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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 $\psi$, $\mu$, and $\chi$ 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 |

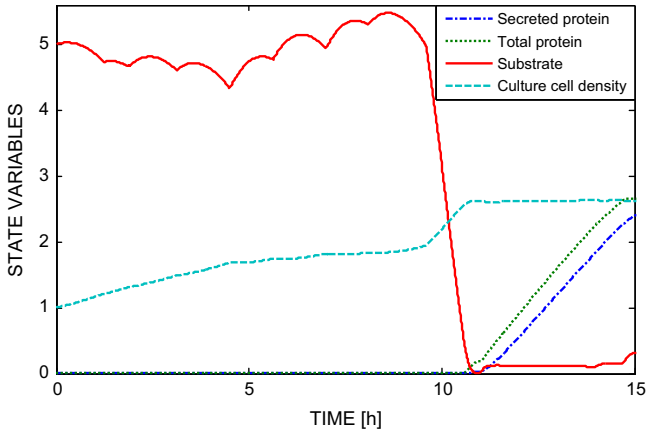


**Fig. 1.** Optimal profiles $[P_{ref}, P_{Tref}, X_{ref}, S_{ref}]^T$, as determined by [16].

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.