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Tracking control of concentration profiles in a fed-batch bioreactor using a linear algebra methodology

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ABSTRACT

Based on a linear algebra approach, this paper aims at developing a novel control law able to track reference profiles that were previously-determined in the literature. A main advantage of the proposed strategy is that the control actions are obtained by solving a system of linear equations. The optimal controller parameters are selected through Monte Carlo Randomized Algorithm in order to minimize a proposed cost index. The controller performance is evaluated through several tests, and compared with other controller reported in the literature. Finally, a Monte Carlo Randomized Algorithm is conducted to assess the performance of the proposed controller.

1. Introduction

The biochemical industry has significantly risen along the last two decades [1–3], with an increasing interest for synthesizing a large amount of products by means of microorganisms [4]. Many processes of the biochemical industry are often operated in a fed-batch form [5]. The fed-batch operation is one of the most popular in the biochemical industry. In this class of bioreactor the substrate is gradually fed into the reactor, but the product is only removed when the process has finished. The principal advantage is the avoidance of substrate overfeeding, which can inhibit the growth of microorganisms.

On the other hand, the fed-batch processes often present some challenging problems that particularly complicate the control of fermenters. For example, most of their dynamic mathematical models are nonlinear and stiff due to the nature of bioprocesses, responses of bioprocesses are slow [5], and typically include time-varying parameters [3] whose variation is typically unknown [6]. These problems make the process control an arduous task [7,8].

In general, control is implemented to fed-batch reactors to maintain the process at the desired operating conditions safely and efficiently, that means to provide a near ideal environment for microorganisms to grow and produce a desired product.

In this type of bioreactors, an important issue of the control problem consists in tracking the set point changes without causing undesirable oscillations or taking long times for reducing the tracking errors. Many efforts have been made in advanced control for fed-batch fermentations in order to deal with the above problems mentioned. Many papers in the literature have reported applications of advanced control in fermentation processes [9–14] concerning online adaptive control, optimal control, fuzzy control, model predictive control (MPC) and nonlinear MPC, adaptive extremum seeking control, etc.

These types of methods have gained increasing popularity because of their strong capability in dealing with process nonlinearity, dynamics and optimization. However, the computational time required to find the solution, the complexity of online implementation, and the insufficient accuracy of online solutions [5], limits its applications to bioprocesses.

The strategy presented in this paper has the advantage of using discrete equations, and therefore a direct implementation in most computer-driven systems is feasible; the methodology for the design of the controller is easy, because the control action is calculated from a system of linear equations; state equations are utilized so the methodology can be extended to MIMO systems; the nonlinear model is used, thus its performance is independent of the operating point; and has a good performance in tracking the set point changes, as can be seen in the simulation section of the

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present paper. Besides, because its simplicity and the mathematical tools that it use, this methodology is applicable to many systems, not only to bioprocess.

Consider a fed-batch reactor with an optimization goal of maximizing the amount of the secreted protein at the end of the process. This optimal control problem has been studied by many authors [15–19]. The main objective of the present work is to design a controller capable of achieving reproducibility between successive batches while tracking previously-defined optimal profiles. In this respect, a comprehensive approach able to track optimal profiles is proposed. To accomplish this objective, the following is assumed: (i) the process is properly represented through a mathematical model; (ii) the desired optimal concentration profiles are known; (iii) all the states variables can be measured; and (iv), the control action that moves the system from its current state to a desired one can be obtained.

In the proposed methodology, the system model is approximated by numerical methods and the control action is calculated under the assumption that the reference profiles are known. Such control action forces the system to move from its current state to the reference one; and the conditions for achieving a zero tracking error are obtained by solving a system of linear equations. The trajectory tracking controller structure arises naturally derived through a handcrafted procedure that is inferred by analyzing the mathematical model of the process.

The paper is organized as follows. Section 2 describes the fed-batch bioreactor and Section 3 develops the methodology for the controller design. In Section 4, the controller parameters are estimated through a Monte Carlo Experiment, and the efficiency of the controller is demonstrated by means of simulated examples. Main conclusions and remarks are summarized in the last section.

2. Fed-batch bioreactor

The system under study is a fed-batch bioreactor for the production of a secreted protein, and was originally proposed by [20]. The protein SUC2-s2 encodes both secreted and intracellular forms of an invertase via two mRNAs [21]. A dynamic model of the process has been developed by [20], together with an optimal operation policy, which ensures the maximization of the foreign protein production by means of a profile calculated for each state variable.

The process is described by the following dynamic model [20]:

$$\begin{cases} \dot{P} = \chi(P_T - P) - \frac{uP}{V} \\ \dot{P}_T = \psi X - \frac{uP_T}{V} \\ \dot{X} = \mu X - \frac{uX}{V} \\ \dot{S} = -Y_{S/X}\mu X + \frac{u(S_F - S)}{V} \end{cases} \tag{1}$$

with

$$\chi(\mu(S)) = \frac{4.75\mu}{0.12+\mu}$$

$$\psi(S) = \frac{Se^{-5S}}{0.1+S}$$

$$\mu(S) = \frac{21.87S}{(S+0.4)(S+62.5)}$$

$$u = \dot{V} \tag{2}$$

In Eqs. (1–2), the state variables are: the amount of secreted protein per culture volume unit (P), the total protein amount per culture volume unit (P_T), the culture cell density (X), the culture glucose concentration (S), and the culture volume (V). Besides, u is the feed flow rate, S_F is the glucose concentration of the feed stream, $Y_{S/X}$ is the yield of glucose per cell mass, and ψ, μ, and χ are the protein expression rate, the specific growth rate of the host cell, and the protein secretion rate, respectively. The last three variables depend on the culture glucose concentration (S), as described by Eq. (2). The ratio u/V is the dilution rate. Initial conditions for the state variables and model parameters are shown in Table 1 [15].

Table 1
Initial conditions for the state variables and model parameters.

State variable/parameter	Value
P_0	0 g/L
P_{T_0}	0 g/L
X_0	1 g/L
S_0	5 g/L
V_0	1 L
S_F	20 g/L
$Y_{S/X}$	7.3

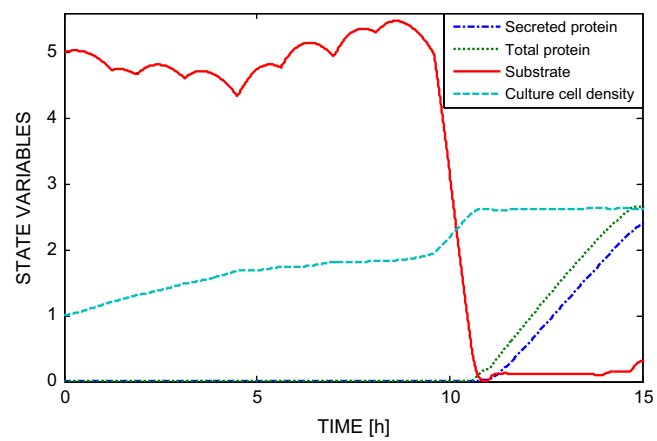

Fig. 1. Optimal profiles $[P_{ref}, P_{Tref}, X_{ref}, S_{ref}]^T$, as determined by [16].

In the current process, u is assumed to be the control variable, as typically adopted in the literature. For further details, see [22,23].

3. Controller design

The maximum amount of the secreted protein at the end of the batch time was determined by [15], by solving an optimization problem. The cost function was defined as follows:

$$\max_u J_0 = P(t_f)V(t_f) \tag{3}$$

where t_f=15 h is the final fermentation time. The optimal profiles are represented as continuous functions in Fig. 1 [15], and are taken as the reference trajectories throughout the work.

Below is presented the methodology for the controller design in order to follow the optimal solution given by [15].

3.1. Problem definition

The main contribution of this paper is the developing of an original control law able to track reference profiles that have been previously-determined in the literature. The controller methodology utilized for solving the problem consists of approximating Eq. (1) through the Euler method. Therefore, the control problem is reduced to the resolution of a system of linear equations. The key to the proposed method is to find the conditions under which the linear equation system has an exact solution. In order to achieve this objective, the feed flow rate u is the only control variable available.

3.2. Controller design

The control action required to follow the state variable profiles of Fig. 1 $[P_{ref}, P_{Tref}, X_{ref}, S_{ref}]^T$ is calculated on the basis of the previously-described process model. To this effect, the discrete version of Eq. (1) can be written through the Euler approximation as:

$$\begin{cases} P^{(n+1)} = P^{(n)} + T_0\left[\chi\left(S^{(n)}\right)\left(P_T^{(n)} - P^{(n)}\right) - \frac{u^{(n)}}{V^{(n)}}P^{(n)}\right] \\ P_T^{(n+1)} = P_T^{(n)} + T_0\left[\psi\left(S^{(n)}\right)X^{(n)} - \frac{u^{(n)}}{V^{(n)}}P_T^{(n)}\right] \\ X^{(n+1)} = X^{(n)} + T_0\left[\mu\left(S^{(n)}\right)X^{(n)} - \frac{u^{(n)}}{V^{(n)}}X^{(n)}\right] \\ S^{(n+1)} = S^{(n)} + T_0\left[-7.3\mu\left(S^{(n)}\right)X^{(n)} + \frac{u^{(n)}}{V^{(n)}}\left(20 - S^{(n)}\right)\right] \end{cases} \tag{4}$$

This system of linear equations can be rearranged in the following matrix form:

$$\begin{bmatrix} \frac{P^{(n)}}{V^{(n)}} \\ \frac{P_T^{(n)}}{V^{(n)}} \\ \frac{X^{(n)}}{V^{(n)}} \\ \frac{20 - S^{(n)}}{V^{(n)}} \end{bmatrix} u^{(n)} = \begin{bmatrix} \chi\left(S^{(n)}\right)\left(P_T^{(n)} - P^{(n)}\right) - \frac{P^{(n+1)} - P^{(n)}}{T_0} \\ \psi\left(S^{(n)}\right)X^{(n)} - \frac{P_T^{(n+1)} - P_T^{(n)}}{T_0} \\ \mu\left(S^{(n)}\right)X^{(n)} - \frac{X^{(n+1)} - X^{(n)}}{T_0} \\ 7.3\mu\left(S^{(n)}\right)X^{(n)} + \frac{S^{(n+1)} - S^{(n)}}{T_0} \end{bmatrix} \tag{5}$$

At every sample time, the linear system of Eq. (5) is used to calculate the control action that ensures the tracking of the optimal trajectories. As a first step, it is necessary to specify the conditions under which the system has an exact solution.

Consider first, the immediately reachable value of each state vector, as proposed here:

$$\begin{aligned} P^{(n+1)} &= P_{ref}^{(n+1)} - K_P\left(P_{ref}^{(n)} - P^{(n)}\right) \\ P_T^{(n+1)} &= P_{T_{ref}}^{(n+1)} - K_{P_T}\left(P_{T_{ref}}^{(n)} - P_T^{(n)}\right) \\ X^{(n+1)} &= X_{ref}^{(n+1)} - K_X\left(X_{ref}^{(n)} - X^{(n)}\right) \\ S^{(n+1)} &= S_{ref}^{(n+1)} - K_S\left(S_{ref}^{(n)} - S^{(n)}\right) \end{aligned} \tag{6}$$

In Eq. (6), each controller parameter fulfils $0 < K_\Lambda < 1$, where $_\Lambda$ represents every state variable, making the tracking errors tend to zero when $n \to \infty$ (see Appendix A). Then, the value of the state variable in the next sample time is a function of: the reference profiles ($\Lambda_{ref}^{(n)}$ and $\Lambda_{ref}^{(n+1)}$), the actual state variable ($\Lambda^{(n)}$) and the controller parameters (K_Λ).

Remark 1. In Eq. (6) note that:

- If $K_\Lambda = 0$, the reference trajectory is reached in only one step.
- If $0 < K_\Lambda < 1$, the system will slowly reach the reference profiles after several steps.

Considering Eq. (6), system (5) can be rearranged like (7), and then written in a compact form as (8):

$$\begin{bmatrix} \frac{P^{(n)}}{V^{(n)}} \\ \frac{P_T^{(n)}}{V^{(n)}} \\ \frac{X^{(n)}}{V^{(n)}} \\ \frac{20 - S^{(n)}}{V^{(n)}} \end{bmatrix} u^{(n)} = \begin{bmatrix} \chi\left(S^{(n)}\right)(P_T^{(n)} - P^{(n)}) - \frac{P_{ref}^{(n+1)} - K_P(P_{ref}^{(n)} - P^{(n)}) - P^{(n)}}{T_0} \\ \psi\left(S^{(n)}\right)X^{(n)} - \frac{P_{T_{ref}}^{(n+1)} - K_{P_T}(P_{T_{ref}}^{(n)} - P_T^{(n)}) - P_T^{(n)}}{T_0} \\ \mu\left(S^{(n)}\right)X^{(n)} - \frac{X_{ref}^{(n+1)} - K_X(X_{ref}^{(n)} - X^{(n)}) - X^{(n)}}{T_0} \\ 7.3\mu\left(S^{(n)}\right)X^{(n)} + \frac{S_{ref}^{(n+1)} - K_S(S_{ref}^{(n)} - S^{(n)}) - S^{(n)}}{T_0} \end{bmatrix} \tag{7}$$

$$\boldsymbol{Au} = \boldsymbol{b} \tag{8}$$

In order that the system of Eq. (8) has an exact solution, the column vector $\boldsymbol{b}$ must be a linear combination of the columns of $\boldsymbol{A}$. One way to ensure this is that vectors $\boldsymbol{A}$ and $\boldsymbol{b}$ be parallel. This condition can be expressed as system (9) [24]; i.e. a system of four nonlinear equations and a single unknown. Each term of Eq. (9) belongs to $\boldsymbol{A}$ or $\boldsymbol{b}$. In Eq. (9), the subscripts denote the position in the array.

$$\begin{cases} \frac{A_1}{A_4} = \frac{b_1}{b_4} \\ \frac{A_2}{A_4} = \frac{b_2}{b_4} \\ \frac{A_3}{A_4} = \frac{b_3}{b_4} \end{cases} \tag{9}$$

The unknown variable of this system is called "sacrificed variable". The values adopted by such variable forces the equation system to have exact solution. The culture glucose concentration, denoted as $S_{ez}^{(n+1)}$, was taken as "sacrificed variable" because it is directly related to all other state variables (see Eqs. (1,2)). The following replacement can be made in system (8): $S_{ref}^{(n+1)}$ by $S_{ez}^{(n+1)}$ and $S_{ref}^{(n)}$ by $S_{ez}^{(n)}$. Then, Eq. (9) can be expressed as follows:

$$\begin{cases} \frac{P^{(n)}}{20 - S^{(n)}} = \frac{\chi(S_{ez}^{(n)})(P_T^{(n)} - P^{(n)}) - \frac{1}{T_0}\left(P_{ref}^{(n+1)} - K_P\left(P_{ref}^{(n)} - P^{(n)}\right) - P^{(n)}\right)}{7.3\mu(S^{(n)})X^{(n)} + \frac{1}{T_0}\left(S_{ez}^{(n+1)} - K_S(S_{ez}^{(n)} - S^{(n)}) - S^{(n)}\right)} \\ \frac{P_T^{(n)}}{20 - S^{(n)}} = \frac{\psi(S_{ez}^{(n)})X^{(n)} - \frac{1}{T_0}\left(P_{T_{ref}}^{(n+1)} - K_{P_T}\left(P_{T_{ref}}^{(n)} - P_T^{(n)}\right) - P_T^{(n)}\right)}{7.3\mu(S^{(n)})X^{(n)} + \frac{1}{T_0}\left(S_{ez}^{(n+1)} - K_S(S_{ez}^{(n)} - S^{(n)}) - S^{(n)}\right)} \\ \frac{X^{(n)}}{20 - S^{(n)}} = \frac{\mu(S_{ez}^{(n)})X^{(n)} - \frac{1}{T_0}\left(X_{ref}^{(n+1)} - K_X\left(X_{ref}^{(n)} - X^{(n)}\right) - X^{(n)}\right)}{7.3\mu(S^{(n)})X^{(n)} + \frac{1}{T_0}\left(S_{ez}^{(n+1)} - K_S(S_{ez}^{(n)} - S^{(n)}) - S^{(n)}\right)} \end{cases} \tag{10}$$

Eq. (10) establishes the conditions that ensure an exact solution for the model of Eq. (7), where $S_{ez}^{(n)}$ is the unknown variable. In Eq. (10), $S_{ez}^{(n)}$ is obtained at the current sampling time, while $S_{ez}^{(n+1)}$ can be calculated through Taylor approximations of zero, first, or second order; i.e.:

(i) Zero-order

$$S_{ez}^{(n+1)} = S_{ez}^{(n)} \tag{11}$$

(ii) First-order

$$\begin{aligned} S_{ez}^{(n+1)} &= S_{ez}^{(n)} + \frac{dS_{ez}}{dt}T_0 \approx S_{ez}^{(n)} + \frac{\left(S_{ez}^{(n)} - S_{ez}^{(n-1)}\right)}{T_0}T_0 \\ S_{ez}^{(n+1)} &\approx 2S_{ez}^{(n)} - S_{ez}^{(n-1)} \end{aligned} \tag{12}$$

(iii) Second-order

$$S_{ez}^{(n+1)} \approx S_{ez}^{(n)} + \left(S_{ez}^{(n)} - S_{ez}^{(n-1)}\right) + \frac{\left(S_{ez}^{(n)} - 2S_{ez}^{(n-1)} - S_{ez}^{(n-2)}\right)}{2} \tag{13}$$

By alternatively using Eq. (11), or Eq. (12), or Eq. (13), the system of Eq. (10) has only one unknown: $S_{ez}^{(n)}$. Finally, in Eq. (9), $S_{ref}^{(n+1)}$ is replaced by $S_{ez}^{(n+1)}$ (Eq. (13)); and $S_{ref}^{(n)}$ is replaced by $S_{ez}^{(n)}$, thus leading to the following system of equations:

$$\begin{bmatrix} \frac{P^{(n)}}{V^{(n)}} \\ \frac{P_T^{(n)}}{V^{(n)}} \\ \frac{X^{(n)}}{V^{(n)}} \\ \frac{20 - S^{(n)}}{V^{(n)}} \end{bmatrix} u^{(n)} = \begin{bmatrix} \chi\left(S_{ez}^{(n)}\right)(P_T^{(n)} - P^{(n)}) - \frac{P_{ref}^{(n+1)} - K_P(P_{ref}^{(n)} - P^{(n)}) - P^{(n)}}{T_0} \\ \psi\left(S_{ez}^{(n)}\right)X^{(n)} - \frac{P_{T_{ref}}^{(n+1)} - K_{P_T}(P_{T_{ref}}^{(n)} - P_T^{(n)}) - P_T^{(n)}}{T_0} \\ \mu\left(S_{ez}^{(n)}\right)X^{(n)} - \frac{X_{ref}^{(n+1)} - K_X(X_{ref}^{(n)} - X^{(n)}) - X^{(n)}}{T_0} \\ 7.3\mu\left(S^{(n)}\right)X^{(n)} + \frac{1.5S_{ez}^{(n)} + 1.5 - S_{ez}^{(n-1)} - 0.5S_{ez}^{(n-2)} - K_S(S_{ez}^{(n)} - S^{(n)}) - S^{(n)}}{T_0} \end{bmatrix} \tag{14}$$

Eq. (14) allows the calculation of the control action, u, which makes the tracking errors tend to zero in every sampling time. The

control action is obtained by least squares [24], i.e.:

$$u = \left(\boldsymbol{A}^T\boldsymbol{A}\right)^{-1}\boldsymbol{A}^T\boldsymbol{b} \tag{15}$$

Remark 2. The difference between the reference and the real profiles is called tracking error, and is given by:

$$\|e^{(n)}\| = \sqrt{\left(P_{ref}^{(n)} - P^{(n)}\right)^2 + \left(P_{T_{ref}}^{(n)} - P_T^{(n)}\right)^2 + \left(X_{ref}^{(n)} - X^{(n)}\right)^2 + \left(S_{ez}^{(n)} - S^{(n)}\right)^2} \tag{16}$$

Theorem 1. *If the system behavior is ruled by (7) and the controller is designed by (15), then, $e^{(n)} \to 0$, $n \to \infty$, when profile tracking problems are considered. Proof of Theorem 1 and the convergence to zero of tracking errors can be seen in Appendix A.*

3.3. Monte Carlo Randomized Algorithm

In the field of systems and control, probabilistic methods have been found useful especially for problems related to robustness of uncertain systems [25]. One of these methods, the Monte Carlo Randomized Algorithm, is widely used in many fields such as the radioactive decay, systems of interacting atoms, the traffic on roads, etc [26]. In the control area, Monte Carlo methods allow to estimate an expectation value and they provide effective tools for the analysis of probabilistically robust control schemes.

Because of its nature, these types of algorithms can give an erroneous result with a nonzero probability. So, it could be posed the natural question of how many simulations must be performed to be sure of finding the correct answer. Under a sufficiently large sample size N, a probabilistic statement can be made as shown below:

Theorem 2. *[25]: Let ε, $\delta \in (0, 1)$, where ε is an a priori specified accuracy, and δ, the confidence interval. If*

$$N \geq \left\lceil \frac{\log \frac{1}{\delta}}{\log \frac{1}{1-\varepsilon}} \right\rceil \tag{17}$$

then, the empirical maximum satisfies the following inequality with probability greater than 1-δ,

$$\mathrm{Prob}_{\Delta}\left\{J(\Delta) \leq \hat{J}_{max}\right\} \geq 1 - \varepsilon \tag{18}$$

That is,

$$\mathrm{Prob}_{\Delta(1,\ldots,N)}\left\{\mathrm{Prob}_{\Delta}\left\{J(\Delta) \leq \hat{J}_{max}\right\} \geq 1 - \varepsilon\right\} > 1 - \delta \tag{19}$$

where J is the *performance function* and $\hat{J}_{max}$, the *empirical maximun*. For further details, see [25].

The theorem says that the empirical maximum is an estimate of the true value within an a priori specified accuracy ε with confidence δ if the sample size N satisfies Eq. (17). The algorithm may not produce an approximately correct answer, but the probability of this event is no greater than δ. It is worthy to emphasize that, in Theorem 2, the sample size N is finite and moreover is not dependent on the size of the uncertain set **B**, the structured set of uncertainty matrices, and the probability density function $f_{\Delta}(\Delta)$, but only on ε and δ. In the next Section, Eq. (17) is used to estimate the number of simulations.

4. Results and discussion

In this Section, the effectiveness of the proposed control law is verified through simulation examples. Five tests are implemented: in the first one, the optimal controller parameters are synthesized through a Monte Carlo Experiment; secondly, the controller performance under normal operating conditions and in different initial conditions are shown; in third place, a perturbation in the control action is included; then, the system is disturbed with a step change; and finally, a Monte Carlo Randomized Algorithm is applied in order to verify the performance of the proposed controller under parameter uncertainty.

4.1. Monte Carlo experiment

In this subsection, the Monte Carlo method is applied to select an optimal set of controller parameters. The bioreactor behavior directly depends on the adjustment parameters K_P, K_{PT}, K_X and K_S. The method is developed as follows: i) M random values of each parameter are selected; ii) a cost function that evaluates the controller performance is set; and iii) the optimal parameters are determined by means of an optimization procedure. A widely used method consists of defining the cost corresponding to the tracking error, which is calculated as the sum of the squared differences between the reference and real profiles of all state variables [27].

The cost function is equal to the cumulative squared error, which can numerically be approximated as follows:

$$C = T_0 \sum_{j=1}^{\#\mathrm{ref}} \sum_{i=1}^{4} \frac{\left(\Lambda_{ref(i)} - \Lambda_{(i)}\right)^2}{2} \tag{20}$$

where Λ represents a given state variable, Λ_{ref} is the reference profile for Λ, *#ref* the number of points of the reference profile and T_0 is the sample time (in all over this paper it is adopted as 36 s). In the case of the culture glucose concentration, the following difference between the profiles is assumed:

$$\left(S_{ez}^{(n)} - S^{(n)}\right)^2 \tag{21}$$

In the bioreactor, this function has four terms. Although the optimum is not guaranteed, the Monte Carlo Experiment provides an approximate solution based on a large number of trials (M). In this paper, it is adopted a confidence value (δ) of 0.01, and an accuracy of 0.007 (ε). Then, from Eq. (17), it is necessary to make 1000 simulations. Hence, 1000 values of each parameter ranging from 0 to 1 were simulated. This parameter range ensures convergence to zero tracking error [28].

In Fig. 2 the values of the cost function are represented for each simulation. The lowest cost is obtained in simulation number 800, where the parameter values were:

$$K_P = 0.23;\ K_{P_T} = 0.14; K_X = 0.52; K_S = 0.23.$$

This algorithm to tune the controller parameter is one of the contributions of the present paper. It is noteworthy that it is a very effective technique for controller tuning because its simplicity and its capability of being implemented online.

4.2. Normal operation conditions

The controller performance is tested when the process is operated under normal conditions (Situation A). The initial conditions are detailed in Table 1. The optimal controller parameters obtained in the previous section are used. Fig. 3 shows the tracking of the reference trajectories without undesirable oscillations. To better reveal the performance of the control law, the tracking error (see Eq. (16)), is shown in Fig. 4.

A second experience (situation B) was carried out by modifying the initial conditions of the bioreactor, which were set 10% below the values corresponding to Situation A. Fig. 5 shows the error in the profile of the culture glucose concentration ("sacrificed variable"). This error is required to follow the reference profiles of the remaining state variables, as is explained in Section 3.2.

As it can be seen in Fig. 5, the initial substrate concentration value is quite different from the normal operation; and the glucose

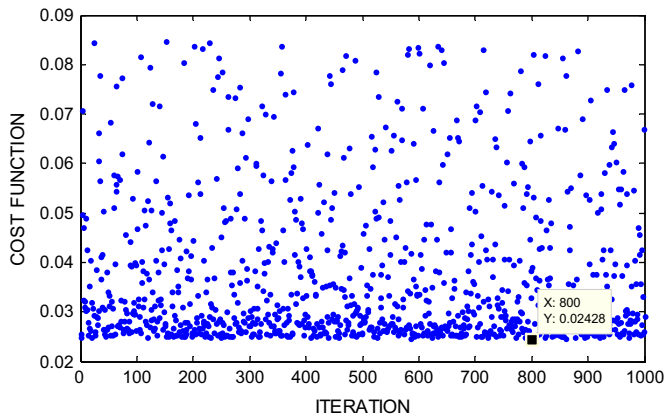

Fig. 2. Cost function for 1000 sets of parameters. The lower cost is highlighted.

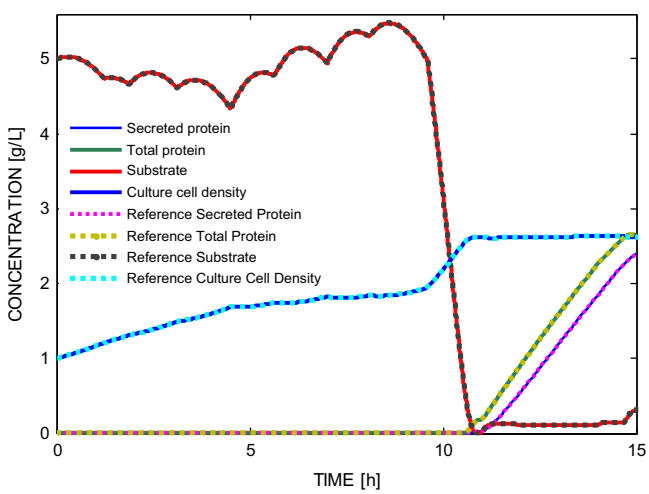

Fig. 3. Situation A: Reference and reached profiles.

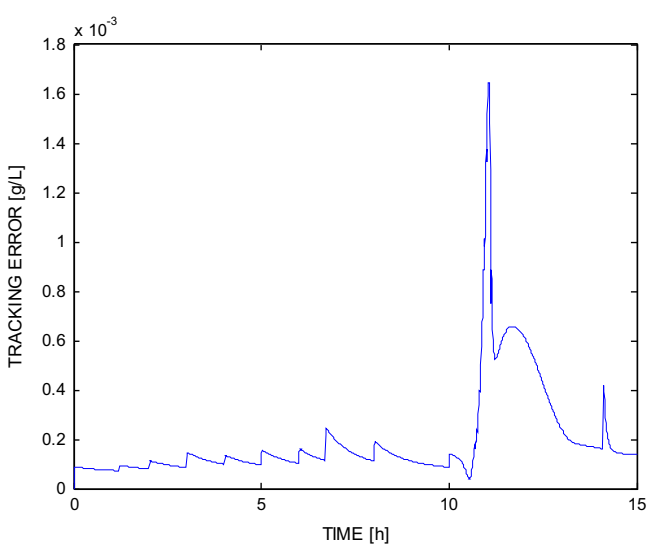

Fig. 4. Situation A: Tracking errors (Eq. (6)).

concentration does not track the reference profile at the beginning of the process. However, after the second hour of operation, the real profile tends to the reference one. Fig. 6 displays the tracking

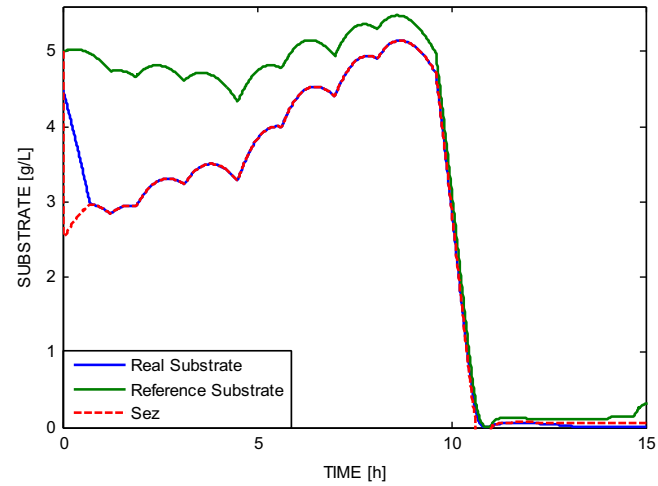

Fig. 5. Culture glucose concentration: reference and real profiles and the sacrificed variable, S_{ez}.

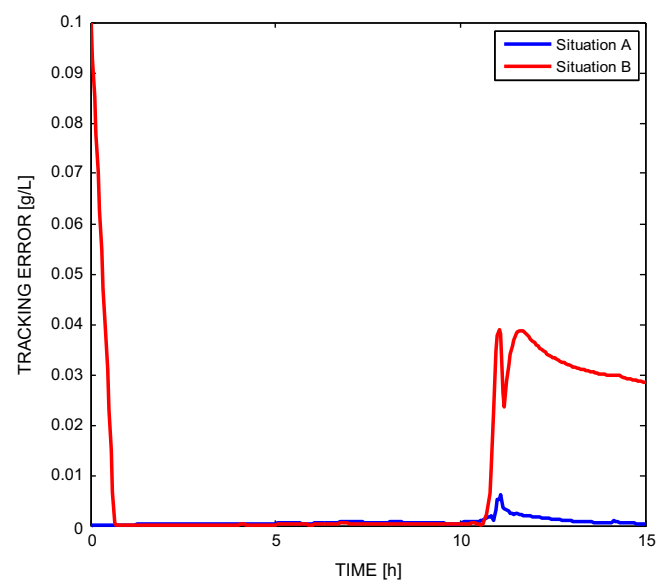

Fig. 6. Tracking errors of both situations, A and B, represented by Eq. (16).

error of both situations A and B. The tracking error remains acceptably bounded in both cases.

4.3. Perturbation in the control action

So as to demonstrate the controller performance, a random perturbation in the control action is included. In this work, a random perturbation using MATLAB® is employed. The control action is affected with a 20% of its value. The function used was "*random (norm, 0, 0.2)*", which is a random white noise that results in non-zero-mean Gaussian disturbances [29]. The control action is calculated through Eq. (22) in each sampling time.

$$u_{perturbed} = u_{unperturbed} \times (\text{random ('norm', 0, 0.2)} + 1) \tag{22}$$

The following figures illustrate the previously described results. The control action with white noise is shown in Fig. 7, and the controller performance is evaluated through the tracking error (Fig. 8).

As shown in Fig. 8, when a Gaussian disturbance is introduced, the tracking error increases. Nevertheless, the tracking error is still

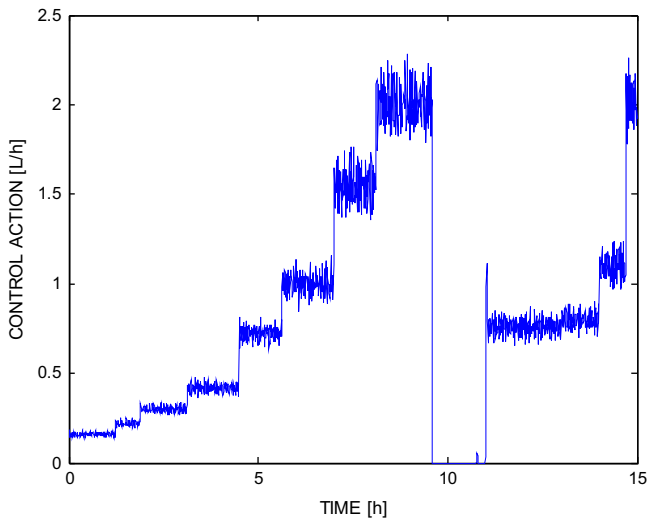

Fig. 7. Control action with non-zero-mean Gaussian disturbances.

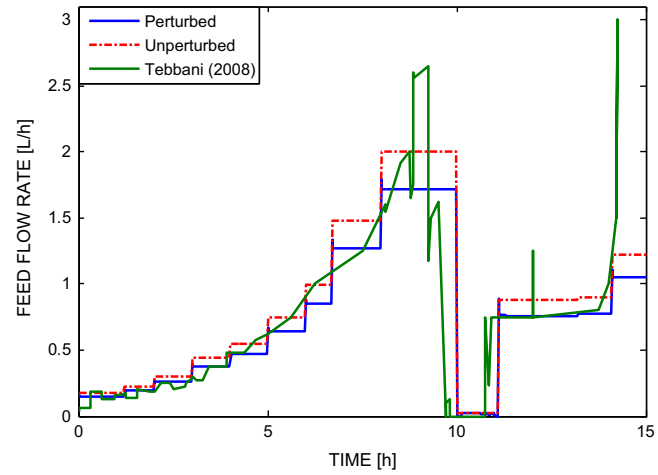

Fig. 9. Comparison of the control actions provided by each controller: perturbed with a step, unperturbed and the controller of Tebbani et al. [19].

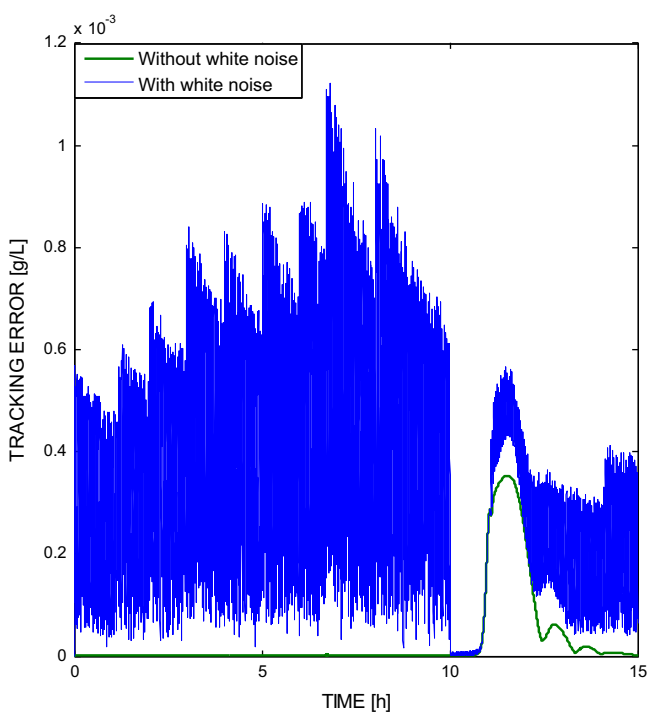

Fig. 8. Tracking error of the controller with white noise compared with the controller without the white noise.

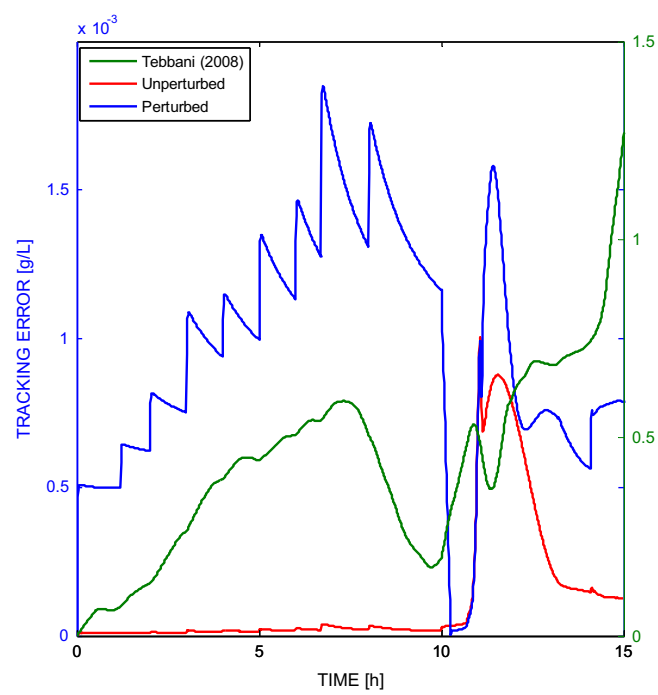

Fig. 10. Comparison of tracking errors (left ordinate axis: perturbed and unperturbed cases; right axis: Tebbani et al. [19]).

low and bounded compared with those obtained by other authors in the literature, as will be seen in the next section.

4.4. Step disturbance in the feed flow rate

Another proof for checking the controller performance consists in introducing a step-change perturbation. As proposed by [19], a feed flow rate 16.67% higher than calculated is adopted. Fig. 9 compares the normal operation of the proposed controller (named Unperturbed), the operation under the step disturbance (Perturbed), and the result given by [19].

Fig. 10 shows that the tracking error obtained with the proposed controller is lower than those obtained by [19]. In addition, if the proposal of [19] is compared with the controller of Section 4.2 (situation B), when the controller has different nominal initial conditions, it is observed that the proposed controller has better performance, although it was operated from other initial conditions.

Compared to [19], the methodology proposed here does not need to perform any linearization. Furthermore, the implementation of the algorithm in digital systems is natural due to the use of discrete equations. However, the principal advantage of our proposal is that it has improved the results of [19], since the tracking errors have been highly decreased.

4.5. Performance of the controller under parameter uncertainty

In this subsection, a Monte Carlo simulation is performed to demonstrate the effectiveness of the controller from the statistical viewpoint [30–32], under parameter uncertainty. The parameters

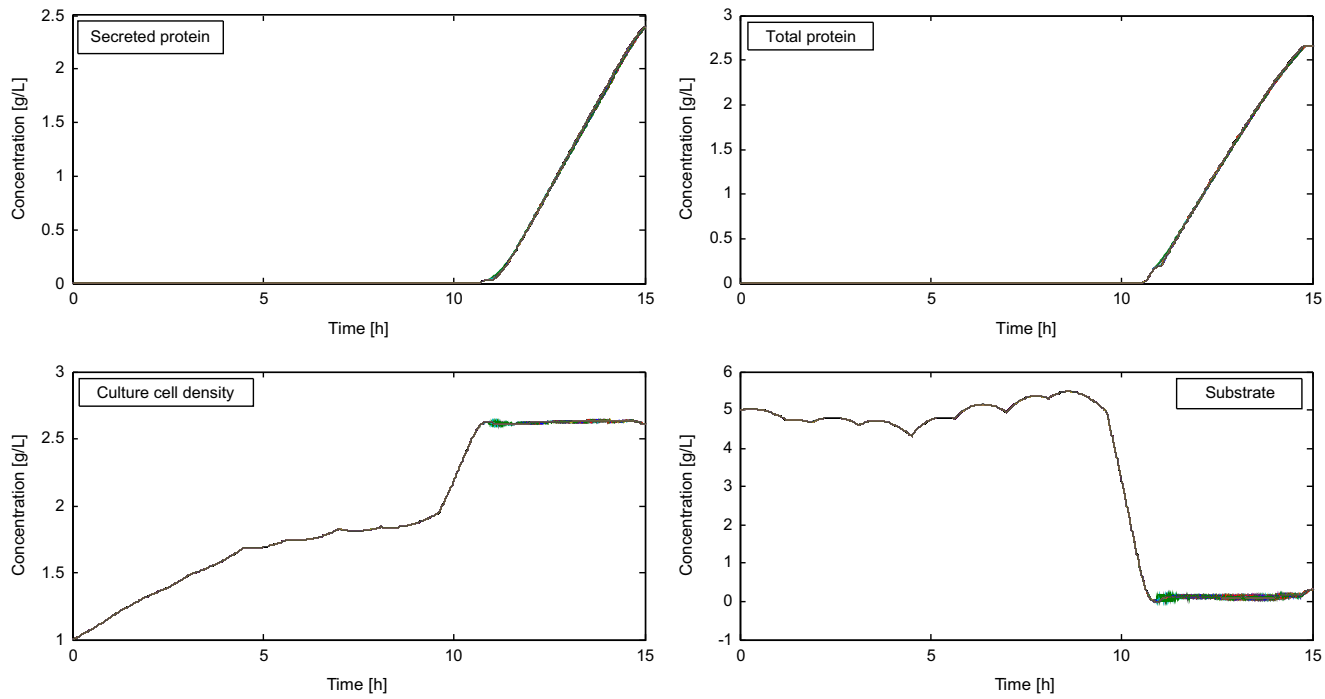

Fig. 11. State variables for the 1000 simulations of the Monte Carlo Experiment.

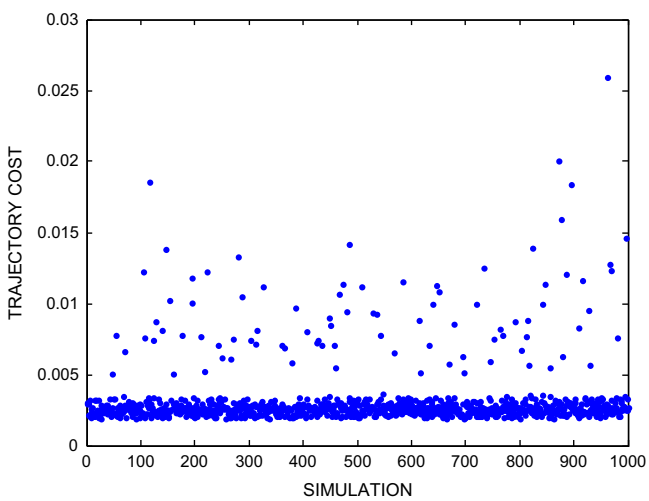

Fig. 12. Cost function for 1000 sets of the system parameters, $Y_{S/X}$ and S_F, of the Monte Carlo Experiment.

of the bioreactor are: the glucose concentration of the feed stream (S_F) and the yield of glucose per cell mass ($Y_{S/X}$). In order to prove the robustness of the controller designed, those parameters are varied N times in a range of $\pm 15\%$ of its nominal values.

As in Section 4.1, it is adopted a confidence value (δ) of 0.01, and an accuracy of 0.007 (ε). Then, from Eq. (17), it is necessary to make 1000 simulations.

Fig. 11 shows the state variables for the 1000 simulations. This figure shows clearly that the performance of the controller is good, because all state variables tend to the reference profiles without undesirable oscillations, although there are a 15% of uncertainly in the bioreactor parameters.

The performance function is defined as

$$J = T_0 \sum_{j=1}^{\#ref} \sum_{i=1}^{4} \frac{(\Lambda_{ref(i)} - \Lambda_{(i)})^2}{2} \tag{23}$$

where Λ represents a given state variable, Λ_{ref} is the reference profile of Λ, $\#ref$ the number of points of the reference profile and T_0 is the sample time. In the case of the culture glucose concentration, the difference between profiles is assumed as in Eq. (18).

Fig. 12 depicts the performance function for 1000 sets of the system parameters, $Y_{S/X}$ and S_F. It is shown that the tracking errors, reflected in the performance function J, remain bounded. Then, it follows that if 1000 simulations with different values randomly chosen of S_F and $Y_{S/X}$ are carried out, and the tracking errors remains bounded, there is a 99% probability that the performance of the controller will be good whatever the parameter values in a range of $\pm 15\%$.

5. Conclusions

A new control law for tracking the optimal concentration profiles in a fed-batch bioreactor has been presented. The proposed method allowed the control of a nonlinear system. The conditions for synthesizing the control actions able to minimize tracking errors were obtained by analyzing a system of linear equations.

A contribution of this work involves the application of a Monte Carlo method that successfully found the controller parameters. The different tests carried out in this work prove the good performance of the proposed controller design procedure, even when compared with a controller of the literature. In fact, the system behavior was tested under the presence of disturbances, reaching better performance than those obtained by [19]. Monte Carlo simulation results are provided to demonstrate the effectiveness of the controller in the presence of parameter uncertainty. Besides, the adopted control technique does not use the linearized model, consequently its performance is independent of the operating point. In general, such methodology can be applied to many nonlinear systems, making it a promising technique for its application to several processes of the biochemical industry. Moreover, the present methodology has the advantage of using

discrete equations, and therefore a direct implementation in most computer-driven systems is feasible.

Acknowledgments

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Appendix A

Proof of Theorem 1. If the system behavior is ruled by (7) and the controller is designed by (15), then, $e^{(n)} \to 0$, $n \to \infty$, when profile tracking problems are considered. Eq. (14) is rewritten in a compact form as (A.1)

$$\begin{bmatrix} A_1 \\ A_2 \\ A_3 \\ A_4 \end{bmatrix} u^{(n)} = \begin{bmatrix} b_1 \\ b_2 \\ b_3 \\ b_4 \end{bmatrix} \tag{A.1}$$

Then, solving (A.1) by means of least squares

$$u^{(n)} = \frac{A_1 b_1 + A_2 b_2 + A_3 b_3 + A_4 b_4}{A_1^2 + A_2^2 + A_3^2 + A_4^2} \tag{A.2}$$

From (A.1):

$$\begin{aligned} \frac{A_1}{A_4} &= \frac{b_1}{b_4} \Rightarrow b_4 = \frac{A_4}{A_1} b_1 \\ \frac{A_2}{A_4} &= \frac{b_2}{b_4} \Rightarrow b_2 = \frac{b_1}{A_1} A_2 \\ \frac{A_3}{A_4} &= \frac{b_3}{b_4} \Rightarrow b_3 = \frac{b_1}{A_1} A_3 \end{aligned} \tag{A.3}$$

Replacing (A.3) in (A.2)

$$u^{(n)} = \frac{b_1}{A_1} = \frac{\chi\left(S_{ez}^{(n)}\right)\left(P_T^{(n)} - P^{(n)}\right) - \left(P_{ref}^{(n+1)} - K_P\left(P_{ref}^{(n)} - P^{(n)}\right) - P^{(n)}/T_0\right)}{P^{(n)}/V^{(n)}} \tag{A.4}$$

Replacing (A.4) in (7)

$$P^{(n+1)} = P_{ref}^{(n+1)} - K_P\left(P_{ref}^{(n)} - P^{(n)}\right) + T_0\left(P_T^{(n)} - P^{(n)}\right)\left[\chi^{(n)} - \chi\left(S_{ez}^{(n)}\right)\right] \tag{A.5}$$

Then, the tracking error is

$$e_{P^{(n+1)}} = P_{ref}^{(n+1)} - P^{(n+1)} \tag{A.6}$$

where (A.5) is replaced

$$e_{P^{(n+1)}} = K_P e_{P^{(n)}} - T_0\left(P_T^{(n)} - P^{(n)}\right)\left[\chi^{(n)} - \chi\left(S_{ez}^{(n)}\right)\right] \tag{A.7}$$

The Taylor approximation of $\chi^{(n)}$ in the desired value $\chi\left(S_{ez}^{(n)}\right)$ is

$$\chi^{(n)} = \chi\left(S_{ez}^{(n)}\right) + \frac{d\chi}{dS}\Big|_{S = S_{ez}^{(n)} + \lambda\left(S^{(n)} - S_{ez}^{(n)}\right) = S_\lambda}\left(S^{(n)} - S_{ez}^{(n)}\right)$$

$$0 < \lambda < 1 \tag{A.8}$$

Replacing (A.8) in (A.7)

$$e_{P^{(n+1)}} = K_P e_{P^{(n)}} - T_0\left(P_T^{(n)} - P^{(n)}\right)\left[\chi\left(S_{ez}^{(n)}\right) + \frac{d\chi}{dS}\Big|_{S = S_\lambda}\left(S^{(n)} - S_{ez}^{(n)}\right) - \chi\left(S_{ez}^{(n)}\right)\right]$$

$$e_{P^{(n+1)}} = K_P e_{P^{(n)}} + \underbrace{T_0\left(P_T^{(n)} - P^{(n)}\right)\frac{d\chi}{dS}\Big|_{S = S_\lambda}}_{\text{Boundednonlinearity}} \underbrace{\left(S^{(n)} - S_{ez}^{(n)}\right)}_{e_{S^{(n)}}} \tag{A.9}$$

Analogously, for P_T, from (A.1):

$$\begin{aligned} \frac{A_2}{A_4} &= \frac{b_2}{b_4} \Rightarrow b_4 = \frac{A_4}{A_2} b_2 \\ \frac{A_1}{A_4} &= \frac{b_1}{b_4} \Rightarrow b_1 = \frac{b_2}{A_2} A_1 \\ \frac{A_3}{A_4} &= \frac{b_3}{b_4} \Rightarrow b_3 = \frac{b_2}{A_2} A_3 \end{aligned} \tag{A.10}$$

Replacing (A.10) in (A.2)

$$\begin{aligned} u^{(n)} &= \frac{A_1^2(b_2/A_2) + A_2 b_2 + A_3^2(b_2/A_2) + A_4^2(b_2/A_2)}{A_1^2 + A_2^2 + A_3^2 + A_4^2} = \frac{b_2}{A_2} \\ &= \frac{\psi\left(S_{ez}^{(n)}\right)X^{(n)} - \left(P_{T_{ref}}^{(n+1)} - K_{P_T}\left(P_{T_{ref}}^{(n)} - P_T^{(n)}\right) - P_T^{(n)}/T_0\right)}{P_T^{(n)}/V^{(n)}} \end{aligned} \tag{A.11}$$

Replacing (A.11) in (7)

$$\begin{aligned} P_T^{(n+1)} &= P_T^{(n)} + T_0\left[\psi^{(n)}X^{(n)} - \psi\left(S_{ez}^{(n)}\right)X^{(n)} + \left(P_{T_{ref}}^{(n+1)} - K_{P_T}\left(P_{T_{ref}}^{(n)} - P_T^{(n)}\right)\right.\right. \\ &\quad \left.\left. - P_T^{(n)}/T_0\right)\right] \\ P_T^{(n+1)} &= P_{T_{ref}}^{(n+1)} - K_{P_T}\left(P_{T_{ref}}^{(n)} - P_T^{(n)}\right) + T_0\left[\psi^{(n)} - \psi\left(S_{ez}^{(n)}\right)\right] \end{aligned} \tag{A.12}$$

Then, calculating the tracking error as

$$e_{P_T^{(n+1)}} = P_{T_{ref}}^{(n+1)} - P_T^{(n+1)} \tag{A.13}$$

where (A.12) is replaced

$$e_{P_T^{(n+1)}} = K_{P_T} e_{P_T^{(n)}} - T_0 X^{(n)}\left[\psi^{(n)} - \psi\left(S_{ez}^{(n)}\right)\right] \tag{A.14}$$

The Taylor approximation of $\psi^{(n)}$ in the desired value $\psi\left(S_{ez}^{(n)}\right)$ is

$$\psi^{(n)} = \psi\left(S_{ez}^{(n)}\right) + \underbrace{\frac{d\psi}{dS}\Big|_{S = S_{ez}^{(n)} + \xi\left(S^{(n)} - S_{ez}^{(n)}\right) = S_\xi}}_{\text{derivativeatamidpoint}}\left(S^{(n)} - S_{ez}^{(n)}\right)$$

$$0 < \xi < 1 \tag{A.15}$$

Replacing (A.15) in (A.14)

$$e_{P_T^{(n+1)}} = K_{P_T} e_{P_T^{(n)}} - T_0 X^{(n)}\left[\psi\left(S_{ez}^{(n)}\right) + \frac{d\psi}{dS}\Big|_{S = S_\xi}\left(S^{(n)} - S_{ez}^{(n)}\right) - \psi\left(S_{ez}^{(n)}\right)\right]$$

$$e_{P_T^{(n+1)}} = K_{P_T} e_{P_T^{(n)}} + \underbrace{T_0 X^{(n)}\frac{d\psi}{dS}\Big|_{S = S_\xi}}_{\text{Boundednonlinearity}} \underbrace{\left(S^{(n)} - S_{ez}^{(n)}\right)}_{e_{S^{(n)}}} \tag{A.16}$$

Analogously, for X, from (A.1):

$$\begin{aligned} \frac{A_3}{A_4} &= \frac{b_3}{b_4} \Rightarrow b_4 = \frac{A_4}{A_3} b_3 \\ \frac{A_1}{A_4} &= \frac{b_1}{b_4} \Rightarrow b_1 = \frac{b_3}{A_3} A_1 \end{aligned}$$

$$\frac{A_2}{A_4}=\frac{b_2}{b_4}\Rightarrow b_2=\frac{b_3}{A_3}A_4 \tag{A.17}$$

Replacing (A.17) in (A.2)

$$u^{(n)}=\frac{A_1^2(b_3/A_3)+A_2^2(b_3/A_3)+A_3b_3+A_4^2(b_3/A_3)}{A_1^2+A_2^2+A_3^2+A_4^2}=\frac{b_3}{A_3}$$
$$=\frac{\mu\left(S_{ez}^{(n)}\right)X^{(n)}-\left(X_{ref}^{(n+1)}-K_X\left(X_{ref}^{(n)}-X^{(n)}\right)-X^{(n)}/T_0\right)}{X^{(n)}/V^{(n)}} \tag{A.18}$$

Replacing (A.18) in (7)

$$X^{(n+1)}=X^{(n)}+T_0\left[\mu^{(n)}X^{(n)}-\mu\left(S_{ez}^{(n)}\right)X^{(n)}+\left(X_{ref}^{(n+1)}-K_X\left(X_{ref}^{(n)}-X^{(n)}\right)-X^{(n)}/T_0\right)\right]$$
$$X^{(n+1)}=X_{ref}^{(n+1)}-K_X\left(X_{ref}^{(n)}-X^{(n)}\right)+T_0\left[\mu^{(n)}-\mu\left(S_{ez}^{(n)}\right)\right] \tag{A.19}$$

Then, calculating the tracking error as

$$e_{X^{(n+1)}}=X_{ref}^{(n+1)}-X^{(n+1)} \tag{A.20}$$

where (A.19) is replaced

$$e_{X^{(n+1)}}=K_Xe_{e_{X^{(n)}}}-T_0X^{(n)}\left[\mu^{(n)}-\mu\left(S_{ez}^{(n)}\right)\right] \tag{A.21}$$

The Taylor approximation of $\mu^{(n)}$ in the desired value $\mu\left(S_{ez}^{(n)}\right)$ is

$$\mu^{(n)}=\mu\left(S_{ez}^{(n)}\right)+\underbrace{\left.\frac{d\mu}{dS}\right|_{S=S_{ez}^{(n)}+\theta\left(S^{(n)}-S_{ez}^{(n)}\right)=S_\theta}}_{\text{derivativeatamidpoint}}\left(S^{(n)}-S_{ez}^{(n)}\right)$$
$$0<\theta<1 \tag{A.22}$$

Replacing (A.22) in (A.21)

$$e_{X^{(n+1)}}=K_Xe_{X^{(n)}}-T_0X^{(n)}\left[\mu\left(S_{ez}^{(n)}\right)+\left.\frac{d\mu}{dS}\right|_{S=S_\theta}\left(S^{(n)}-S_{ez}^{(n)}\right)-\mu\left(S_{ez}^{(n)}\right)\right]$$
$$e_{X^{(n+1)}}=K_Xe_{X^{(n)}}+\underbrace{T_0X^{(n)}\left.\frac{d\mu}{dS}\right|_{S=S_\theta}}_{\text{Boundednonlinearity}}\underbrace{\left(S^{(n)}-S_{ez}^{(n)}\right)}_{e_{S^{(n)}}} \tag{A.23}$$

In the same way, for S, from (A.1):

$$\frac{A_1}{A_4}=\frac{b_1}{b_4}\Rightarrow b_1=\frac{b_4}{A_4}A_1$$
$$\frac{A_2}{A_4}=\frac{b_2}{b_4}\Rightarrow b_2=\frac{b_4}{A_4}A_2$$
$$\frac{A_3}{A_4}=\frac{b_3}{b_4}\Rightarrow b_3=\frac{b_4}{A_4}A_3 \tag{A.24}$$

Replacing (A.24) in (A.2)

$$u^{(n)}=\frac{A_1^2(b_4/A_4)+A_2^2(b_4/A_4)+A_3^2(b_4/A_4)+A_4b_4}{A_1^2+A_2^2+A_3^2+A_4^2}=\frac{b_4}{A_4}$$
$$=\frac{7.3\mu^{(n)}X^{(n)}+\left(S_{ez}^{(n+1)}-K_S\left(S_{ez}^{(n)}-S^{(n)}\right)-S^{(n)}/T_0\right)}{\left(20-S^{(n)}\right)/V^{(n)}} \tag{A.25}$$

Replacing (A.25) in (7)

$$S^{(n+1)}=S^{(n)}+T_0\left[-7.3\mu^{(n)}X^{(n)}+7.3\mu^{(n)}X^{(n)}+\frac{S_{ez}^{(n+1)}-K_S(S_{ez}^{(n)}-S^{(n)})-S^{(n)}}{T_0}\right]$$

$$S^{(n+1)}=S_{ez}^{(n+1)}-K_S(S_{ez}^{(n)}-S^{(n)}) \tag{A.26}$$

Then, calculating the tracking error as

$$e_{S^{(n+1)}}=S_{ref}^{(n+1)}-S^{(n+1)} \tag{A.27}$$

where (A.26) is replaced, leading to

$$e_{S^{(n+1)}}=S_{ez}^{(n+1)}-S_{ez}^{(n+1)}+K_S\left(S_{ez}^{(n)}-S^{(n)}\right)$$
$$e_{S^{(n+1)}}=K_Se_{S^{(n)}} \tag{A.28}$$

Finally, joining (A.9),(A.16),(A.23) and (A.28):

$$\begin{bmatrix}e_{P^{(n+1)}}\\e_{P_T^{(n+1)}}\\e_{X^{(n+1)}}\\e_{S^{(n+1)}}\end{bmatrix}=\underbrace{\begin{bmatrix}K_P&0&0&0\\0&K_{P_T}&0&0\\0&0&K_X&0\\0&0&0&K_S\end{bmatrix}\begin{bmatrix}e_{P^{(n)}}\\e_{P_T^{(n)}}\\e_{X^{(n)}}\\e_{S^{(n)}}\end{bmatrix}}_{\text{Linearsystem}}+\underbrace{T_0\begin{bmatrix}\left(P_T^{(n)}-P^{(n)}\right)\left.\frac{d\chi}{dS}\right|_{S=S_\lambda}\\X^{(n)}\left.\frac{d\psi}{dS}\right|_{S=S_\xi}\\X^{(n)}\left.\frac{d\mu}{dS}\right|_{S=S_\theta}\\0\end{bmatrix}}_{\text{Boundednonlinearitythattendstozero}}e_{S^{(n)}} \tag{A.29}$$

Eq. (A.29) represents a linear system and a bounded nonlinearity that tends to zero when $0<K_\Lambda<1$ and $n\to\infty$, thus proving that the tracking errors tend to zero [28]. ∎

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