jwp00 | ACSJCA | JCA11.1.4300/W Library-x64 | research.3f (R4.0.i9 HF05:4883 | 2.1) 2018/07/18 12:44:00 | PROD-WS-118 | rq_86036 | 7/30/2018 09:34:24 | 11 | JCA-DEFAULT

I&EC research
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pubs.acs.org/IECR

Tracking Control of Optimal Profiles in a Nonlinear Fed-Batch Bioprocess under Parametric Uncertainty and Process Disturbances

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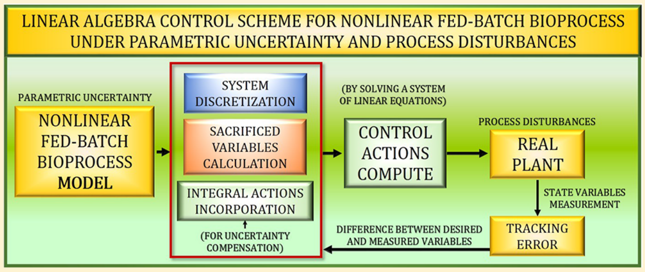
ABSTRACT: The problem of optimal profiles tracking control under uncertainties for a nonlinear fed-batch bioprocess is addressed in this paper. Based on the results reported by Pantano et al. [*Ind. Eng. Chem. Res.* **2017**, *56*, 6043], this work aims to improve the control system response against parametric uncertainty and process disturbances. The methodology is simple and easy to implement, but with excellent results. The design parameters are optimized by a randomized Monte Carlo algorithm. Besides, demonstration of the tracking error convergence to zero when the system is subjected to uncertainties is included in the article. The control system performance is tested through simulations, showing the improvement achieved.



1. INTRODUCTION

Bioreactor performance is determined not only by productivity but also by process quality, which is mainly affected by the disturbances in the process variables. Therefore, finding a way to control these distortions is the main task to guarantee quality.[2]

During the past decade, many researchers further investigated several control techniques applied to different bioprocesses,[3−7] especially after the implementation of "quality by design" for biopharmaceuticals by the U.S. Food and Drug Administration (FDA).[8] Particularly in fed-batch bioreactors many strategies were studied to improve the efficiency and reproducibility of bioprocesses.[9−14] However, the problem that arises is the gap between scientific research and the industry requirements. For example, usually research works on optimization and control strategies rarely consider model uncertainties, which are unavoidable in industrial processes;[15−17] this could lead to a poor real-life representation and, consequently, to a bad performance with severe risks.[18−20]

Unfortunately, the high degree of nonlinearity of the bioprocesses and the lack of high-quality experimental data make modeling the system a challenge. Therefore, the resulting model presents a high degree of uncertainty. As a consequence, there are several mathematical models for the same biological process, including different structures and parameters but concordant with the available information on said processes.

Uncertainties are one of the main obstacles in the development of advanced controllers for high-accuracy trajectory tracking control.[21] Not surprisingly, therefore, parametric uncertainty has remained high on the agenda of unsolved problems in control for the past three decades.[22] The main types of uncertainties that can be considered in a bioprocess are the uncertain values of parameters (most frequent), time-varying model parameters, uncertain nonlinearities, and unmodeled dynamics, among others. Besides that, there are external disturbances that are not modeled and affect the process variables, too.[23−25]

Many existing works focus on the model uncertainty quantification due to the lack of knowledge of model parameters and the underlying physics by combining the results from both computer simulations and physical experiments.[26−31] Generally, one of the most-used strategies for the model parameter identification and/or estimation involves an off-line optimization using a nominal model of the process.[32−40] The main disadvantage of this methodology is that the variability of microorganisms decreases the possibility of batch-to-batch repeatability.

Other techniques that are used for model parameter estimation, which try to improve the results obtained with nominal optimization methodologies, are those called "run-to-run" optimization, in which the information is extracted from previous runs and used to optimize the operation of subsequent ones.[41−48] However, the value of this improvement should be critically evaluated regarding the low-variability objective that is so important in the pharmaceutical and polymer industries.[49]

In the past two decades, several research projects have ventured into on-line optimization of the model parameters.[50−54] This kind of optimization is difficult to perform since the available models might only be locally valid and thus inappropriate for predicting final concentrations.[49]

On the other hand, several feedback control strategies are studied to deal with bioprocess uncertainties. Adaptive control

Received: April 24, 2018
Revised: July 16, 2018
Accepted: July 19, 2018
Published: July 19, 2018

DOI: 10.1021/acs.iecr.8b01791
Ind. Eng. Chem. Res. XXXX, XXX, XXX−XXX

techniques, for example, are an important option to control bioreactors under uncertainties.[29,55−57] Also, fuzzy control systems have been successfully applied to several bioreactors.[58,59] Alternative methodologies for controlling bioprocesses under model uncertainties are trajectory-based control,[60] model predictive control,[61] and hybrid control.[62] However, the application of these techniques in a real plant is quite difficult because of its complex design and implementation.

For the particular case of recombinant protein production with a double feed stream (Lee−Ramirez bioreactor[63]), Pantano et al.[1] developed a control strategy for tracking control of predefined optimal profiles. In that work, the control design includes a neural network state estimation for unmeasurable variables, enabling the closed loop implementation. The methodology is characterized by its simplicity, versatility, and accuracy. Advanced mathematical knowledge is not required for design; only basic understanding of linear algebra is needed. The main technique advantage is that control actions computed are obtained solving linear system equations, ensuring the convergence to zero of tracking errors. Besides, that control technique has been applied successfully in several systems,[5,64−69] and therefore has a high potential for applicability in all bioprocess environments.

The objective of this work is to design an improved control strategy to achieve the tracking control of optimal protein concentration, cell density, and volume profiles obtained in ref 70, with a minimum tracking error, when the system is subjected to parametric uncertainty and perturbations in the process. To achieve this goal, a term of uncertainty is incorporated into the original controller design, which is used to represent a wide range of model mismatches as well as perturbations in the process. Then, some integral terms of tracking error are incorporated into the controller design to compensate the uncertainty. In a similar way to the original methodology, the necessary and sufficient conditions are analyzed so that the system has an exact solution, but now taking into account the new terms. Finally, the control actions are found solving linear system equations.

The main contribution of this work is the extension of the proposed methodology in Pantano et al.,[1] to provide a positive answer to the challenging problem of tracking control in multivariable nonlinear systems with additive uncertainty and process disturbances. In this way, a more realistic problem can be solved taking into account that a complete and exact knowledge of the process model is never possible and, usually, the external perturbations in the real process dynamics are unavoidable. It is important to emphasize that this approach is achieved without significantly increasing the controller design complexity. Also, another important contribution is the demonstration of convergence to zero of the tracking error under parametric uncertainties and process disturbances.

The paper is organized as follows. First, a review of the original controller design is presented in section 2. Then, the extended controller methodology for contemplation of uncertainties developed in section 3. The results and discussion of the simulation tests, which include the adjustment of the parameters of the controller and the control system under parametric uncertainty and perturbations in the control actions, are shown in section 4. Finally, section 5 outlines the main conclusions of this work.

2. ORIGINAL CONTROLLER DESIGN

The controller methodology proposed in ref 1 is mainly based on approximating the mathematical model (1) by employing Euler method, which, despite its simplicity, presents good results. The aim of this controller design is to find the control actions values that follow desired paths with minimal tracking error.

The case study proposed in ref 1 for control is the Lee−Ramirez fed-batch bioreactor. The mathematical model is taken from Tholudur and Ramirez.[71]

The fed-batch bioreactor is described by the following model (1).

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

where

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

$$R = \left(\frac{f_{\max}^0 x_3}{K_{CN} + x_3\left(1 + \frac{x_3}{Ks}\right)}\right)\left(\frac{f_I^0 + x_5}{K_I + x_5}\right) \tag{3}$$

$$K_1 = K_2 = \frac{k_{11}x_5}{K_{IX} + x_5} \tag{4}$$

A more detailed description of the process can be found in ref 1. The nominal model parameter sets were validated and presented by Lee and Ramirez.[72] The glucose feeding rate, u_1 (L/h), and inducer feeding rate, u_2 (L/h), are the two available sources as control actions for the fed-batch bioreactor. The reactor volume x_1, cell density x_2, and foreign protein concentration x_4 are the variables whose optimal profiles are proposed to follow.

Controller Methodology. A differential equation system can be approximated according to the numerical integration rule of Euler as follow:

$$\dot{x}_i = \frac{x_{i,n+1} - x_{i,n}}{T_s} \tag{5}$$

where x_i is the i state variable in n and $n + 1$ time instants, and T_s is the sampling time.

Although there exist general numerical computation algorithms in the literature for model approximation,[47,73,74] the Euler rule is a proper choice for this case since the approximation is only used to find the best manner to go from

DOI: 10.1021/acs.iecr.8b01791
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the current state to the following one, and not to duplicate the entire system evolution.

Taking into account eq 5, the mathematical model that represents the bioprocess can be rewritten, as follows:

$$\overbrace{\begin{pmatrix} x_{1,n+1} \\ x_{2,n+1} \\ x_{3,n+1} \\ x_{4,n+1} \\ x_{5,n+1} \end{pmatrix}}^{\mathbf{z}_{n+1}} = \overbrace{\begin{pmatrix} x_{1,n} \\ x_{2,n} \\ x_{3,n} \\ x_{4,n} \\ x_{5,n} \end{pmatrix}}^{\mathbf{z}_{n}} + \dots$$

$$+ \left[\overbrace{\begin{pmatrix} 0 \\ x_{2,n}\mu \\ -\dfrac{x_{2,n}\mu}{Y} \\ x_{2,n}R \\ 0 \end{pmatrix}}^{\xi_n(\mathbf{z}_n)} + \overbrace{\begin{pmatrix} 1 & 1 \\ -\dfrac{x_{2,n}}{x_{1,n}} & -\dfrac{x_{2,n}}{x_{1,n}} \\ \dfrac{N - x_{3,n}}{x_{1,n}} & -\dfrac{x_{3,n}}{x_{1,n}} \\ -\dfrac{x_{4,n}}{x_{1,n}} & -\dfrac{x_{4,n}}{x_{1,n}} \\ -\dfrac{x_{5,n}}{x_{1,n}} & \dfrac{I - x_{5,n}}{x_{1,n}} \end{pmatrix}}^{\beta_n(\mathbf{z}_n,\, \mathbf{u}_n)} \overbrace{\begin{pmatrix} u_{1,n} \\ u_{2,n} \end{pmatrix}}^{\mathbf{u}_n} \right] T_s \quad (6)$$

Denote by $\mathbf{z}_n$ and $\mathbf{z}_{n+1}$ the state vectors at the current time and at the next one, respectively. $\xi_n(\mathbf{z}_n)$ and $\beta_n(\mathbf{z}_n, \mathbf{u}_n)$ are the input matrices and $\mathbf{u}_n$ is the control actions vector.

Then, in a generic form, the system can be expressed as follows:

$$\mathbf{z}_{n+1} = \mathbf{z}_n + [\xi(\mathbf{z}_n) + \beta(\mathbf{z}_n, \mathbf{u}_n)\mathbf{u}_n]T_s \quad (7)$$

Now, assuming a proportional approaching to the error:

$$\overbrace{\mathbf{z}_{\text{ref},n+1} - \mathbf{z}_{n+1}}^{\mathbf{e}_{n+1}} = K\,\overbrace{(\mathbf{z}_{\text{ref},n} - \mathbf{z}_n)}^{\mathbf{e}_n} \quad (8)$$

with

$$\overbrace{\begin{pmatrix} x_{1,\text{ref},n+1} \\ x_{2,\text{ref},n+1} \\ x_{3,\text{ref},n+1} \\ x_{4,\text{ref},n+1} \\ x_{5,\text{ref},n+1} \end{pmatrix}}^{\mathbf{z}_{\text{ref},n+1}} - \overbrace{\begin{pmatrix} x_{1,n+1} \\ x_{2,n+1} \\ x_{3,n+1} \\ x_{4,n+1} \\ x_{5,n+1} \end{pmatrix}}^{\mathbf{z}_{n+1}}$$

$$= \overbrace{\begin{pmatrix} k_1 & 0 & 0 & 0 & 0 \\ 0 & k_2 & 0 & 0 & 0 \\ 0 & 0 & k_3 & 0 & 0 \\ 0 & 0 & 0 & k_4 & 0 \\ 0 & 0 & 0 & 0 & k_5 \end{pmatrix}}^{\mathbf{K}} \left[\overbrace{\begin{pmatrix} x_{1,\text{ref},n} \\ x_{2,\text{ref},n} \\ x_{3,\text{ref},n} \\ x_{4,\text{ref},n} \\ x_{5,\text{ref},n} \end{pmatrix}}^{\mathbf{z}_{\text{ref},n}} - \overbrace{\begin{pmatrix} x_{1,n} \\ x_{2,n} \\ x_{3,n} \\ x_{4,n} \\ x_{5,n} \end{pmatrix}}^{\mathbf{z}_n} \right] \quad (9)$$

where $x_{i,\text{ref},n}$ and $x_{i,\text{ref},n+1}$ are the reference values obtained from the optimal operating profiles in the n time and the next sample time, respectively, k_i is the controller parameter for the i variable, and $\mathbf{K}$ is the control parameter matrix; $\mathbf{e}_n$ and $\mathbf{e}_{n+1}$ are the tracking errors (difference between the reference and actual profiles).

Then, the immediately reachable value for the state variables is

$$\mathbf{z}_{n+1} = \mathbf{z}_{\text{ref},n+1} - \mathbf{K}\overbrace{(\mathbf{z}_{\text{ref},n} - \mathbf{z}_n)}^{\mathbf{e}_n} \quad (10)$$

It is important to remark that the optimal profiles to follow were obtained by an open-loop simulation of the bioprocess using the optimal feeding policies achieved by Balsa-Canto et al.[70]

In this way, the actual state variables in the following sampling time ($x_{i,n+1}$) only depend on the reference profiles, the actual state variables at the current time, and the controller parameters (all values are known).

Consequently, substituting (10) in (6) and rearranging the system equations:

$$\overbrace{\begin{pmatrix} 1 & 1 \\ -1 & -1 \\ (N - x_{3,n}) & -x_{3,n} \\ -1 & -1 \\ -1 & (I - x_{5,n}) \end{pmatrix}}^{\mathbf{A}} \overbrace{\begin{pmatrix} u_{1,n} \\ u_{2,n} \end{pmatrix}}^{\mathbf{u}}$$

$$= \overbrace{\begin{pmatrix} \left(\dfrac{x_{1,\text{ref},n+1} - k_1(x_{1,\text{ref},n} - x_{1,n}) - x_{1,n}}{T_s}\right) \\ \left(\dfrac{x_{2,\text{ref},n+1} - k_2(x_{2,\text{ref},n} - x_{2,n}) - x_{2,n}}{T_s}\right)\dfrac{x_{1,n}}{x_{2,n}} - x_{2,n}\mu \\ \left(\dfrac{x_{3,ez,n+1} - k_3(x_{3,ez,n} - x_{3,n}) - x_{3,n}}{T_s}\right)x_{1,n} + \dfrac{\mu}{Y}x_{2,n}x_{1,n} \\ \left(\dfrac{x_{4,\text{ref},n+1} - k_4(x_{4,\text{ref},n} - x_{4,n}) - x_{4,n}}{T_s}\right)\dfrac{x_{1,n}}{x_{4,n}} - Rx_{2,n}\dfrac{x_{1,n}}{x_{4,n}} \\ \left(\dfrac{x_{5,ez,n+1} - k_5(x_{5,ez,n} - x_{5,n}) - x_{5,n}}{T_s}\right)x_{1,n} \end{pmatrix}}^{\mathbf{b}} \quad (11)$$

The optimal profiles to follow are those corresponding to x_1, x_2, and x_4, which are known. The only unknown variables of this system are defined as "sacrificed variables" $x_{i,ez}$, corresponding in this case to $x_{3,ez}$ and $x_{5,ez}$. As can be seen in eq 11, the system normally has no solution (five equations and two unknowns). Therefore, the key of the control technique proposed in ref 1 is that the values adopted by "sacrificed variables" force the equation system (11) to have an exact solution, which implies the tracking error is not only minimal, but is equal to zero.

As mentioned above, the equation system (11) does not have an exact solution; therefore, to accomplish the target of this control methodology, that system must have an exact solution. Then, a Gaussian elimination process is carried out to find the necessary and sufficient condition for the system to have an exact solution (the resultant expression can be seen in ref 1). Therefore, the unknown variables, $x_{3,ez}$ and $x_{5,ez}$ ("sacrificed variables") are computed for each sampling time. Once the values of the sacrificed variables are found, the system (11) has an exact solution and can be solved by the

DOI: 10.1021/acs.iecr.8b01791
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least-squares method for the calculation of the control variables ($u_{1,n}$ and $u_{2,n}$, $\mathbf{u}$ vector).

$$(\mathbf{A}^T\mathbf{A})\mathbf{u} = \mathbf{A}^T\mathbf{b} \Rightarrow \mathbf{u} = (\mathbf{A}^T\mathbf{A})^{-1}\mathbf{A}^T\mathbf{b} \tag{12}$$

The control actions ($u_{1,n}$ and $u_{2,n}$) applied at time n allow following the desired trajectories with a minimal error.

Tracking Error. The tracking error is defined as the value of the difference between the reference and real trajectories. In a generic way, the tracking error for each state variable is defined as

$$e_{i,n} = x_{i,\mathrm{ref},n} - x_{i,n}, \qquad \text{for } i = 1, 2, 3, 4, 5 \tag{13}$$

The dimensionless tracking error (for desired variables) at n instant of time is calculated as

$$\|e_{\mathrm{ad},n}\| = \sqrt{\left(\frac{e_{1,n}}{x_{1,\mathrm{ref,max}}}\right)^2 + \left(\frac{e_{2,n}}{x_{2,\mathrm{ref,max}}}\right)^2 + \left(\frac{e_{4,n}}{x_{4,\mathrm{ref,max}}}\right)^2} \tag{14}$$

and the total tracking error

$$E_{\mathrm{T}} = T_s \sum_n \|e_{\mathrm{ad},n}\| \tag{15}$$

The reference final values for the desired variables are $x_{1,\mathrm{ref,max}} = 1.9$ L, $x_{2,\mathrm{ref,max}} = 13.92$ g/L, and $x_{4,\mathrm{ref,max}} = 3.1$ g/L.

Note that the total tracking error (TTE, eq 15) is dimensionless.

Taking into account eqs 8 and 11, the original control system proposed in ref 1 (that did not take into account parametric uncertainties or process perturbations for the controller design) can be denoted as

$$\overbrace{\begin{pmatrix} e_{1,n+1} \\ e_{2,n+1} \\ e_{3,n+1} \\ e_{4,n+1} \\ e_{5,n+1} \end{pmatrix}}^{\mathbf{e}_{n+1}} = \begin{pmatrix} k_1 & 0 & 0 & 0 & 0 \\ 0 & k_2 & 0 & 0 & 0 \\ 0 & 0 & k_3 & 0 & 0 \\ 0 & 0 & 0 & k_4 & 0 \\ 0 & 0 & 0 & 0 & k_5 \end{pmatrix} \overbrace{\begin{pmatrix} e_{1,n} \\ e_{2,n} \\ e_{3,n} \\ e_{4,n} \\ e_{5,n} \end{pmatrix}}^{\mathbf{e}_n} + \ldots + T_s \overbrace{\begin{pmatrix} 0 & 0 \\ -x_2 e_{3,ez,n}\mu_\lambda & -x_2 e_{5,ez,n}\mu_\theta \\ 0 & 0 \\ -x_2 e_{3,ez,n}R_\lambda & -x_2 e_{5,ez,n}R_\theta \\ 0 & 0 \end{pmatrix}}^{\text{bounded linearity} \to 0} \tag{16}$$

Equation 16 demonstrates that the tracking errors for all variables tend to zero when $0 < k_i < 1$, $i = 1, 2, 3, 4, 5$, and $n \to \infty$. A demonstration can be seen in ref 1.

3. CONTROLLER DESIGN UNDER PARAMETRIC UNCERTAINTY AND PROCESS DISTURBANCES

In this section, a methodology for the parametric uncertainties and process disturbance handling is presented.

In order to quantify the model mismatch and process disturbances, an additive uncertainty is incorporated into the original controller design. According to eq 7, the real bioprocess model is assumed:

$$\overbrace{\overbrace{\mathbf{z}_{n+1} = \mathbf{z}_n + [\xi(\mathbf{z}_n) + \beta(\mathbf{z}_n, \mathbf{u}_n)\mathbf{u}_n]T_s}^{\text{model}} + \mathbf{E}_n}^{\text{real system}} \tag{17}$$

where $\mathbf{E}_n$ quantifies the uncertainty. Note that this term of uncertainty can be used to model a wide class of model mismatches as well as perturbed systems.

The mismatch model and external perturbations might depend on the state variables or the system input. Therefore, considering a real plant: $\mathbf{z}_{n+1} = g(\mathbf{z}_n, \mathbf{u}_n)$, the additive uncertainty can be expressed as $\mathbf{E}_n = g(\mathbf{z}_n, \mathbf{u}_n) - \hat{g}(\mathbf{z}_n, \mathbf{u}_n)$, where $\hat{g}(z_n, u_n)$ is the nonlinear system model in discrete time. Now, note that if $\mathbf{z}$ and $\mathbf{u}$ are bounded and g is Lipschitz, as it will be assumed, then $\mathbf{E}_n$ can be modeled as a bounded uncertainty.[75,76]

Analogously to the procedure followed for eq 16, but now taking into account the additive uncertainty, the next concluding expression is obtained:

$$\begin{pmatrix} e_{1,n+1} \\ e_{2,n+1} \\ e_{3,n+1} \\ e_{4,n+1} \\ e_{5,n+1} \end{pmatrix} = \begin{pmatrix} k_1 & 0 & 0 & 0 & 0 \\ 0 & k_2 & 0 & 0 & 0 \\ 0 & 0 & k_3 & 0 & 0 \\ 0 & 0 & 0 & k_4 & 0 \\ 0 & 0 & 0 & 0 & k_5 \end{pmatrix} \begin{pmatrix} e_{1,n} \\ e_{2,n} \\ e_{3,n} \\ e_{4,n} \\ e_{5,n} \end{pmatrix} + \ldots + T_s \overbrace{\begin{pmatrix} 0 & 0 \\ -x_2 e_{3,ez,n}g_\lambda & -x_2 e_{5,ez,n}g_\theta \\ 0 & 0 \\ -x_2 e_{3,ez,n}R_\lambda & -x_2 e_{5,ez,n}R_\theta \\ 0 & 0 \end{pmatrix}}^{\text{bounded nonlinearity} \to 0} - \overbrace{\begin{pmatrix} E_{1,n} \\ E_{2,n} \\ E_{3,n} \\ E_{4,n} \\ E_{5,n} \end{pmatrix}}^{\mathbf{E}_n} \tag{18}$$

Looking at eq 18, it can be seen how the additive uncertainty directly affects the tracking error. Anyway, the presence of the term $\mathbf{E}_n$ makes the tracking error not converge to zero.

The main contribution of this work is to compensate the uncertainty and achieve the tracking error convergence to zero when the process moves forward. Therefore, the objective is to compensate the uncertainty and achieve the tracking error convergence to zero when the process moves forward.

Integral Action. In order to deal with the additive uncertainty effect on the tracking error, the incorporation of an integral action in the state variable system is proposed. Therefore, depending on the supposition of the time variation of $\mathbf{E}_n$, a series of the tracking error integrators are added in the control actions calculation.

In a real system, it is assumed that the effects of additive uncertainties on tracking errors are unknown and each component of $E_{\varphi,n}$ can be represented by a polynomial of m order.

As definitions, the first order difference for additive uncertainty is $\delta\mathbf{E}_n = \mathbf{E}_{n+1} - \mathbf{E}_n$, the second order difference $\delta^2\mathbf{E}_n = \delta(\delta\mathbf{E}_n) = \delta(\mathbf{E}_{n+1} - \mathbf{E}_n) = \mathbf{E}_{n+2} - 2\mathbf{E}_{n+1} + \mathbf{E}_n$; analogously, the qth order difference can be expressed as $\delta^q\mathbf{E}_n = \delta(\delta^{q-1}\mathbf{E}_n)$.[77] Note that the qth order difference of a $q - 1$ polynomial order is zero.

DOI: 10.1021/acs.iecr.8b01791
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Constant Uncertainty. If uncertainties remain constant throughout the process, i.e., $\mathbf{E}_n$ = const, then the first order difference is equal to zero: $\delta\mathbf{E}_n = \mathbf{E}_{n+1} - \mathbf{E}_n = 0$.

The integral action proposed is defined as

$$\mathbf{U}_{1,n+1} = \mathbf{U}_{1,n} + \int_{nT_s}^{(n+1)T_s} \mathbf{e}(t)\, dt \cong \mathbf{U}_{1,n} + \mathbf{e}_n T_s \tag{19}$$

where $\mathbf{e}(t)$ is the continuous time error in the state vector and $\mathbf{U}_{1,n+1}$ is the integral of the error. The subscript "1" means the first integral of error, and n is the instant of time.

According to eq 10, but now considering parametric uncertainties and process disturbances, the control action can be computed taking into account the new terms:

$$\mathbf{z}_{n+1} = \mathbf{z}_{\text{ref},n+1} - \mathbf{K}\overbrace{(\mathbf{z}_{\text{ref},n} - \mathbf{z}_n)}^{\mathbf{e}_n} + \mathbf{L}_1\mathbf{U}_{1,n+1} \tag{20}$$

where $\mathbf{L}_1$ is the matrix corresponding to integral action with a constant uncertainty.

Then, for each variable:

$$\overbrace{\begin{pmatrix} x_{1,\text{ref},n+1} \\ x_{2,\text{ref},n+1} \\ x_{3,\text{ref},n+1} \\ x_{4,\text{ref},n+1} \\ x_{5,\text{ref},n+1} \end{pmatrix}}^{\mathbf{z}_{\text{ref},n+1}} - \overbrace{\begin{pmatrix} x_{1,n+1} \\ x_{2,n+1} \\ x_{3,n+1} \\ x_{4,n+1} \\ x_{5,n+1} \end{pmatrix}}^{\mathbf{z}_{n+1}} = \overbrace{\begin{pmatrix} k_1 & 0 & 0 & 0 & 0 \\ 0 & k_2 & 0 & 0 & 0 \\ 0 & 0 & k_3 & 0 & 0 \\ 0 & 0 & 0 & k_4 & 0 \\ 0 & 0 & 0 & 0 & k_5 \end{pmatrix}}^{\mathbf{K}} \left[\overbrace{\begin{pmatrix} x_{1,\text{ref},n} \\ x_{2,\text{ref},n} \\ x_{3,\text{ref},n} \\ x_{4,\text{ref},n} \\ x_{5,\text{ref},n} \end{pmatrix}}^{\mathbf{z}_{\text{ref},n}} - \overbrace{\begin{pmatrix} x_{1,n} \\ x_{2,n} \\ x_{3,n} \\ x_{4,n} \\ x_{5,n} \end{pmatrix}}^{\mathbf{z}_n} \right] + \ldots + \underbrace{\overbrace{\begin{pmatrix} L_{1,1} & 0 & 0 & 0 & 0 \\ 0 & L_{1,2} & 0 & 0 & 0 \\ 0 & 0 & L_{1,3} & 0 & 0 \\ 0 & 0 & 0 & L_{1,4} & 0 \\ 0 & 0 & 0 & 0 & L_{1,5} \end{pmatrix}}^{\mathbf{L}_1} \overbrace{\begin{pmatrix} U_{1,1} \\ U_{1,2} \\ U_{1,3} \\ U_{1,4} \\ U_{1,5} \end{pmatrix}}^{\mathbf{U}_{1,n}}}_{\text{constant integral action}} \tag{21}$$

Now, following the procedure carried out for the original controller, eq 21 is replaced in the mathematical model of the system represented in eq 6:

$$\begin{pmatrix} 1 & 1 \\ -1 & -1 \\ (N - x_{3,n}) & -x_{3,n} \\ -1 & -1 \\ -1 & (I - x_{5,n}) \end{pmatrix} \begin{pmatrix} u_{1,n} \\ u_{2,n} \end{pmatrix} = \ldots = \begin{pmatrix} \left(\dfrac{x_{1,\text{ref},n+1} - k_1(x_{1,\text{ref},n} - x_{1,n}) + L_{1,1}U_{1,1,n+1} - x_{1,n}}{T_s}\right) \\ \left(\dfrac{x_{2,\text{ref},n+1} - k_2(x_{2,\text{ref},n} - x_{2,n}) + L_{1,2}U_{1,2,n+1} - x_{2,n}}{T_s}\right)\dfrac{x_{1,n}}{x_{2,n}} - x_{2,n}\mu \\ \left(\dfrac{x_{3,ez,n+1} - k_3(x_{3,ez,n} - x_{3,n}) + L_{1,3}U_{1,3,n+1} - x_{3,n}}{T_s}\right)x_{1,n} + \dfrac{\mu}{Y}x_{2,n}x_{1,n} \\ \left(\dfrac{x_{4,\text{ref},n+1} - k_4(x_{4,\text{ref},n} - x_{4,n}) + L_{1,4}U_{1,4,n+1} - x_{4,n}}{T_s}\right)\dfrac{x_{1,n}}{x_{4,n}} - Rx_{2,n}\dfrac{x_{1,n}}{x_{4,n}} \\ \left(\dfrac{x_{5,ez,n+1} - k_5(x_{5,ez,n} - x_{5,n}) + L_{1,5}U_{1,5,n+1} - x_{5,n}}{T_s}\right)x_{1,n} \end{pmatrix} \tag{22}$$

The next step is to find the necessary condition for the system (eq 22) to have an exact solution, which is achieved through a Gaussian elimination process similar to that presented in ref 1. In this way, the values of the variables sacrificed for each sampling time are found. Then, the control actions can be calculated using eq 12.

Now, to demonstrate that the tracking error of the real system under perturbations converges to zero, simple mathematical operations are carried out:

Expressing eq 18 in the following summarized way:

$$\mathbf{e}_{n+1} = -\mathbf{K}\mathbf{e}_n + \text{NL}_n - \mathbf{E}_{1,n+1} \tag{23}$$

Adding the integral term

$$\mathbf{e}_{n+1} = -\mathbf{K}\mathbf{e}_n + \text{NL}_n + \mathbf{L}_1\mathbf{U}_{1,n+1} - \mathbf{E}_{1,n+1} \tag{24}$$

Replacing eq 19 in eq 24:

$$\mathbf{e}_{n+1} = \mathbf{K}\mathbf{e}_n + \text{NL}_n + \mathbf{L}_1\mathbf{U}_{1,n} + \mathbf{L}_1\mathbf{e}_n T_s + \mathbf{E}_{1,n+1} \tag{25}$$

Increasing eq 25 in one sampling time:

$$\mathbf{e}_{n+2} = \mathbf{K}\mathbf{e}_{n+1} + \text{NL}_{n+1} + \mathbf{L}_1(\mathbf{U}_{1,n+1} + \mathbf{e}_{n+1}T_s) + \mathbf{E}_{1,n+2} \tag{26}$$

Clearing the integral term from eq 24, replacing in eq 26, and rearranging:

$$\mathbf{e}_{n+2} = -\mathbf{e}_{n+1}(-1 - \mathbf{K} + \mathbf{L}_1T_s) - \mathbf{K}\mathbf{e}_n - (\text{NL}_{n+1} - \text{NL}_n) + \overbrace{(E_{2,n+1} - E_{2,n})}^{\delta E_{2,n} = 0} \tag{27}$$

Therefore, the sets of parameters $\mathbf{K}$ and $\mathbf{L}_1$ are optimized for the stability assurance of eq 27. The nonlinearity term ($\text{NL}_{n+1} - \text{NL}_n$) tends to zero because it depends on the error in the sacrificed variables, which tends to zero, too. Then $\mathbf{e}_n \to 0$ as $n \to \infty$ despite the uncertainties, if they are considered constant.

Linear Uncertainty. If uncertainties can be represented by a linear function, where the second order difference is equal to zero: $\delta^2\mathbf{E}_n = \delta(\delta\mathbf{E}_n) = \delta(\mathbf{E}_{n+1} - \mathbf{E}_n) = \mathbf{E}_{n+2} - 2\mathbf{E}_{n+1} + \mathbf{E}_n = 0$, then a new integrator must be considered. In a similar way to

DOI: 10.1021/acs.iecr.8b01791
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the procedure before, but now introducing two integral actions defined by $\mathbf{U}_1$ and $\mathbf{U}_2$:

$$U_{\varphi,2,n+1} = U_{\varphi,2,n} + \int_{nT_s}^{(n+1)T_s} \mathbf{U}_{\varphi,1}(t)\,\mathrm{d}t \cong U_{\varphi,2,n} + \mathbf{U}_{\varphi,1,n+1}T_s \quad (28)$$

where the subscript "2" means an integrator for a linear perturbation.

Then, a new term is added to eq 20:

$$\mathbf{z}_{n+1} = \mathbf{z}_{\mathrm{ref},n+1} - \mathbf{K}\overbrace{(\mathbf{z}_{\mathrm{ref},n} - \mathbf{z}_n)}^{\mathbf{e}_n} + \mathbf{L}_1\mathbf{U}_{1,n+1} + \mathbf{L}_2\mathbf{U}_{2,n+1} \quad (29)$$

The new parameter $\mathbf{L}_2$ corresponds to double integral action. In a similar way as simple integral action, the demonstration of convergence to zero of the tracking error for the double integral action is operating as before, and taking into account that $\delta^2\mathbf{E}_n = 0$, the final expression for tracking error is

$$\begin{aligned}\mathbf{e}_{n+3} &= -\mathbf{e}_{n+2}(-\mathbf{K} + T_s(\mathbf{L}_1 + \mathbf{L}_2T_s) - 2) \\ &- \mathbf{e}_{n+1}(2\mathbf{K} - \mathbf{L}_1T_s + 1) + ... + \mathbf{K}\mathbf{e}_n \\ &\overbrace{(\mathrm{NL}_{n+2} - \mathrm{NL}_{n+1} + \mathrm{NL}_n)}^{\text{bounded nonlinearity}} + \overbrace{(\mathbf{E}_{n+2} - 2\mathbf{E}_{n+1} + E_{2,n})}^{\delta^2E_{2,n}=0}\end{aligned} \quad (30)$$

Now, as can be seen in (30), under constant or linear varying uncertainty, this has no influence on the error dynamics. The parameters $\mathbf{K}$, $\mathbf{L}_1$, and $\mathbf{L}_2$ are optimized for the stability assurance of eq 30, as shown in the previous case.

Now, in a generic way, if the uncertainties can be approximated by $q - 1$ order polynomial, the influence of $\mathbf{E}_n$ on $\mathbf{e}_n$ will be eliminated by introducing q integrators.

Optimization of Controller Parameters. There is a recurrent problem for this kind of controllers, and it is how to define the best tuning parameters to achieve a good closed-loop response. In this subsection an algorithm based on Monte Carlo randomized experiment is proposed to find the optimal controller parameters.

In the original controller presented in ref 1, the controller parameters are represented by $\mathbf{K} = \{k_1, k_2, k_3, k_4, k_5\}$, and the conditions for the tracking error tending to zero according to eq 27 are that $0 < k_i < 1$, $i = \{1, 2, 3, 4, 5\}$. But now, integral actions are added; therefore the amount of parameters to select increases and the conditions change:

$$\overbrace{k_1, k_2, k_3, k_4, k_5}^{\mathbf{K}\ (\text{original controller})},\quad \overbrace{L_{1,1}, L_{1,2}, L_{1,3}, L_{1,4}, L_{1,5}}^{\mathbf{L}_1\ (\text{integral action, constant uncertainty})},\quad \overbrace{L_{2,1}, L_{2,2}, L_{2,3}, L_{2,4}, L_{2,5}}^{\mathbf{L}_2\ (\text{integral action, linear uncertainty})}$$

In a generic form, for the integral action, the parameters are denoted by $L_{m,i}$, where m is the number of integrators and i corresponds to each state variable.

To choose the optimization criteria of the parameters considering the integral actions, resort to the characteristic equations (27) and (30) (simple and double integral actions, respectively). In the case of the controller without integral action, the characteristic equation can be rewritten as

$$r - k_i = 0 \quad (31)$$

Therefore, the parameters are directly the roots of polynomial.

For a simple integral action (one integrator, constant uncertainty), the characteristic equation is (27) and can be rewritten as

$$r^2 + r(-1 - k_i + L_{1,i}T_s) + k_i = 0 \quad (32)$$

Thus, clearing the parameters according to the roots:

$$\begin{aligned}k_i &= r_1r_2 \\ L_{1,i} &= (-r_1 - r_2 + r_1r_2 + 1)/T_s\end{aligned} \quad (33)$$

For a double integral action (two integrators, linear uncertainty), the characteristic equation is (30) and can be rewritten as

$$\begin{aligned}&r^3 + r^2(-k_i + T_s(L_{1,i} + L_{2,i}T_s) - 2) + r(2k_i - L_{1,i}T_s + 1) \\ &- k_i = 0\end{aligned} \quad (34)$$

Clearing the parameters

$$\begin{aligned}k_i &= r_1r_2r_3 \\ L_{1,i} &= (2r_1r_2r_3 + 1 - r_1r_2 - r_1r_3 - r_2r_3)/T_s \\ L_{2,i} &= (-r_1 - r_2 - r_3 - r_1r_2r_3 + 1 + r_1r_2 + r_1r_3 + r_2r_3)/T_s^2\end{aligned} \quad (35)$$

Thus, for the tracking error to tend to zero and to ensure the system stability, the roots of the polynomial must be between 0 and 1.

The performance index used to optimize the controller parameters is to minimize the total tracking error (15):

$$\mathbf{C} = \min_{\mathbf{K},\mathbf{L}}(E_{\mathrm{T}}) \quad (36)$$

4. RESULTS AND DISCUSSION

In this section, the behavior of the controller against parametric uncertainty and perturbations in the process is evaluated through simulations. First, a Monte Carlo algorithm to tune the optimal controller parameters is carried out. Then, the system is tested under parametric uncertainty and process disturbances, comparing the system responses with and without integral action.

Controller Tuning. In order to determine the optimal controller parameters, a Monte Carlo algorithm (MCRA) is carried out. This methodology has been recently employed for controller tuning[1,64,78] with satisfactory results.

According to the criteria for parameter selection discussed in section 3, the procedure for the simulation is detailed below.

Controller Tuning without Integral Action (m = 0). In this case, the methodology employed is the same as in ref 1, where 1000 simulations are performed. Considering eq 31, for each simulation a random value $r_i \in (0,1)$ is assigned for each state variable, then the control actions and the performance index (36) are computed. Once the simulations are finished, the optimal controller parameter set is corresponding to the minimum $\mathbf{C}$.

DOI: 10.1021/acs.iecr.8b01791
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Controller Tuning with an Integral Action (m = 1). Again, 1000 simulations are performed, but now the parameters are calculated according to eq 33.

Controller tuning with a double integral action (m = 2). Once the 1000 simulations are performed, the controller parameters are computed according to eq 35.

The necessary information to carry out the simulations is taken from ref 1. The final time and sampling time are $T_f = 10$ h and $T_s = 0.1$ h, respectively.

Table 1 shows the optimized values for the controller parameters. Depending on the value of *m*, there will be 5, 10, or 15 parameters.

Table 1. Optimal Controller Parameters

param	$m = 0$	$m = 1$	$m = 2$
k_1	0.2805	0.0038	0.0404
k_2	0.6761	0.9412	0.9412
k_3	0.6520	0.7941	0.6589
k_4	0.1694	0.2032	0.3842
k_5	0.1266	0.5382	0.5382
$L_{1,1}$	–	8.8102	0.0851
$L_{1,2}$	–	0.0088	2.3546
$L_{1,3}$	–	1.1183	1.2538
$L_{1,4}$	–	1.4755	2.4587
$L_{1,5}$	–	0.6504	1.0085
$L_{2,1}$	–	–	0.2588
$L_{2,2}$	–	–	1.5285
$L_{2,3}$	–	–	3.0497
$L_{2,4}$	–	–	1.9246
$L_{2,5}$	–	–	2.7533

Disturbances and Uncertainties Handling. For the quantification of uncertainties and disturbances in the simulation work, an approach consists of specifying only the upper and lower limits within which the real disturbance or uncertainty is assumed to evolve. The idea of this approach is thus to replace the knowledge of exact values of unknown inputs by a known range of the values within which they evolve.[79]

Parametric Uncertainty. In the bioprocesses, the model parameters vary in an unpredictable manner.[80] This can lead to a structural instability in the dynamic behavior of the system.[20] Therefore, a strict and efficient control system is necessary.

In several research fields, probabilistic methods have been found to be useful for dealing with problems related to robustness of systems affected by uncertainties.[81] In particular, the Monte Carlo randomized algorithm has been used for uncertainty quantification in many applications such as the Rothermel model,[48] river flow rate forecast,[82] radioactive decay, power system generation, and traffic on roads,[83] among others. From the point of view of process control, Monte Carlo methods are effective tools for the analysis of probabilistically robust control schemes.[65,81] In this subsection the system is simulated considering errors on modeling using the MCRA method. The procedure consists of replacing the exact model parameters values by a range of them within which they can vary. The defined range for model parameters is ±20% of the nominal values. Then, $N = 1000$ simulations are executed using the optimized controller parameters set.

Taking into account the worst case of uncertainty, all the model parameters are varied. In the first instance, the control system is tested without integral action. Then one integrator is added and finally, two integrators are added. The results are compared below.

The tracking of optimal profiles for the three cases is shown in Figure 1.

Figure 2 shows the TTE for 1000 simulations to evaluate the controller performance under parametric uncertainty for three cases: no integrator (a), one integrator (b), and two integrators (c). As can be seen, the total tracking error range is visibly reduced when integral actions are added.

In Table 2, the total tracking errors for the three cases are shown. Now, taking the average value of TTE for each case and translating it to percentage, the improvement of the controller with integral action can be easily quantified (see Figure 3). Note that the error is reduced by 48% by adding one integral action and 61% with two integrators.

The above figures show that the integral actions incorporated into the controller are effective and give robustness to the control system.

Perturbation in the Control Actions. In all processes there are also disturbances acting on the plant in addition to parametric uncertainties, modifying the expected values of the

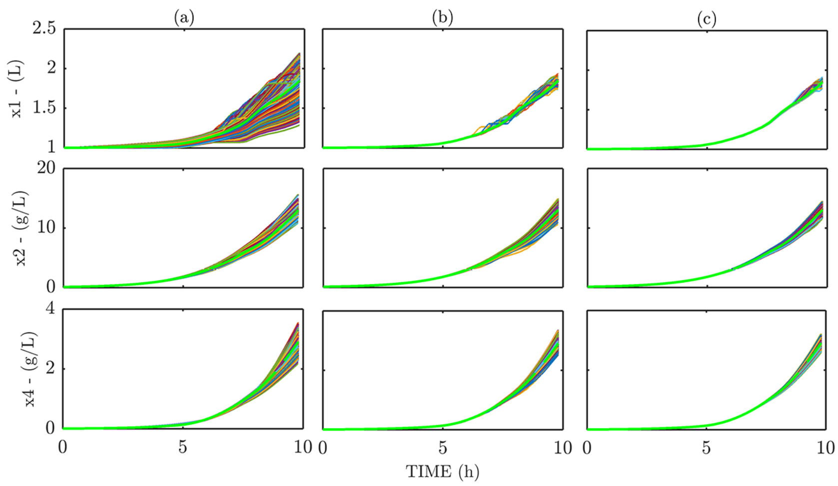

Figure 1. Tracking of optimal profiles for 1000 simulations under parametric uncertainty (±20%) . (a) Nonintegral action ($m = 0$), (b) one integral action ($m = 1$), and (c) two integral actions. Green lines show the reference values.

DOI: 10.1021/acs.iecr.8b01791
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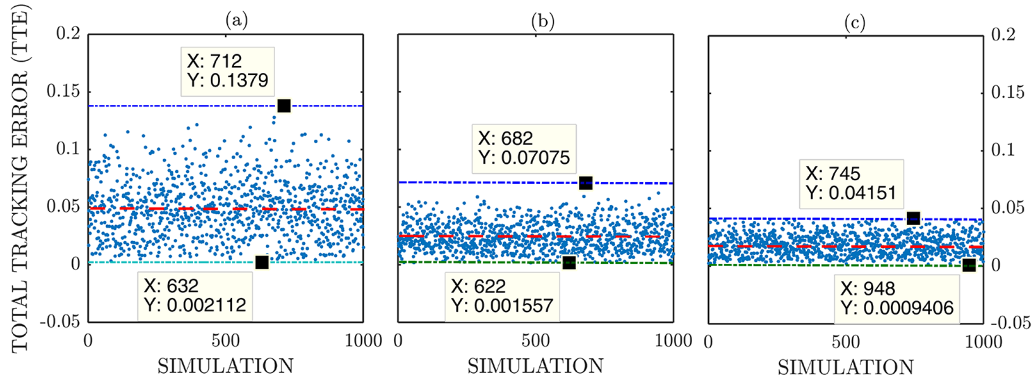

Figure 2. Total tracking error for 1000 simulations under parametric uncertainty (±20%) . (a) Nonintegral action, proposed by Pantano et al.[1] (m = 0), (b) one integral action (m = 1), and (c) two integral actions (m = 2) . Central dashed lines show the mean values.

Table 2. Reduction of TTE by Adding Integrators under Parametric Uncertainty

	m = 0	m = 1	m = 2
TTE	0.0472	0.0245	0.0186
%	100	52	39

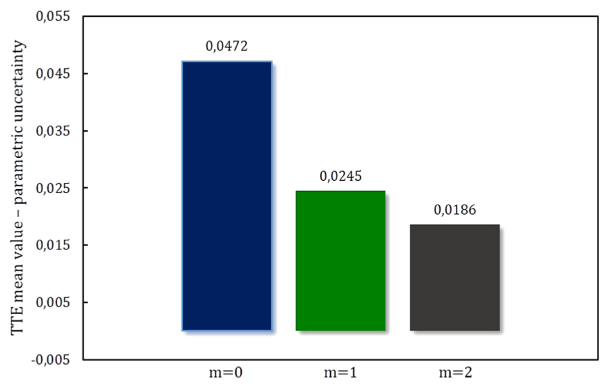

Figure 3. TTE mean value for the three cases. Process simulation under parametric uncertainty (20%).

system variables. Therefore, a random perturbation in the control actions taking into account parametric uncertainties is simulated for the controller evaluation. The two control actions are perturbed by 30% of calculated values:

$$u_{1,\text{perturbed}} = u_{1,\text{unperturbed}}(1 + \text{random}(\text{unif}, 0, 0.3) + 1)$$

$$u_{2,\text{perturbed}} = u_{2,\text{unperturbed}}(1 + \text{random}(\text{unif}, 0, 0.3) + 1)$$

Figure 4 shows the controller adjustment to hold the tracking error in a minimal value spite of perturbations in the control actions and parametric uncertainties.

Table 3 shows the TTE for the controllers. Note how, again, by adding only one integral action the tracking error is reduced by 68%. The response improves by 75% with two integrators.

Table 3. TTE for Perturbed System with Parametric Uncertainty

	m = 0	m = 1	m = 2
TTE	0.1036	0.0335	0.0253
%	100	32	24

Figure 5 shows a bar diagram of the cumulative error (TTE) for the real system under parametric uncertainties and

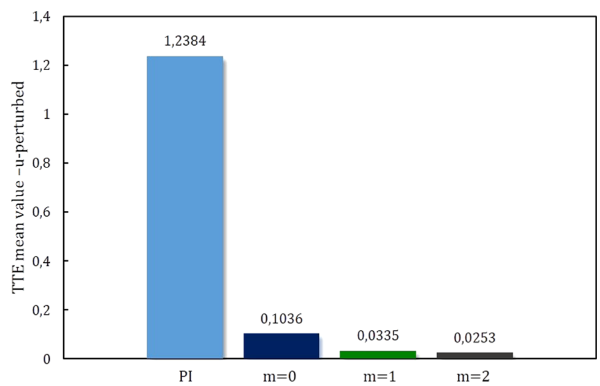

Figure 5. TTE for the three cases. Process simulation under parametric uncertainty and perturbations in the control actions.

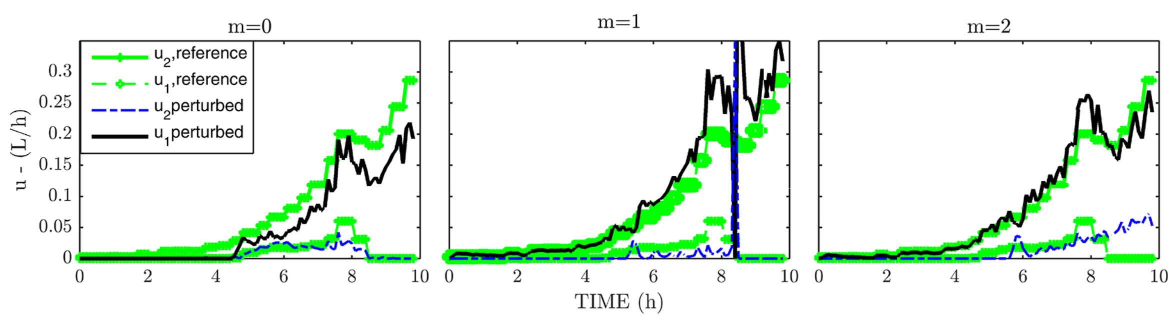

Figure 4. Perturbed control actions considering parametric uncertainty.

DOI: 10.1021/acs.iecr.8b01791
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perturbation in the control actions. This is presented for the original controller proposed in Pantano et al.[1] ($m = 0$), and for the two controllers proposed in this paper: one integrator ($m = 1$) and two integrators ($m = 2$). In addition, as a comparison, TTE is shown for a classic PI controller, which was automatically tuned by a Matlab autotuning function.

As can be seen in this section, the simulation work demonstrates the effectiveness of the controller proposed in this work, by adding integral actions to the design, in order to solve the problems of control under parametric uncertainty and process disturbances.

5. CONCLUSION

This paper proposes an improved control system for fed-batch production of recombinant protein, a multivariable and nonlinear bioprocess which is highly susceptible to model and process disturbances due to its biological nature. The original controller proposed in ref 1 achieved the tracking of optimal profiles of volume, cell density, and protein concentration (main product) with a minimum error through the development of an effective control law based on linear algebra. The technique proposed in this work extends the original controller design to take into account parametric uncertainty and process disturbances. Several simulations were carried out to test the controller performance. The system was evaluated under parametric uncertainties (±20%) and random perturbations in the control actions (±30%), improving the system response up to 70% by adding some integral actions of the tracking error in the control actions computation. The optimal controller parameters (with and without integrators) were successfully found through a Monte Carlo experiment. Although this method has low complexity, the results are reliable and the method solves a real problem for bioprocess control.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was partially funded by the following Argentine institutions: National Council of Scientific and Technological Research (CONICET) and Universidad Nacional de San Juan (UNSJ).

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DOI: 10.1021/acs.iecr.8b01791
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