An algebra approach for nonlinear multivariable fed-batch bioprocess control

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Abstract: In this paper, a linear algebra-based controller design is proposed. This technique allows tracking, with minimum error, predefined optimal profiles in nonlinear and multivariable systems. To achieve this, control actions are obtained by solving a linear equation system. The controller parameters are selected with a Monte Carlo algorithm. The methodology is applied in a fed-batch penicillin production process, where the control action is the feed flow rate and the tracked profiles are the concentration of biomass, product and subtract inside the reactor. Different tests are shown to prove the good performance of the controller adding: parametric uncertainty and perturbations in the control action and in the initial conditions

Keywords: nonlinear dynamics control; fed-batch fermentation; penicillin production; profiles tracking control.

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1 Introduction

The increasing interest in environmentally friendly processes has led to an intensive development of bioprocesses (Petre and Selişteanu, 2013). These biological processes consist in the use of diverse microscopic organisms in order to obtain different products. They are frequently used on food and drugs production, for environment bioremediation, for energy and biofuels production, and even for the synthesis of polymers (Chung et al., 2015). There are several types of biological reactors designs and many operating modes for micro-organisms growth and metabolites production (Mohammadi et al., 2011). Fed-batch bioprocesses represent the biggest challenge among of them (Ashoori et al., 2009). They consist in change one or more nutrients and other substances (inducers, inhibitors or catalysers) feed rate along the process while cells and products remain in the fermenter until the operation ends (Hecklau et al., 2015). This operation policy avoids microorganism starvation induced by underfeeding and the formation of unwanted products by overfeeding; furthermore, the introduction of appropriate feed rate strategies can minimise substrate inhibition and catabolite repression; this allows obtaining higher production yields (Jin et al., 2014) and minimising production costs (Ochoa, 2016; Liu et al., 2013; Jin et al., 2014). However, they have some challenges from the process control point of view:

1 complex dynamic behaviour of microorganisms, represented with strong modelling approximations

2 dynamics are usually nonlinear and sometimes unstable

3 the presence of numerous external disturbances (Liang and Chen, 2003)

4 online measurements of most representative variables are not always available.

Because of all these difficulties, it is necessary to implement a control algorithms specifically developed for each bioprocess (De Battista et al., 2012).

It is important to determine the feed policy that allows us to obtain the maximum production of the key product. Many researchers have developed optimisation methods to find it (Skolpap et al., 2008; Ochoa, 2015; Banga et al., 2005; Aghajani et al., 2014; Mutingi, 2016). However, once the optimal feed policy is known, it is of the utmost importance to develop specific control architecture. It should be noted that it is not recommended to use a PI, PID or another classic controller, because the controller parameters change over time (Arivalahan et al., 2013). Jin et al. (2014) propose a hybrid intelligent control method to enable automatic substrate feeding. De Battista et al. (2012) expose a control system based on the minimal model paradigm, requiring only biomass and volume measurement along with some bounds on the reaction rate. Ashoori et al. (2009) present a model predictive control based on a detailed unstructured model for penicillin production in a fed-batch fermenter. Many other authors have developed nonlinear controllers for bioprocesses too (Chang et al., 2016; Fu and Chai, 2007; Pantano et al., 2017a; Lehouche et al., 2012; Pantano et al., 2017b).

In this paper, a controller design based on linear algebra for multivariable and nonlinear systems is proposed. To implement this technique, it is assumed that the mathematical model of the process is available, the desired concentration profiles (herein

called 'reference') and all the states variables are known in each instant of time. The controller structure arises from the mentioned mathematical model, so it can be applied in many systems, for example: Gandolfo et al. (2014) and Rosales et al. (2015). Moreover, the control actions are obtained as a solution of a linear equation system in each sampling time, therefore the controller design is fast and easy, because only algebra knowledge is needed to understand and apply this methodology. Furthermore, it is versatile against different disturbances, which is demonstrated through different tests: parametric uncertainty and perturbations in the control action and in the initial conditions. It is important to highlight the error convergence to zero in each test (the mathematical demonstration is also presented in the appendix). The controller parameters are selected with a Monte Carlo randomised algorithm. The controller is applied in a penicillin production process.

The paper is organised as follows. In Section 2, the penicillin bioprocess and its mathematical model are described. Section 3 explains the controller design and the controller parameters selection. Section 4 presents some simulated test in order to prove the performance of the designed controller. Finally, conclusions are exposed.

2 System and process description

The system under study is a fed-batch bioreactor for penicillin production. The microorganism and the substrate used are *Penicillum crysogenum* and glucose, respectively. The dynamic system was originally proposed in Cuthrell and Biegler (1989), and many optimisation and control papers using this system have been written since then. It is a single input multi output system, where the input is the substrate feed rate, and the outputs are biomass, product (penicillin) and substrate concentrations. The optimal substrate feed rate for penicillin biosynthesis has been obtained in different ways: analytically (Lim et al., 1986), by dynamic programming (Luus, 1993), by an evolutionary approach (Ronen et al., 2002) and using orthogonal collocation (Riascos and Pinto, 2004), among others. Hereafter, the optimal profiles presented by Riascos and Pinto (2004) was taken as the reference. The mathematical model that represents the process is:

$$\begin{cases} \dot{X}(t) = \mu(X,S)X - \left(\dfrac{X}{S_F V}\right)U \\ \dot{P}(t) = \rho(S)X - K_{deg}P - \left(\dfrac{P}{S_F V}\right)U \\ \dot{S}(t) = -\mu(X,S)\left(\dfrac{X}{Y_{X/S}}\right) - \rho(S)\left(\dfrac{P}{Y_{P/S}}\right) - \left(\dfrac{m_s S}{K_m + S}\right)X + \left(1 - \dfrac{S}{S_F}\right)\dfrac{U}{V} \end{cases} \tag{1}$$

where

$$\mu(X,S) = \mu_{max}\left(\frac{S}{K_{XG}X + S}\right) \tag{2}$$

$$\rho(S) = \rho_{max}\left(\frac{S}{K_{PP} + S(1 + S / K_{in})}\right)$$

$$\dot{V}(t) = \frac{U}{S_F}$$

Here, the state variables are: biomass concentration (X), product per culture volume unit (P), and the culture glucose concentration (S). V is the culture volume. The control variable is the substrate feed rate (U). SF is the substrate feed concentration, $\mu(X, S)$ is the specific biomass growth rate and $\rho(S)$ is the specific penicillin production rate. Note that μ is a function of biomass and glucose concentrations, and ρ is only a function of substrate concentration. These relations have been developed in order to provide information about the metabolic activity of the microorganism.

Initial variable values are shown in Table 1, whereas parameter definitions and values are in Table 2.

Table 1 Initial variable values for penicillin biosynthesis

Variable	*Initial value*
X(g/L)	1.5
P(g/L)	0.0
S(g/L)	0.0
V(L)	7.0

Table 2 Parameters of penicillin biosynthesis model

Parameter	*Definition*	*Value*
μ_{max}	Maximum specific biomass growth rate (h^{-1})	0.11
ρ_{max}	Maximum specific production rate (g P/g X h)	0.0055
K_{XG}	Saturation parameter for biomass growth (g S/g X)	0.006
K_{PP}	Saturation parameter for production (g S/L)	0.0001
K_{in}	Inhibition parameter for production (g S/L)	0.1
K_{deg}	Product degradation rate (h^{-1})	0.001
K_m	Saturation parameter for maintenance consumption (g S/L)	0.0001
m_s	Maintenance consumption rate (g S/g X h)	0.029
$Y_{X/S}$	Yield factor for substrate to biomass (g X/g S)	0.47
$Y_{P/S}$	Yield factor for substrate to product (g P/g S)	1.2
S_F	Feed concentration (g S/L)	500

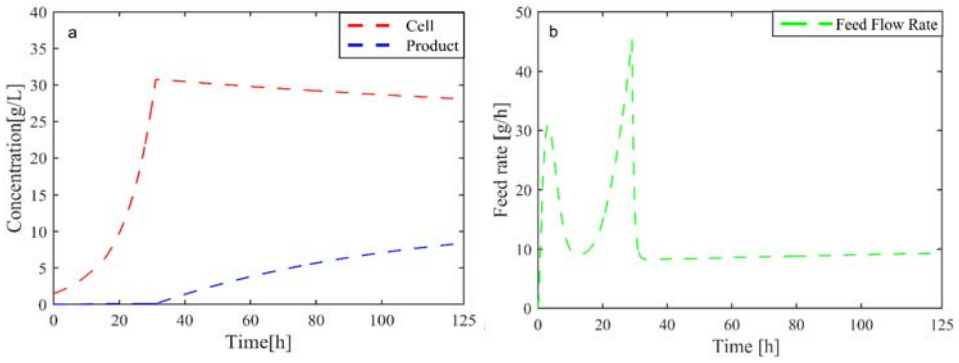
3 Controller design

“Most control structures are based on the use of a design model. A mathematical model provides a map from inputs to responses and the quality of a model depends on how closely its responses match those of the true plant. Therefore, a model set which includes the true physical plant can never be constructed.” (Zhou et al., 1996). For this reason, it is

necessary the design of a controller that allows tracking, with minimal error, previously determined profiles (calculated with a model and specific initial conditions) even in presence of perturbations, and parameters or initial conditions variation.

As it was aforementioned, to implement this technique it is assumed that the mathematical model of the process is available, the references profiles and all the states variables are known in each instant of time (Tan et al., 2017). The reference profiles to follow are the biomass and product concentration inside the reactor. Figure 1 shows the mentioned reference profiles and the feed flow rate used to obtain them, taken from Riascos and Pinto (2004).

Figure 1 Reference profiles (X_{ref}, P_{ref}) (see online version for colours)



(a) (b)

Source: Determined in Riascos and Pinto (2004)

Now, the objective is to find the control action that allows us to reach those references. The steps to follow are:

Step 1 Define the sample time, the references and the states variables.

Step 2 Approximate the differential equations with a numerical method.

Step 3 Propose an expression to approximate the states variables in the next sampling time.

Step 4 Select the controller parameters.

Step 5 Define and calculate the denominated sacrificed variable.

Step 6 Calculate the control action using last squares.

3.1 Controller design

Initially, the model differential equations from equation (1) are approximated using Euler method:

$$\left(\frac{d\sigma}{dt}\right) = \frac{\sigma_{n+1} - \sigma_n}{T_S} \tag{3}$$

where σ represents each state variable, σ_n is the state variable in the present sampling time, while σ_{n+1} is the value in the next measurement instant. T_S is the sampling time; for this study is adopted a value of 0.1 *h*. The process lasts $T_f = 125$ *h*.

The state variables values in $n + 1$ are approximated with:

$$\underbrace{\sigma_{ref\,n+1} - \sigma_{n+1}}_{error_{n+1}} = k_\sigma \underbrace{(\sigma_{ref\,n} - \sigma_n)}_{error_n} \rightarrow \sigma_{n+1} = \sigma_{ref\,n+1} - k_\sigma (\sigma_{ref\,n} - \sigma_n) \tag{4}$$

Here, k_σ represents the controller parameters k_X, k_P and k_S. They take values between zero and one ($0 < k_\sigma < 1$), which makes the tracking error tends to zero when n tends to infinity. Looking at equation (4), when $k_\sigma = 0$, the real profile reaches the reference in only one step, and when $0 < k_\sigma < 1$, the error approaches gradually to zero. See the Appendix for the demonstration.

Then, substituting equation (4) in equation (3), it is obtained the next expression:

$$\left(\frac{d\sigma}{dt}\right) = \frac{\overbrace{\left[\sigma_{ref\,n+1} - k_\sigma(\sigma_{ref\,n} - \sigma_n)\right]}^{\sigma_{n+1}} - \sigma_n}{T_S} \tag{5}$$

Equation (5) approximates the derivatives and proposes a way of replacement for the state variables in the next sampling instant. This allows calculating the control action in an easy way. Replacing equation (5) in the mathematical model, equation (1):

$$\begin{cases} \dot{X}(t) = \dfrac{\left(X_{ref\,n+1} - k_X\left(X_{ref\,n} - X_n\right) - X_n\right)}{T_S} = \mu\left(X_n, S_n\right) X_n - \left(\dfrac{X_n}{S_F V_n}\right) U_n \\ \dot{P}(t) = \dfrac{\left(P_{ref\,n+1} - k_P\left(P_{ref\,n} - P_n\right) - P_n\right)}{T_S} = \rho\left(S_n\right) X_n - K_{deg} P_n - \left(\dfrac{P_n}{S_F V_n}\right) U_n \\ \dot{S}(t) = \dfrac{\left(S_{ref\,n+1} - k_S\left(S_{ref\,n} - S_n\right) - S_n\right)}{T_S} = -\mu\left(X_n, S_n\right)\left(\dfrac{X_n}{Y_{X/S}}\right) - \rho\left(S_n\right)\left(\dfrac{P_n}{Y_{P/S}}\right) \\ \qquad -\left(\dfrac{m_s S_n}{K_m + S_n}\right) X_n + \left(1 - \dfrac{S_n}{S_F}\right)\dfrac{U_n}{V_n} \end{cases} \tag{6}$$

This linear equations system can be expressed in a matrix form, where state variables are placed as a function of the control action:

$$\overbrace{\begin{pmatrix} -X_n \\ -P_n \\ S_f - S_n \end{pmatrix}}^{A} \underbrace{\frac{U_n}{S_f V_n}}_{u} = \underbrace{\begin{pmatrix} \dfrac{\left(X_{ref\,n+1} - k_X\left(X_{ref\,n} - X_n\right) - X_n\right)}{T_0} - \mu\left(X_n, S_n\right) X_n \\ \dfrac{\left(P_{ref\,n+1} - k_P\left(P_{ref\,n} - P_n\right) - P_n\right)}{T_0} - \rho\left(S_n\right) X_n + K_{deg} P_n \\ \dfrac{\left(S_{ref\,n+1} - k_S\left(S_{ref\,n} - S_n\right) - S_n\right)}{T_0} + \mu\left(X_n, S_n\right)\left(\dfrac{X_n}{Y_{X/S}}\right) \\ +\rho\left(S_n\right)\left(\dfrac{X_n}{Y_{P/S}}\right) + \left(\dfrac{m_s S_n}{K_m + S_n}\right) X_n \end{pmatrix}}_{b} \tag{7}$$

Equation (7) is generically expressed as follows:

$$\begin{pmatrix} a_1 \\ a_2 \\ a_3 \end{pmatrix} \frac{U}{S_f V} = \begin{pmatrix} b_1 \\ b_2 \\ b_3 \end{pmatrix} \tag{8}$$

Then, from equation (8) could be obtained the control action. To achieve this, system equation (8) must have an exact solution. In order to assure this, A and b must be parallel (Strang, 2006). There are several ways to make the system satisfy this condition, one of them is:

$$\begin{cases} \dfrac{a_3}{a_1} = \dfrac{b_3}{b_1} \\ \dfrac{a_3}{a_2} = \dfrac{b_3}{b_2} \end{cases} \rightarrow \begin{cases} a_3 b_1 = b_3 a_1 \\ a_3 b_2 = b_3 a_2 \end{cases} \tag{9}$$

Replacing in equation (9) each matrix component it leads to:

$$\begin{cases} \left(S_f - S_n\right)\left(\left(\dfrac{X_{ref\,n+1} - k_X\left(X_{ref\,n} - X_n\right) - X_n}{T_S}\right) - \mu\left(X_n, S_n\right) X_n\right) \\ = \left(\left(\dfrac{S_{ref\,n+1} - k_S\left(S_{ref\,n} - S_n\right) - S_n}{T_S}\right) + \mu\left(X_n, S_n\right)\left(\dfrac{X_n}{Y_{X/S}}\right)\right. \\ \left. + \rho\left(S_n\right)\left(\dfrac{X_n}{Y_{P/S}}\right) + \left(\dfrac{m_s S_n}{K_m + S_n}\right) X_n\right)\left(-X_n\right) \\ \left(S_f - S_n\right)\left(\left(\dfrac{P_{ref\,n+1} - k_P\left(P_{ref\,n} - P_n\right) - P_n}{T_S}\right) - \rho\left(S_n\right) X_n + K_{deg} P_n\right) \\ = \left(\left(\dfrac{S_{ref\,n+1} - k_S\left(S_{ref\,n} - S_n\right) - S_n}{T_S}\right) + \mu\left(X_n, S_n\right)\left(\dfrac{X_n}{Y_{X/S}}\right)\right. \\ \left. + \rho\left(S_n\right)\left(\dfrac{X_n}{Y_{P/S}}\right) + \left(\dfrac{m_s S_n}{K_m + S_n}\right) X_n\right)\left(-P_n\right) \end{cases} \tag{10}$$

To solve equation (10) the 'sacrificed variable' is defined, denoted by the subscript 'ez'. To select it, it is essential to examine and interpret the role of each variable in the process. In a bioprocess, the substrate concentration, which can be adjusted by varying the supply flow rate, directly affects the rate of substrate consumption, growth rate of cells, and the formation rate of products or by products (Öztürk et al., 2016). Considering this, S is chosen as sacrificed variable. Replacing S_{ref} by S_{ez} in equation (10) and operating, the sacrificed variable is obtained.

Once S_{ez} is known, the control action at any sampling time can be calculated from equation (8) using least squares (Strang, 2006):

$$\frac{U}{S_f V} = \left(A^T A\right)^{-1} A^T b \tag{11}$$

3.2 Controller parameters selection

The bioreactor performance is directly affected by the controller parameters (k_σ). Consequently, those parameters must be selected carefully. To compare the performance between simulations the tracking error is defined as:

$$\|e_n\| = \sqrt{\left(X_{refn} - X_n\right)^2 + \left(P_{refn} - P_n\right)^2 + \left(S_{ezn} - S_n\right)^2} \tag{12}$$

From equation (12) is defined the 'total error' as:

$$\mathrm{E}_C = \sum_{n=1}^{M} \|e_n\| \tag{13}$$

where $C = 1, 2, \ldots, N$ and $M = T_f/T_S$.

The problem of searching for an object in an unknown environment is central to many areas of computer science, optimisation, numerical analysis and operational research (Wang and Kao, 2014). Moreover, randomised algorithms are a useful tool for analysing the performance of complex uncertain systems (Calafiore, 2009). In this paper, a Monte Carlo randomised algorithm is applied. With this approach, the computational complexity can be reduced in comparison with other algorithms (Tempo and Ishii, 2007; Dimov et al., 2015). Furthermore, many authors choose this method because of its reliability and its simple application (Mohammadi et al., 2014; De Oliveira et al., 2012; Cheein and Scaglia, 2014).

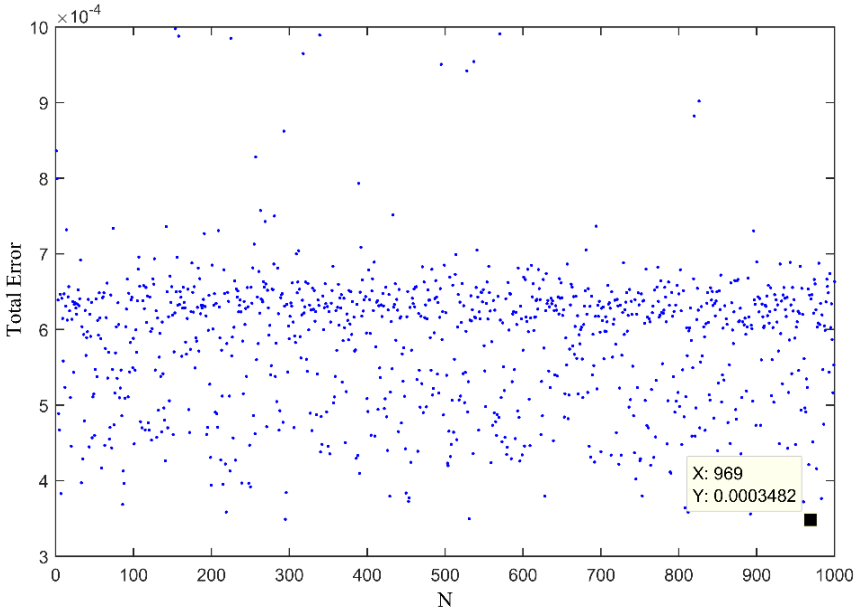
The procedure consists in simulate the process N times, using random sets of k_σ values. For each simulation E_C is calculated. Finally, the set of k_σ that allow obtaining the minimal E_C is selected.

The number of simulations (N) is calculated with an appropriate accuracy and confidence, in order to limit the possibility of a wrong answer. To determine N, we use the next expression (Tempo and Ishii, 2007):

$$N \geq \left\lceil \frac{\log \frac{1}{\delta}}{\log \frac{1}{1-\varepsilon}} \right\rceil \tag{14}$$

where δ is the confidence and ε is the accuracy. Depending on the precision to be obtained, δ and ε values are selected. For this study, $\delta = 0.01$ and $\varepsilon = 0.005$. Thus, by means of equation (14), $N = 1{,}000$.

Figure 2 Total error for 1,000 simulations (see online version for colours)



Note: The lowest error is highlighted.

Figure 2 shows the total error for the *N* simulations, where the lowest error is highlighted. It was obtained with the parameters presented in Table 3.

Table 3 Optimal controller parameters

kX	0.9798
kP	0.976
kS	0.8979

4 Simulation results

This section describes the controller behaviour. With the purpose of evaluate it, some simulation tests are made, which are explained in the next subsections.

4.1 Controller operation under normal conditions

To simulate under normal conditions, the initial state variables of Table 1, the process parameters of Table 2, and the controller parameters of Table 3 are used. It is considered that there are no disturbances in the external environment that could affect the process.

Figure 3 Comparison between (a) reference and real cells concentration, (b) reference and real product concentration, (c) reference and calculated control action and (d) tracking error tending to zero as the process progress (see online version for colours)

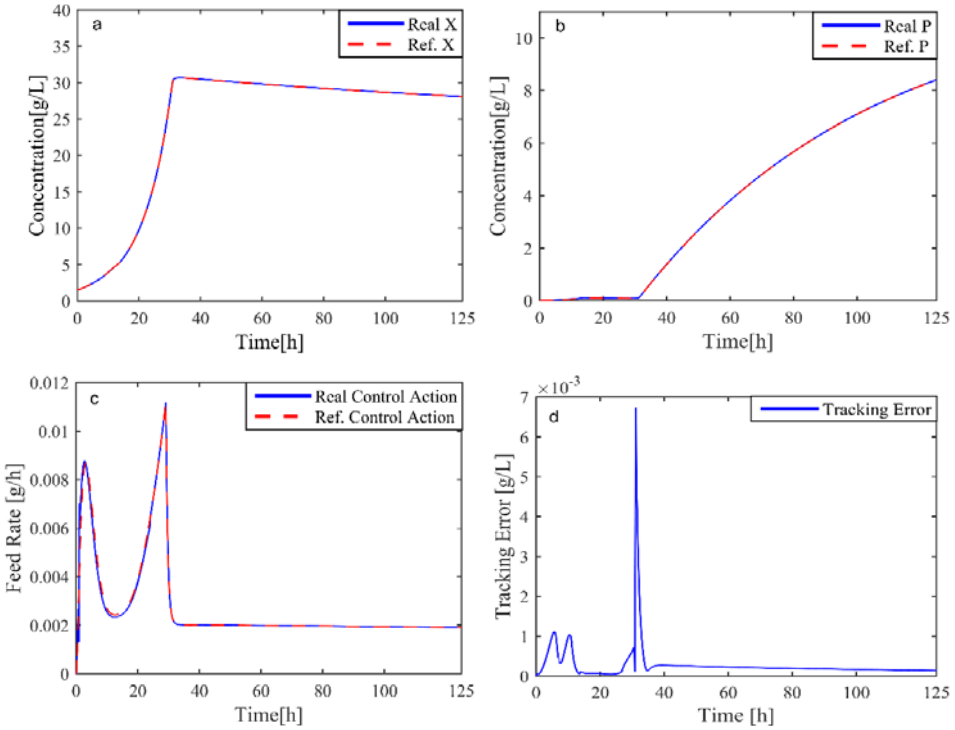


Figure 3 shows how the real cells and product concentration follow perfectly the references. Moreover, the control action profile obtained with the controller is compared with the reference of Riascos and Pinto (2004). Finally, note how the tracking error tends to zero as the process moves forward.

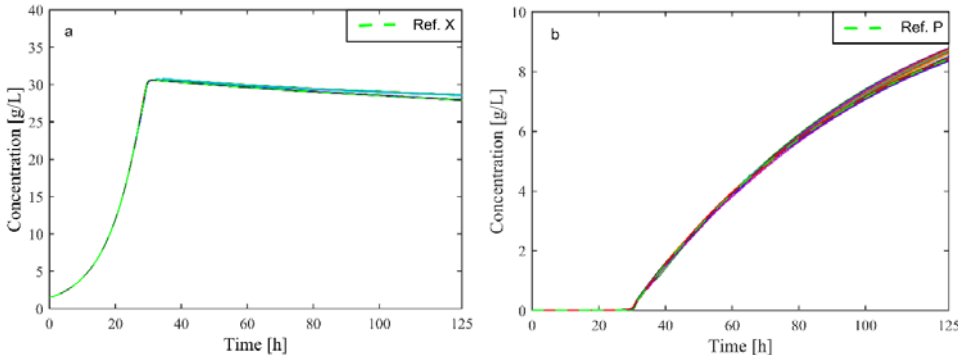
4.2 Test under parametric uncertainty

The difficulty in determining model parameters is a typical characteristic of bioprocesses. Moreover, they can change along the process (Wechselberger et al., 2010). With this test, the controller performance is verified when parameter uncertainty is present in the bioreactor.

For this test, the Monte Carlo algorithm already presented is used. The experiment consists in simulate all the process N times, while the most sensitive system parameters are changed randomly in a +5 or 10% of their original values (Table 2). N is calculated with equation (14), with $\delta = 0.01$ and $\varepsilon = 0.005$. The system parameters affected with uncertainty are: K_p, K_{in}, K_m, $Y_{P/S}$.

Figure 4 shows how the concentration profiles vary when model parameters are modified N times. The deviation that profiles suffer regarding the references is practically nil.

Figure 4 Comparison between (a) references and biomass concentration and (b) references and product concentration, under parametric uncertainty (see online version for colours)



4.3 Test with perturbations in the control action

In any process exists unforeseen contingencies that must be solved in time to avoid production to be altered. Bioprocesses are not the exception. Therefore, in order to show the controller performance in this situation, the control action is affected in a ±20% of its original value with a random perturbation. This can be explained as a random noise that results in a non-zero-mean Gaussian disturbances (George, 2014).

Figure 5 Comparison between (a) reference and perturbed control action, (b) reference and real cells concentration, (c) reference and real product concentration and (d) tracking error remaining at acceptable levels (see online version for colours)

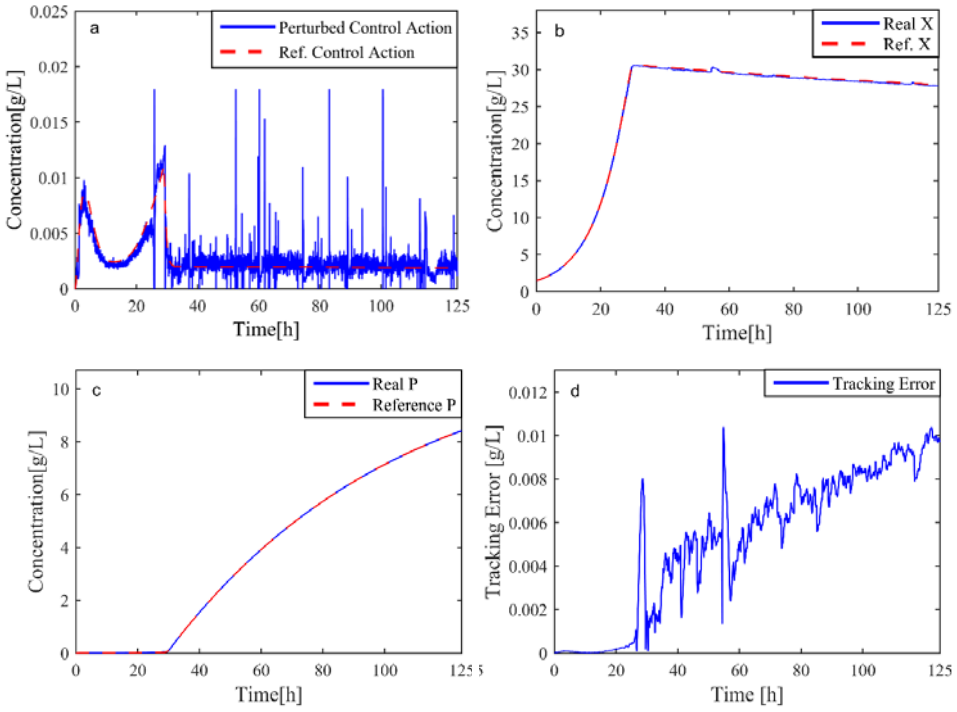
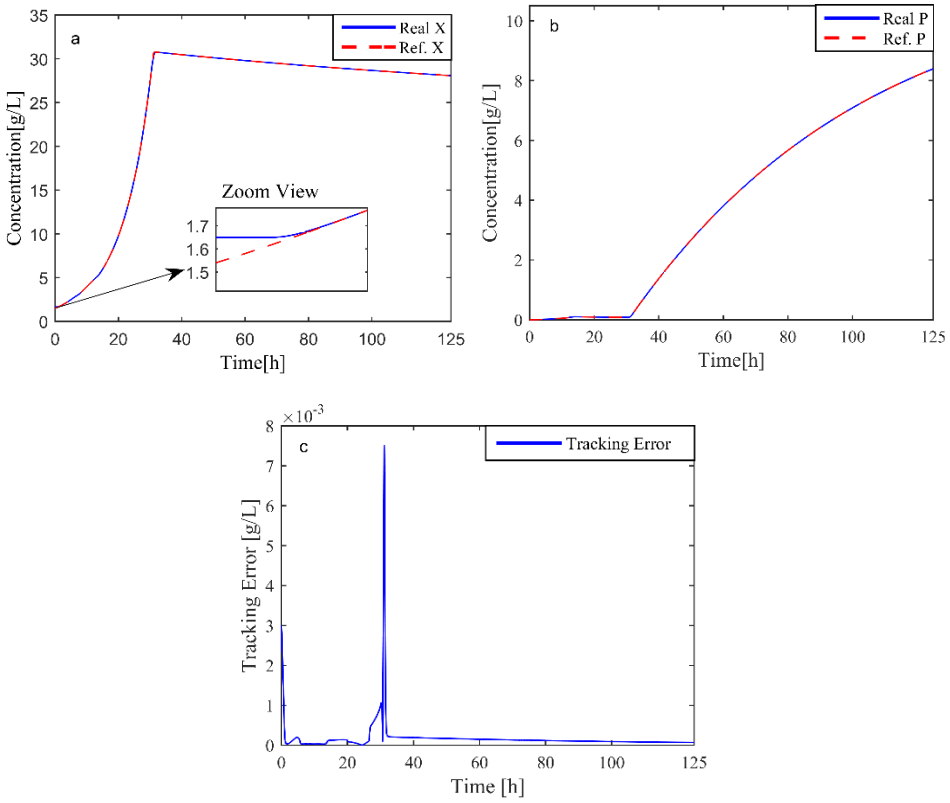


Figure 5 shows the difference between the perturbed control actions and the reference one. Also, shows how the reference profiles are tracked though the perturbation added in the control action. It is important to highlight that the tracking error increases with the perturbation added but remains at acceptable levels.

4.4 Test with perturbations in the initial conditions

Any bioprocess operated in a fed-batch mode depends on the system starting conditions, because it has infinite memory. If initial conditions are different from the nominal ones, the system may never reach the steady state. When situation like this occur, the controller proposed modify the substrate feed rate in order to reach the desired concentrations. This fact is demonstrated with the following test.

Figure 6 Comparison between (a) reference and biomass concentration with different initial conditions, (b) reference and product concentration with different initial conditions and (c) tracking error (see online version for colours)



Here, the initial conditions of the process are changed in ±10%. Figure 6 shows how the cells and product concentrations follow the references and keep minimal the tracking error.

5 Results and discussion

In the first experience, it can be observed that under normal operation conditions all the state variables reaches the reference profiles with minimum error (see Figure 3). However, in order to consider more realistic operating conditions, several tests were made:

- Parametric uncertainties: applying the Monte Carlo method, 1,000 simulations were made adding ±5 or 10% of uncertainty in the most sensitive system parameters. Figure 4 shows the system response: the controller performance is remarkable though the existence of parametric uncertainty.
- Perturbations in the control action: in this simulation, the control action is affected with ±20% of its original value with a random noise. As Figure 5 shows, the control action remains bounded and the tracking error do not greatly increased its value.
- Perturbations of ±10% in the initial conditions: from Figure 6 can be seen that the system reaches the references, although the initial conditions differs from the nominal values, described in Table 1.

6 Conclusions

It was presented a control technique based on linear algebra. With this methodology, the control action is obtained in order to track optimal concentration profiles taken from the literature. As an example, the technique was applied in a penicillin production process in a fed-batch bioreactor.

This controller has several advantages over others approaches: it has less mathematical complexity because it works with linear equations; it is independent of the operating point because it does not use the linearised model; it allows obtaining the control action as a solution of a linear equations system, in spite of the nonlinearities of the mathematical model. Moreover, this controller is versatile against different changes and disturbances; this was supported by the different tests made. One of the limitations of this technique is the availability of states online measurements at each sampling time however this can be solved by designing virtual sensors. In future publications, the use of state estimators based on neural networks and through Bayesian regression will be developed.

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Appendix

When equation (4) approximation form is used, the values of the k_σ parameters must be between zero and one ($0 < k_\sigma < 1$), because that makes the tracking error tends to zero when n tends to infinity. With the final purpose of demonstrate this fact, the next steps must to be followed:

Replacing S_{refn+1} by S_{ez} in equation (7), and then expressing it in matrix form:

$$\begin{pmatrix} A_1 \\ A_2 \\ A_3 \end{pmatrix} \frac{U_n}{S_f V_n} = \begin{pmatrix} b_1 \\ b_2 \\ b_3 \end{pmatrix} \tag{A1}$$

Then, solving equation (A1) with least squares

$$\frac{U_n}{S_f V_n} = \left(A^T A\right)^{-1} A^T b = \frac{A_1 b_1 + A_2 b_2 + A_3 b_3}{A_1^2 + A_2^2 + A_3^2} \tag{A2}$$

From equation (A1)

$$\begin{aligned} &\frac{A_1}{A_3} = \frac{b_1}{b_3} \rightarrow b_3 = \frac{A_3}{A_1} b_1 \\ &\frac{A_2}{A_3} = \frac{b_2}{b_3} \rightarrow b_2 = \frac{A_2}{A_1} b_1 \end{aligned} \tag{A3}$$

Substituting equation (A3) in equation (A2)

$$\begin{aligned} \frac{U_n}{S_f V_n} &= \frac{A_1 b_1 + \left(A_2^2 / A_1\right) b_1 + \left(A_3^2 / A_1\right) b_1}{A_1^2 + A_2^2 + A_3^2} = \frac{\left(b_1 / A_1\right)\left(A_1^2 + A_2^2 + A_3^2\right)}{A_1^2 + A_2^2 + A_3^2} \\ &= \frac{b_1}{A_1} = \frac{\left(\left(X_{refn+1} - k_X\left(X_{refn} - X_n\right) - X_n\right)\right) / T_0 - \mu\left(X_n, S_{ezn}\right) X_n}{-X_n} \end{aligned} \tag{A4}$$

Replacing equation (A4) in equation (7)

$$X_{n+1} = X_{refn+1} - k_X\left(X_{refn} - X_n\right) + T_0\left[\mu\left(X_n, S_n\right) - \mu\left(X_n, S_{ezn}\right)X_n\right] \tag{A5}$$

Then, the tracking error for the biomass concentration is

$$e_{Xn+1} = X_{refn+1} - X_{n+1} \tag{A6}$$

Changing equation (A5) in equation (A6)

$$e_{Xn+1} = k_X\left(X_{refn} - X_n\right) - T_0\left[\mu\left(X_n, S_n\right) - \mu\left(X_n, S_{ezn}\right)\right]X_n \tag{A7}$$

The Taylor approximation of $\mu(X_n, S_n)$ in the desired value $\mu\ (X_n, S_{ezn})$ is

$$\mu\left(X_n, S_n\right)() = \mu\left(X_n, S_{ezn}\right) + \left.\frac{d\mu\left(X_n, S\right)}{dS}\right|_{S=S_{ezn}+\lambda(S_n-S_{ezn})=S_\lambda}\left(S_n - S_{ezn}\right) \tag{A8}$$

$$where \rightarrow 0 < \lambda < 1$$

Replacing equation (A8) in equation (A7)

$$\begin{aligned} e_{Xn+1} &= k_X\left(X_{refn} - X_n\right) - T_0\left[\begin{array}{l}\mu\left(X_n, S_{ezn}\right) + \left.\dfrac{d\mu\left(X_n, S\right)}{dS}\right|_{S=S_\lambda} \\ \underbrace{\left(S_n - S_{ezn}\right)}_{-e_{S_n}} - \mu\left(X_n, S_{ezn}\right)\end{array}\right]X_n \\ e_{Xn+1} &= k_X\left(X_{refn} - X_n\right) + T_0\left.\frac{d\mu\left(X_n, S\right)}{dS}\right|_{S=S_\lambda} e_{S_n}X_n \end{aligned} \tag{A9}$$

In the same way it is demonstrated for *P*.

From equation (A1)

$$\begin{aligned} \frac{A_2}{A_3} = \frac{b_2}{b_3} \rightarrow b_3 = \frac{A_3}{A_2}b_2 \\ \frac{A_1}{A_3} = \frac{b_1}{b_3} \rightarrow b_1 = \frac{A_1}{A_2}b_2 \end{aligned} \tag{A10}$$

Substituting equation (A10) in equation (A2)

$$\begin{aligned} \frac{U_n}{S_f V_n} &= \frac{\left(A_1^2 / A_2\right)b_2 + A_2 b_2 + \left(A_3^2 / A_2\right)b_2}{A_1^2 + A_2^2 + A_3^2} = \frac{\left(b_2 / A_2\right)\left(A_1^2 + A_2^2 + A_3^2\right)}{A_1^2 + A_2^2 + A_3^2} \\ &= \frac{b_2}{A_2} = \frac{\left(\left(P_{refn+1} - k_P\left(P_{refn} - P_n\right) - P_n\right)/T_0\right) - \rho\left(S_{ezn}\right)X_n + K_{\deg}P_n}{-P_n} \end{aligned} \tag{A11}$$

Replacing equation (A11) in equation (7)

$$P_{n+1} = P_{refn+1} - k_P\left(P_{refn} - P_n\right) + T_0\left[\rho\left(S_n\right) - \rho\left(S_{ezn}\right)\right]X_n \tag{A12}$$

Then, the tracking error for the penicillin concentration is

$$e_{Pn+1} = P_{refn+1} - P_{n+1} \tag{A13}$$

Changing equation (A12) in equation (A13)

$$e_{Pn+1} = k_P\left(P_{refn} - P_n\right) - T_0\left[\rho\left(S_n\right) - \rho\left(S_{ezn}\right)\right]X_n \tag{A14}$$

The Taylor approximation of $\rho(S_n)$ in the desired value $\rho\ (S_{ezn})$ is

$$\rho\left(S_n\right) = \rho\left(S_{ezn}\right) + \left.\frac{d\rho(S)}{dS}\right|_{S=S_{ezn}+\psi\left(S_n - S_{ezn}\right)=S\psi}\left(S_n - S_{ezn}\right)$$
$$where \rightarrow 0 < \psi < 1 \tag{A15}$$

Replacing equation (A15) in equation (A14)

$$e_{Pn+1} = k_P\left(P_{refn} - P_n\right) - T_0\left[\rho\left(S_{ezn}\right) + \left.\frac{d\rho(S)}{dS}\right|_{S=S_\psi}\underbrace{\left(S_n - S_{ezn}\right)}_{-e_{S_n}} - \rho\left(S_{ezn}\right)\right]X_n$$
$$e_{Pn+1} = k_P\left(P_{refn} - P_n\right) + T_0\left.\frac{d\rho(S)}{dS}\right|_{S=S_\psi} e_{S_n}X_n \tag{A16}$$

The demonstration is similar for *S*.

From equation (A1)

$$\frac{A_1}{A_3} = \frac{b_1}{b_3} \rightarrow b_1 = \frac{A_1}{A_3}b_3$$
$$\frac{A_2}{A_3} = \frac{b_2}{b_3} \rightarrow b_2 = \frac{A_2}{A_3}b_3 \tag{A17}$$

Replacing equation (A17) in equation (A2)

$$\frac{U_n}{S_f V_n} = \frac{\left(A_1^2 / A_3\right)b_3 + \left(A_2^2 / A_3\right)b_3 + A_3 b_3}{A_1^2 + A_2^2 + A_3^2} = \frac{\left(b_3 / A_3\right)\left(A_1^2 + A_2^2 + A_3^2\right)}{A_1^2 + A_2^2 + A_3^2} = \frac{b_3}{A_3}$$
$$\left(\left(S_{ezn+1} - k_S\left(S_{ezn} - S_n\right) - S_n\right)/T_0\right) + \mu\left(X_n, S_n\right)\frac{X_n}{Y_{X/S}}$$
$$= \frac{+\rho\left(S_n\right)\frac{X_n}{Y_{P/S}} + \frac{m_s S_n}{K_m + S_n}X_n}{S_f - S_n} \tag{A18}$$

Replacing equation (A18) in equation (7)

$$S_{n+1} = S_{ezn+1} - k_S\left(S_{ezn} - S_n\right) \tag{A19}$$

Then, the tracking error for the substrate is

$$e_{Sn+1} = S_{refn+1} - S_{n+1} \tag{A20}$$

Changing equation (A12) in equation (A13)

$$\begin{aligned} e_{Sn+1} &= S_{ezn+1} - \left(S_{ezn+1} - k_S \left(S_{ezn} - S_n \right) \right) \\ &= k_S \left(S_{ezn} - S_n \right) = k_S e_{Sn} \end{aligned} \tag{A21}$$

Finally, joining equation (A9), equation (A16) and equation (A21)

$$\begin{pmatrix} e_{Xn+1} \\ e_{Pn+1} \\ e_{Sn+1} \end{pmatrix} = \underbrace{\begin{pmatrix} k_X & 0 & 0 \\ 0 & k_P & 0 \\ 0 & 0 & k_S \end{pmatrix} \begin{pmatrix} e_{Xn} \\ e_{Pn} \\ e_{Sn} \end{pmatrix}}_{L} + \underbrace{T_0 X_n \begin{pmatrix} \left. \frac{d\mu(X_n, S)}{dS} \right|_{S=S_\lambda} \\ \left. \frac{d\rho(S)}{dS} \right|_{S=S_\psi} \\ 0 \end{pmatrix} e_{Sn}}_{NL} \tag{A22}$$

In equation (A22), L represents a linear system that tends to zero when $k\sigma$ values are between zero and one; while NL is a bounded nonlinearity that tends to zero because e_{Sn} has a tendency to zero, moreover, it is multiplied by a limited term (T_0X_n). This proves that the tracking error tends to zero when n tends to infinity (Scaglia et al., 2010).