatrix}}^{b} \tag{5}$$

Note 1. The variables x_6 and x_7 are not directly related with the control variables, therefore, are not considered in the controller design.

According to the rule of numerical integration of Euler, the differential equations can be approximated as follow:

$$\dot{x}_i = \frac{x_{i,n+1} - x_{i,n}}{T_0} \tag{6}$$

Where T_0 is the sample time, $x_{i,n}$ represents the state variable i in n instant and $x_{i,n+1}$ the state variable i in $(n+1)$ instant.

Defining the following expression:

$$\overbrace{x_{i,ref,n+1} - x_{i,n+1}}^{error_{i,n+1}} = k_i \overbrace{(x_{i,ref,n} - x_{i,n})}^{error_{i,n}} \tag{7}$$

Where, $x_{i,ref,n}$ and $x_{i,ref,n+1}$ are the reference values in the n instant and the next sample time respectively, the constant k_i is the controller parameter for the variable i.

Then, the immediately reachable value of each state variable is:

$$x_{i,n+1} = x_{i,ref,n+1} - k_i \overbrace{(x_{i,ref,n} - x_{i,n})}^{error_{i,n}} \tag{8}$$

Therefore, the values of the real state variables in the next sample time ($x_{i,n+1}$) are function of the reference profiles, the actual state variable and the controller parameters. So, all values are known.

Consequently, substituting (8) in (6):

$$\dot{x}_i = \frac{\overbrace{\left[x_{i,ref,n+1} - k_i (x_{i,ref,n} - x_{i,n})\right]}^{x_{i,n+1}} - x_{i,n}}{T_0} \tag{9}$$

Now, replacing (9) in each differential expression appearing in (5), the process model can be rewritten, see (10).

The values of x_1, x_2, and x_4 are the references to follow, therefore are known (the reference values as well as the real system values). Note that, the Eq. (10) is a system of five equations and two unknowns, which normally has no solution. Therefore, the unknown variables of this system are defined as "*sacrificed variables*" and are written as $x_{i,ez}$ corresponding, in this case, to $x_{3,ez}$ and $x_{5,ez}$. The key of this technique is that the values adopted by such variables forces the equation system (10) to have exact solution, which implies error not only be minimal, but equal zero.

$$\begin{pmatrix} 1 & 1 \\ -1 & -1 \\ (N-x_{3,n}) & -x_{3,n} \\ -1 & -1 \\ -1 & (I-x_{5,n}) \end{pmatrix} \begin{pmatrix} u_{1,n} \\ u_{2,n} \end{pmatrix} = \begin{pmatrix} \left(\frac{x_{1,ref,n+1}-k_1\left(x_{1,ref,n}-x_{1,n}\right)-x_{1,n}}{T_0}\right) \\ \left(\frac{x_{2,ref,n+1}-k_2\left(x_{2,ref,n}-x_{2,n}\right)-x_{2,n}}{T_0}\right)\frac{x_{1,n}}{x_{2,n}} - x_{1,n}g \\ \left(\frac{x_{3,ez,n+1}-k_3\left(x_{3,ez,n}-x_{3,n}\right)-x_{3,n}}{T_0}\right)x_{1,n} + \frac{g}{Y}x_{2,n}x_{1,n} \\ \left(\frac{x_{4,ref,n+1}-k_4\left(x_{4,ref,n}-x_{4,n}\right)-x_{4,n}}{T_0}\right)\frac{x_{1,n}}{x_{4,n}} - Rx_{2,n}\frac{x_{1,n}}{x_{4,n}} \\ \left(\frac{x_{5,ez,n+1}-k_5\left(x_{5,ez,n}-x_{5,n}\right)-x_{5,n}}{T_0}\right)x_{1,n} \end{pmatrix} \tag{10}$$

To simplify the mathematical treatment, the equations system is expressed as follows:

$$\begin{pmatrix} a_{31} & a_{32} \\ a_{51} & a_{52} \\ a_{11} & a_{12} \\ a_{21} & a_{22} \\ a_{41} & a_{42} \end{pmatrix} \begin{pmatrix} u_1 \\ u_2 \end{pmatrix} = \begin{pmatrix} b_3 \\ b_5 \\ b_1 \\ b_2 \\ b_4 \end{pmatrix} \Rightarrow Au = b \tag{11}$$

The order of the rows are altered to the Gaussian elimination because the system presents three linearly dependents rows.

To accomplish the target, the system (10) must have exact solution. Then, the vector ***b*** must be contained in the space formed by the columns of ***A***, ie, the vector ***b*** must be a linear combination of the column vectors of matrix ***A***.

In order to find the values of the $x_{i,ez}$ so that the system to have exact solution, the Gauss elimination process is carried out.

Then, the *necessary* and *sufficient condition* for the system to have exact solution is:

$$\begin{aligned} 0 &= (a_{31}a_{52} - a_{32}a_{51})(a_{31}b_1 - b_3a_{11}) - (a_{31}b_5 - b_3a_{51})(a_{31}a_{12} - a_{32}a_{11}) \\ 0 &= (a_{31}a_{52} - a_{32}a_{51})(a_{31}b_2 - b_3a_{21}) - (a_{31}b_5 - b_3a_{51})(a_{31}a_{22} - a_{32}a_{21}) \\ 0 &= (a_{31}a_{52} - a_{32}a_{51})(a_{31}b_4 - b_3a_{41}) - (a_{31}b_5 - b_3a_{51})(a_{31}a_{42} - a_{32}a_{41}) \end{aligned} \tag{12}$$

This equations system is solved for each sampling period by iteration methods, where the unknown variables $x_{3,ez,n+1}$ and $x_{5,ez,n+1}$ (*sacrificed variables*) are calculated.

Once the values of $x_{3,ez,n+1}$, $x_{5,ez,n+1}$ are found, the matrix ***A*** and ***b*** are completely known at (n) time. Therefore, the control variables $u_{1,n}$ and $u_{2,n}$ (***u*** vector) can be calculated solving the system (10) by the least squares method:

$$(A^T A)u = A^T b \Rightarrow u = (A^T A)^{-1} A^T b \tag{13}$$

The solution allows finding the control actions ($u_{1,n}$ and $u_{2,n}$) to be applied at time n to follow the desired trajectories with a minimal error.

Note 2. The following constraints on the control variables are considered [25]: $0.0 \leq u_1 \leq 1.0$ and $0.0 \leq u_2 \leq 1.0$.

Note 3. In Eq. (8) note that:

▪ If $k_i = 0$, the reference trajectory is reached in only one step. The parameters k_i, $i = \{1,2,3,4,5\}$, satisfied $0 < k_i < 1$, which allows the tracking error tends to zero.

The tracking error is the value of the difference between the reference and real trajectory, and is calculated as:

$$\left\|e_n\right\| = \sqrt{e_{1,n}{}^2 + e_{2,n}{}^2 + e_{4,n}{}^2} \; ; \; \mathrm{E}=\mathrm{T}_0 \sum_n \left\|e_n\right\| \tag{14}$$

$$e_{1,n} = \frac{x_{1,ref,n} - x_{1,n}}{x_{1,\max}} \tag{15}$$

$$e_{2,n} = \frac{x_{2,ref,n} - x_{2,n}}{x_{2,\max}} \tag{16}$$

$$e_{4,n} = \frac{x_{4,ref,n} - x_{4,n}}{x_{4,\max}} \tag{17}$$

Where: $x_{1,max}$*= 1,9 L,* $x_{2,max}$*= 13,92 g/L,* and $x_{4,max}$*= 3,1 g/L*

Note that the tracking error is dimensionless.

Theorem 1. If the system behavior is ruled by (10) and the controller is designed by (13), then, $e_{i,n} \rightarrow 0$, $n \rightarrow \infty$, when profile tracking problems are considered. The proof of this theorem is not shown because space reasons.

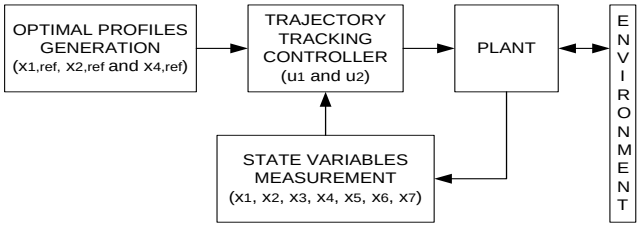

Figure 1

Architecture of the trajectory tracking controller.

Figure 1 shows the architecture of the control system proposed herein. In this work, the optimal profiles are taken from literature [25], the focus is in the trajectory tracking of such profiles.

4.- RESULTS AND DISCUSSION

In order to evaluate the performance of the controller, various simulation tests employing Matlab® were carried out. First, a randomized algorithm to synthetize the optimal controller parameters (k_i). Then, a simulation under normal operating conditions using the optimal values of the controller parameters found in previous section. Finally, a simulation considering parametric uncertainty.

4.1.- TUNING OPTIMAL CONTROLLER PARAMETERS.

The aim in this subsection is to find the values of the controller parameters, for which the tracking error is minimal (the bioreactor behavior directly depends on the adjustment of parameters k_i). To achieve the target, a Montecarlo experiment is performed.

In the field of systems and control, Montecarlo methods have been found useful especially for problems related to robustness of uncertain systems [28].

In this work, the Montecarlo experiment consisted on randomize the controller parameters and then simulate the process, this is repeated a large number of trials (N) and the tracking error is calculated in every one.

Now, considering by definition that Montecarlo randomized algorithm (MCRA) is a randomized algorithm that may

produce an incorrect result, but the probability of such an incorrect result is bounded [29], the number of simulations necessary to ensure a certain degree of confidence and accuracy (confidence boundaries) is achieved using the following expression [28]:

$$N \geq \left\lceil \frac{\log \frac{1}{\delta}}{\log \frac{1}{1-\varepsilon}} \right\rceil \tag{18}$$

Where δ= confidence and ε= accuracy. It is fixed δ= 0.01 and ε= 0.005. Therefore, N ≥ 920.

The initial conditions used to simulate the system are shown in Table 1. Feeding concentrations and parameters values can be seen in Table 2.

Table 1
Initial conditions for the state variables [*g/L*].

$x_{1.0}$	$x_{2.0}$	$x_{3.0}$	$x_{4.0}$	$x_{5.0}$	$x_{6.n}$	$x_{7.0}$
1.0	*0.1*	*40.0*	*0.01*	*0.01*	*1.0*	*0.01*

The final time for the process is T_f = 10 *h* and the sample time for simulations is T_0 = 0.1 *h*

Table 2
Feeding concentrations and parameters [27].

N (g/L)	*I(g/L)*	*Y*	*p* (h^{-1})
40	*100*	*0.51*	*0.09*

The k_i values found for the minimum tracking error after 1000 simulations are presented in Table 3.

Table 3
Optimal *k* values after Montecarlo experiment.

k_1	k_2	k_3	k_4	k_5
0.9501	*0.5463*	*0.1459*	*0.1563*	*0.2624*
E=0.0014 – Iteration Nº 202				

4.2.- NORMAL CONDITIONS OPERATION.

This section shows the results of the simulation of the closed loop control using the controller proposed in this work without environmental disturbances. The optimal controller parameters achieved in the previous subsection and the state variables initial values are used. The evolution of the controlled system can be seen in the following figures.

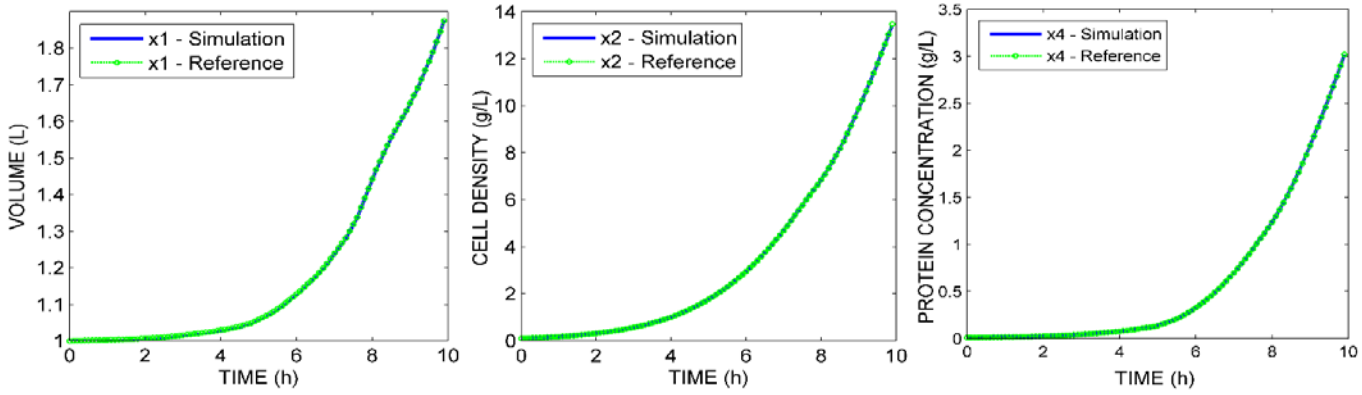

Figure 2

Tracking optimal profiles of desired variables (x_1, x_2, and x_4) in normal operation conditions.

A very good controller performance can be observed, the optimal desired profiles are successfully tracking as can be seen in Fig. 2.
Note that the tracking error defined by (14), remains low and acceptably bounded as shows Fig. 3.

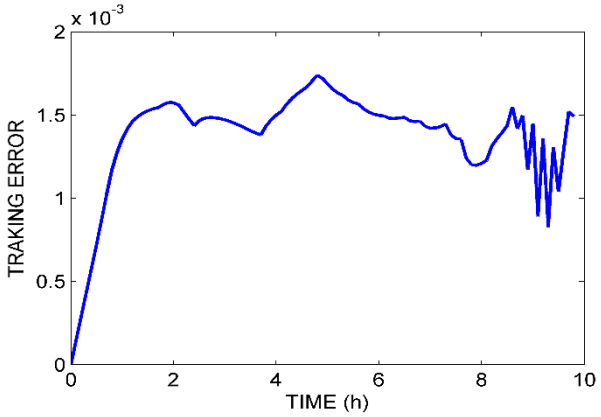

Figure 3

Tracking error (e) in normal operation conditions.

It is noteworthy that not only the desired variables follow the optimal profiles, but also the other variables track their respective reference profiles, as can be seen in Figure 4.

4.3.- PARAMETRIC UNCERTAINTY.

In this subsection, the MC Method is applied to make an analysis of the system in case of appearing modeling errors. First, a sensitivity analysis and hierarchy of parameters based on their influence on the closed loop was performed: a random variation (±20% of their nominal values) is introduced for each parameter separately, and the total error E is evaluated using 500 simulations, see Table 4. Therefore, the parameters considered under disturbance are those more influents: μ_{max}, f^0_{max}, K_{CN}, k_{11} *and* K_I. The concentration of nutrient feed stream $\boldsymbol{N}$ and the concentration of inducer in the inducer feed stream $\boldsymbol{I}$ are considered too, because its variation is common in bioprocesses.

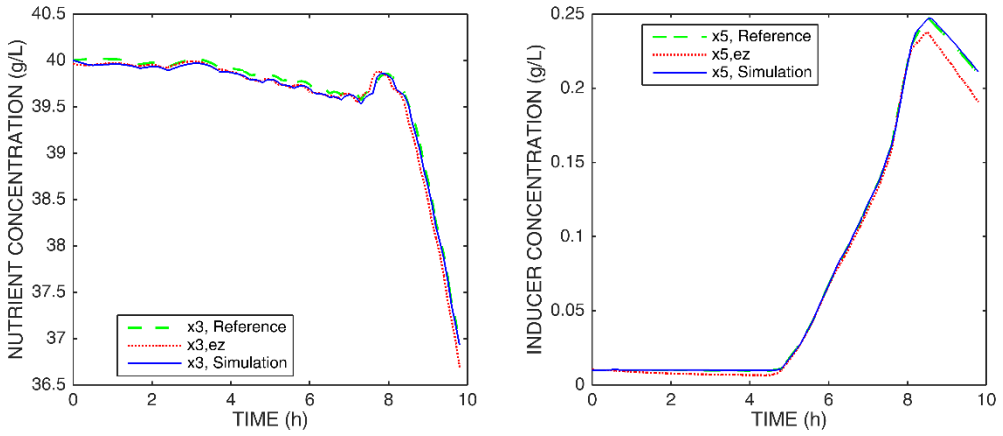

Figure 4

Tracking optimal profiles of sacrificed variables (x_3 and x_5) in normal operation conditions.

Once the parameters have been chosen, an error (±20%) is introduced in the model parameters and perform 500 simulations (N = 500). In each simulation the parameters are chosen in a random way by MC sampling experiment [30].

The initial conditions and the sampling time are the same used in the previous subsection.
The number of simulations taken to carry out this test is considering the confidence $\delta = 0.01$ and accuracy $\varepsilon = 0.01$. Therefore, replacing in (18), $N \geq 500$.

Table 4
Parameters values and Maximum Total Error after their variation (±20%).

Parameter	*Value*	*Units*	E_{max}	E_{min}
μ_{max}	*1.0000*	h^{-1}	*0.200*	*0.010*
f^0_{max}	*0.2330*	h^{-1}	*0.090*	*0.010*
K_{CN}	*14.350*	-	*0.090*	*0.010*
k_{11}	*0.0900*	h^{-1}	*0.010*	*0.002*
K_I	*0.0220*	*g/L*	*0.010*	*0.001*
K_{CI}	*0.2200*	*g/L*	*0.007*	*0.001*
K_{IX}	*0.0340*	*g/L*	*0.007*	*0.001*
N	*100*	*g/L*	*0.004*	*0.001*
I	*4*	*g/L*	*0.002*	*0.001*
Y	*0.51*	-	*0.002*	*0.001*
f^0_I	*0.0005*	*g/L*	*0.001*	*0.001*

Figure 5 shows the behavior of the system with the controller proposed in this work, which presents a good response against parametric uncertainty. It is relevant to clarify that the value of x_1 represents the sum of the control actions that are necessary to achieve trajectory tracking, which is why there is a greater perturbation in this variable.
It is noteworthy that the controller design is focused in the tracking optimal profile of the desired variables, not of control variables. This is one of the advantages, since it allows control of the system even under disturbances.

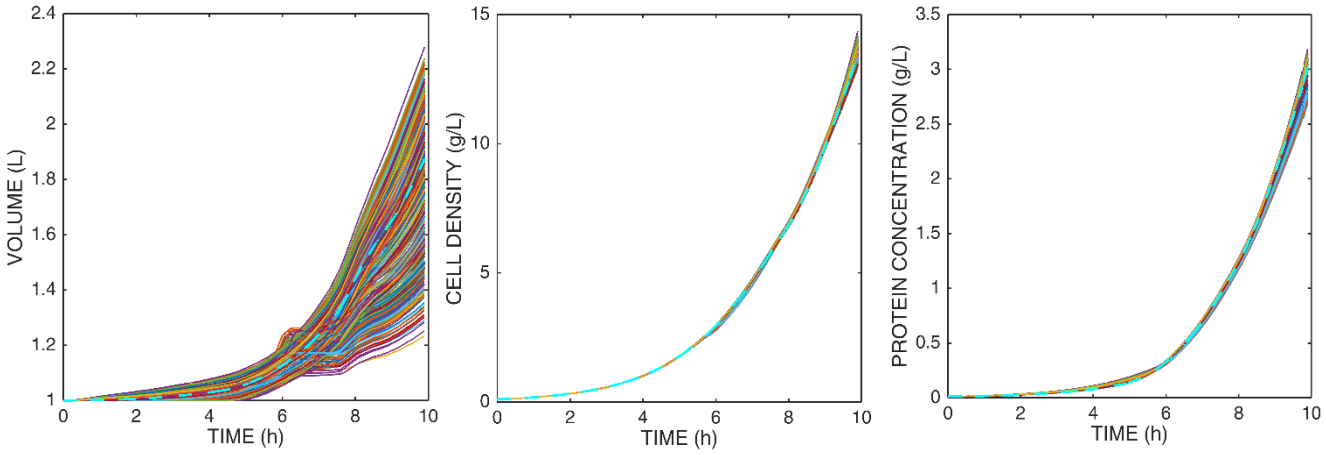

Figure 5
Tracking optimal profiles (desired variables x_1, x_2, and x_4) under parametric uncertainty (parameter variation according Table 4, 500 simulations).

The control law developed in this work achieves the tracking trajectory of three optimal profiles with only two control actions, applying a simple knowledge of lineal algebra. The simulation tests carried out show a very good performance of the control system.

5.- CONCLUSIONS

The controller design of an important biological system consisting on seven differential equations with three desired variables and two control actions was presented in this work. The advantages of the methodology employed is its simplicity and accuracy since reduces the controller design to a resolution of a linear equations system for the calculation of the control actions, which achieve the tracking optimal trajectories of desired variables with a minimal tracking error, even under parametric uncertainties. This methodology can be implemented only with basic knowledge of linear algebra.
The optimal controller parameters were successfully found through a Montecarlo experiment. Moreover, through closed-loop simulation tests, this proposed control structure was shown to be simple and efficient, even considering the mismatches in the model parameters.

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