Biochemical Engineering Journal 105 (2016) 177–188

Contents lists available at ScienceDirect

Biochemical Engineering Journal

journal homepage: www.elsevier.com/locate/bej

Regular article

A new approach for finding smooth optimal feeding profiles in fed-batch fermentations

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ARTICLE INFO

Article history:
Received 4 May 2015
Received in revised form 24 August 2015
Accepted 6 September 2015
Available online 9 September 2015

Keywords:
Optimization
Smooth control profiles
Substrate shock
Ethanol
Fed-batch culture
Penicillin

ABSTRACT

In this work, a new approach for smooth control profiles parameterization (requiring a small number of parameters) is presented and especially recommended for bioprocess applications because of the smoothness of the profiles obtained, which are not only continuous time functions but also differentiable along the whole control interval. The importance of smooth profiles relays on the fact that abrupt changes in the cells' environment may affect the metabolism of the cell, usually leading to a decrease in the process productivity. The parameterization proposed in this work is based on sinusoidal functions, which not only describe smooth functions but also are flexible and naturally constrained. Two very well-known bioprocess case studies have been successfully addressed by using the new parameterization approach.

1. Introduction

Due to the rapid evolution of the biotechnology industry, during the last years many efforts have been oriented to optimization and control of continuous and semi-continuous bioprocesses, in order to minimize their production costs while increasing the yield and productivity [1]. In the same way, fed-batch fermentation has become an important mode of operation in the bioprocess industry due to its capability for avoiding inhibition by substrate (due to overfeeding as usually occurs in batch mode), and to the fact that nothing is withdrawn from the reactor, which helps to maintain a sterile environment, suitable to preserve the microorganisms' population [2]. Controlling fed-batch bioprocesses is a challenging dynamic optimization problem that has received extensive attention since the 80s [3] and still remains as an open issue. There are three basic numerical solution methods that can be used for solving dynamic optimization problems [4–6]:

1. HJCB (Hamilton–Jacobi–Carathéodory–Bellman) based methods, in which by means of the optimality principle, the optimization problem is transformed into the resolution of a Partial Differential Equations (PDE) problem.
2. Indirect methods, in which the original problem is formulated as a Boundary Value Problem (BVP) that can be solved by means of gradient, multiple shooting or collocation methods.
3. Direct Optimization methods, in which the original problem is transcribed into a Nonlinear Programming Problem (NLP). Depending on the solution strategy used to solve the transcribed problem, the direct methods are classified into sequential, simultaneous or quasi-sequential methods.

A detailed explanation of the mentioned methods is out of the scope of this paper. The reader is referred specially to the works by Zhao [7] and Srinivasan et al. [5] in which the methods as well as their advantages and disadvantages are very well exposed. The focus of this paper is the smooth parameterization (described by continuous and differentiable functions) of the input variables to solve the dynamic optimization problem via direct methods. Independently of the approach, the parameterization of the input variables (which are the main decision variables) must necessarily be done. It is precisely this parameterization that has been claimed as the only disadvantage of the direct methods because the accuracy of the solution strongly depends on the selection of the parameterization which is chosen arbitrarily [5], usually using a piecewise polynomial representation especially of zero-order due to their computational convenience and easiness of implementation. Such kind of zero order piecewise parameterizations lead to step-type feeding profiles (with variable amplitude and/or duration). Although many theoretical works have used step

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http://dx.doi.org/10.1016/j.bej.2015.09.004
1369-703X/

profiles for solving the optimization problem for fed-batch bioprocesses [8–23]; it is important to notice that in real applications, such profiles can expose the cells to repeated cycles of excessive to insufficient nutritional conditions, or large, sudden changes in the environment of the cells, which may cause undesirable effects on the cell's viability and metabolism, and may therefore seriously affect the production of the metabolites that are the valuable products in the process [24–27]. Another usual approach is the piecewise parameterization by means of linear polynomials [4,13,28–31]. Although this kind of profile is not as abrupt as the step-type, it is not smooth either. On the other hand, smoother profiles can be obtained increasing the order of the piecewise polynomials, but this result in an increase in the number of decision variables for the optimization problem. Recently, the work by Martinez et al. [32] remarks the convenience of using smooth continuous feeding profiles in real bioprocess applications. The authors argue that based on the fact that bioreactor dynamics slowly unfolds cell responses to environmental changes, smooth feeding profiles are more appealing to drive the physiological state along a profitable trajectory of states.

In this paper, a parameterization based on sinusoidal functions is proposed in order to find smooth continuous profiles that maximize a specific objective function, avoiding sudden changes that may be aggressive for the cells (reducing the substrate shock) and at the same time using a reduced number of parameters. This smooth parameterization is important especially when the effect of substrate shocks on the productivity is not explicitly considered by the dynamic model of the process. Despite the advantages mentioned, it must be noticed that the drawback of the proposed parameterization is that practical implementation of such sinusoidal feeding profile requires the use of a PLC or a computer based control system. Furthermore, the actuator coupled to the control system should allow continuous variation of the manipulated variables. For example, pumps with variable speed drives or proportional control valves should be used.

In summary, the problem of finding optimal feeding profiles in fed-batch processes is usually solved using direct dynamic optimization methods by parameterizing the control profiles as piecewise polynomial functions, which in most cases are non-smooth profiles neither continuous nor differentiable. This paper presents an alternative method for control vector parameterization leading to smooth profiles especially suitable for bioprocesses applications, and it is organized as follows. In Section 2, the dynamic optimization problem is stated. Section 3 briefly explains the piecewise parameterization framework. Furthermore, in Section 4, two approaches for smooth control vector parameterization are presented, where especial emphasis is done on the new smooth sinusoidal approach proposed in this work, as an alternative parameterization method suitable for bioprocess applications. The sinusoidal parameterization is then applied in Section 5, in order to find the optimal feeding profile in two very well-known fed-batch bioprocess case studies: the ethanol and penicillin production from glucose. The dynamic optimization problem is solved using the direct sequential dynamic framework, in which a stochastic optimization method is used as solution method [33]. The smooth profiles obtained are compared to different conventional non-smooth piecewise parameterizations previously reported in the literature.

2. Dynamic optimization problem

In general, the dynamic optimization problem for finding the optimal substrate feed rate profile (often called optimal control problem) can be stated as Problem P1 (Eqs. (1)–(7)):

Problem P1:

$$\min_{\boldsymbol{u},t_f} J = \min_{\boldsymbol{u},t_f} \left[\Phi(\boldsymbol{x}(t_f)) + \int_{t_0}^{t_f} L\left(\boldsymbol{x}(t), \boldsymbol{u}(t), \boldsymbol{\theta}(t), t\right) \mathrm{d}t \right] \quad (1)$$

Subject to:

$$\frac{\mathrm{d}\boldsymbol{x}}{\mathrm{d}t} = \boldsymbol{f}\left(\boldsymbol{x}(t), \boldsymbol{u}(t), \boldsymbol{\theta}(t)\right) \quad (2)$$

$$\boldsymbol{x}(t_0) = \boldsymbol{x}_0 \quad (3)$$

$$\boldsymbol{g}(\boldsymbol{x}(t), \boldsymbol{u}(t), \boldsymbol{\theta}(t)) = 0 \quad (4)$$

$$\boldsymbol{h}(\boldsymbol{x}(t), \boldsymbol{u}(t), \boldsymbol{\theta}(t)) \le 0 \quad (5)$$

$$\boldsymbol{x}^l \le \boldsymbol{x}(t) \le \boldsymbol{x}^U \quad (6)$$

$$\boldsymbol{u}^l \le \boldsymbol{u}(t) \le \boldsymbol{u}^U \quad (7)$$

where J is a suitable objective function to be maximized (i.e. productivity, yield, etc) or minimized (costs, environmental impact, etc.), and is composed of two kinds of operational objectives. The first one described by the function Φ is related to the state of the process at the final time t_f, and is called the Mayer term. The second term L, known as the Lagrange term, represents an economical objective related to the dynamic behaviour of the state variables during the transition from the initial time (t_0) to the final time (t_f) and can be regarded as a trajectory term. Eqs. (2)–(7) show the equality as well as the inequality constraints that must be satisfied during the solution of Problem P1. Some constraints must be satisfied over the whole process time (i.e. path constraints), while others must be only satisfied at the end of the process (i.e. endpoint constraints). Eq. (2) represents the dynamic behaviour of the state's vector $\boldsymbol{x}$, whose initial condition $\boldsymbol{x}_0$ is given by Eq. (3). Eqs. (4) and (5) represent the equality and inequality algebraic constraints, while Eqs. (6) and (7) constraint the control vector $\boldsymbol{u}$ and the state variables $\boldsymbol{x}$ to their lower and upper bounds. Finally, $\boldsymbol{\theta}(t)$ is a vector related to the time-dependent model parameters.

In general, the decision variables of the optimization problem P1 are the values of the n-dimensional variables $\boldsymbol{u}$ (control vector) and the final time t_f. However, in order to obtain control profiles comparative to previously reported results for the case studies considered here, the final time has been fixed. Additionally, the model parameters are considered time-independent and the objective function will depend only on the final state of the process (i.e. the objective is to reach high quality of the product at the end of the batch). Thus, the optimization problem can be simplified into Problem P2 (Eqs. (8)–(14)):

Problem P2:

$$\min_{\boldsymbol{u}} J = \min_{\boldsymbol{u}} \Phi(\boldsymbol{x}(t_f)) \quad (8)$$

Subject to:

$$\frac{\mathrm{d}\boldsymbol{x}}{\mathrm{d}t} = \boldsymbol{f}(\boldsymbol{x}(t), \boldsymbol{u}(t)) \quad (9)$$

$$\boldsymbol{x}(t_0) = \boldsymbol{x}_0 \quad (10)$$

$$\boldsymbol{g}(\boldsymbol{x}(t), \boldsymbol{u}(t)) = 0 \quad (11)$$

$$\boldsymbol{h}(\boldsymbol{x}(t), \boldsymbol{u}(t)) \le 0 \quad (12)$$

$$\boldsymbol{x}^l \le \boldsymbol{x}(t) \le \boldsymbol{x}^U \quad (13)$$

$$\boldsymbol{u}^l \le \boldsymbol{u}(t) \le \boldsymbol{u}^U \quad (14)$$

Solving the dynamic optimization problem stated in Problem P2 will result in the optimal control profile that minimizes an end point-based objective function. It is important to remark that although the case studies presented in Section 5 correspond to