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Optimal control of bioreactors: a simultaneous approach for complex systems

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Abstract

The inherent features of dynamic bioprocesses prevent the application of conventional optimization algorithms, hence making necessary the development of tailored methods and strategies. On the other hand, the optimization of biotechnological processes may generate significant improvements in operating conditions and policies. Fed-batch bioprocesses are specific examples where complexity and difficulty depend on the model characteristics, the operating limits (path constraints) and the production target (objective function). We propose the use of orthogonal collocation into a simultaneous optimization approach to solve these problems. Initially, the methodology is applied to a simplified model for the biosynthesis of penicillin from glucose. Then, it is applied to a cybernetic structured model for the fermentative production of polyhydroxyalkanoates (PHAs). Results show that the discretization of differential-algebraic equation (DAE) systems by orthogonal collocation in finite elements efficiently transforms dynamic optimization problems into nonlinear programming (NLP) problems, thus enabling to solve complex problems with several control variables satisfying the approximation error tolerance.

Keywords: Bioreactors; Orthogonal collocation; Optimal control; Simultaneous optimization; Polyhydroxyalkanoates

1. Introduction

Dynamic processes represent a great variety of operations, in particular all processes that are run in batch or fed-batch mode. When optimal control policies are determined off-line, suitable set-point trajectories to be followed by feedback controllers are generated. The computation of optimal control policies in fed-batch processes requires special effort due to problem characteristics and to the presence of path constraints in the state and control variables. Moreover, adding the possible existence of discontinuities and non-differentiabilities in the variable profiles and differential equations, a complex dynamic optimization problem is generated, whose solution strategies must be investigated.

In fed-batch processes, in most cases the control vector appears linearly in state equations; then, the optimal control policy cannot directly determine because the gradient of the Hamiltonian does not provide any information about it [5]. Various methods for determining optimal feed profiles in fed-batch fermentations have been proposed. For instance, Yamane et al. [24] considered the specific growth rate and Guthke and Knorre [11] considered the substrate concentration as the control variables rather than the substrate feed rate; these approaches transform the original singular problem into a non-singular one. Modak [16] studied the choice of non-original control variables on fed-batch fermentations as an approach to transform singular problems to non-singular ones; the author concludes that the resulting operation policies are identical if some conditions on the model are satisfied, but in some cases the obtained results are suboptimal when compared with the results for feed rate as control variable. Lim et al. [13] developed a methodology to determine the characteristics of the optimal feed rate profiles for various types of fermentation and kinetic models with few variables.

In iterative dynamic programming (IDP) control variables are discretized and state constraints are indirectly handle employing penalty functions; the IDP optimizes the last subinterval (stage) first; after, the preceding stage is optimized regarding the control trajectory in the last stage as fixed and optimal; this procedure is repeated backwards to first stage. Balchen et al. [1] observed poor convergence when penalty functions are used to handle state constraints; however, problems of moderate complexity have been solved [21]. Using variable stage lengths and random search, accurate optimal

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control policies have been obtained with a small number of time stages [15]. Other approaches as evolutionary algorithms [6,20] have been used to solve dynamic optimization problems with moderate complexity.

Optimal control problems (OCPs), or differential-algebraic optimization problems (DAOPs), cannot be directly solved by nonlinear programming (NLP) techniques because the optimization of continuous profiles is an infinite dimensional problem. On the other hand, methods based on singular control theory solve problems with few variables and without algebraic constraints. Some approaches proposed to solve these problems are based on the discretization of variables that converts the dynamic optimization problem into a finite dimensional NLP. The first discretizes only the control variables (sequential method or control vector parameterization), and the DAE system is integrated using standard integration algorithms; hence, the optimization is carried out in the space of the decision variables. A set of chemical and biochemical engineering problems have been solved with this approach [2,23]. The second approach relies on the discretization of all variables (simultaneous method); thus, the optimization is carried out in the full space of the discretized variables, enabling the direct solution of problems with constraints on state and control variables.

The application of orthogonal collocation to the simultaneous solution of OCP was proposed by Biegler [3], where differential equations are discretized using orthogonal collocation with Lagrange polynomials; the DAE is then transformed into a set of equality constraints and solved as an NLP. Afterwards, Cuthrell and Biegler [7,8] employed finite elements to improve the approximation of non-smooth profiles. The approximation error was successfully minimized in [22] with a direct error enforcement strategy.

Kurtanjek [12] employed orthogonal polynomials to approximate the state and control profiles and penalty functions to satisfy the constraints on the state and control variables and maximized the Hamiltonian at the collocation points, which is possible due to the use of substrate concentration as control variable rather than the feed rate. Optimal profiles for temperature and feed flow rates are estimated for different orders of approximation polynomial, i.e. the number of interior collocation points. The author concluded that the objective function value and the control profiles converge with the increment in the order, and that a low order ($N = 5$) is sufficient to obtain a satisfactory solution. A four-variable model for a fermentative process was used and the smooth transitions in the profiles avoided the need for finite elements.

The present work aims to develop and to evaluate a mathematical programming technique based on the method of orthogonal collocation with finite elements for the simultaneous optimization of dynamic processes, taking two fed-batch biochemical reactors as case studies. Previous works [7,12] employed orthogonal collocation to optimize the operation of fed-batch bioprocesses but no comparison of the methodology performance was made with other approaches. Additionally, complex models have not been addressed and neither the evaluation of the accuracy of approximation at unconstrained points. The next section, the transformation from the OCP to an NLP and the control of approximation error are developed. Section 3 considers two OCPs; initially, a simplified model is employed to evaluate the methodology performance and later a complex problem, which concerns the optimization of polyhydroxyalkanoates (PHAs) production, is solved. Section 4 concludes the paper.

2. Methodology

2.1. Discretization and approximation by orthogonal collocation on finite elements

Consider the optimal control problem (OCP) that is stated as follows:

$$
\begin{aligned}
&\min_{u^1(t),\ldots,u^{\mathrm{NC}}(t),t} \Phi[z^1(t),\ldots,z^{\mathrm{NS}}(t),u^1(t),\ldots,u^{\mathrm{NC}}(t),t] \\
&\text{s.t.}\quad z^j(t) = F^j[z^1(t),\ldots,z^{\mathrm{NS}}(t),u^1(t),\ldots,u^{\mathrm{NC}}(t),t], \qquad j=1,\ldots,\mathrm{NS} \\
&\qquad h[z^1(t),\ldots,z^{\mathrm{NS}}(t),u^1(t),\ldots,u^{\mathrm{NC}}(t),t] = 0 \\
&\qquad g[z^1(t),\ldots,z^{\mathrm{NS}}(t),u^1(t),\ldots,u^{\mathrm{NC}}(t),t] \le 0 \\
&\qquad z^j(0) = Z_0^j, \qquad j=1,\ldots,\mathrm{NS} \\
&\qquad Z^{j\mathrm{L}} \le z^j(t) \le Z^{j\mathrm{U}}, \qquad j=1,\ldots,\mathrm{NS} \\
&\qquad U^{m\mathrm{L}} \le u^m(t) \le U^{m\mathrm{U}}, \qquad m=1,\ldots,\mathrm{NC}
\end{aligned}
$$

where Φ is the objective function, $z^j(t)$ are state variable profiles, Z_0^j are initial values for state variables, $\dot{Z}^j(t)$ are the set of differential-algebraic equations (DAEs) that define the dynamics of the process, $u^m(t)$ are control variable profiles, h and g are vectors of equality and inequality constraints, NS and NC are the number of state and control variables, and finally ($U^{m\mathrm{L}}$, $U^{m\mathrm{U}}$) and ($Z^{j\mathrm{L}}$, $Z^{j\mathrm{U}}$) are lower and upper bounds for control and state profiles, defined by the operating limits.

To convert the OCP into an NLP, the DAEs are discretized by orthogonal collocation on finite elements. The processing time ($t \subset [0, t_f]$) is divided into NE finite elements and normalized in each one; the element limits admit discontinuities on the profiles (Fig. 1); and the relationship between

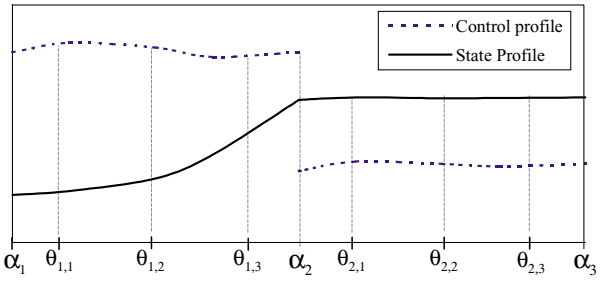

Fig. 1. Discontinuities and non-differentiable points at the element limits.

process time and normalized time ($\theta \subset [0, 1]$) is as follows:

$$t_{n,i} = [\alpha_n + \theta_i(\alpha_{n+1} - \alpha_n)]t_f, \quad n = 1, \ldots, \mathrm{NE},\ i = 1, \ldots, K \tag{1}$$

where α_n are element limits that are included as additional degrees of freedom, and θ_i are collocation points that correspond to the roots of the orthogonal Legendre polynomial (which belongs to the class of Jacobi polynomials). Rice and Do [19] showed that the choice of the collocation points is critical and concluded that Jacobi polynomials are particularly attractive. Note that a more compact notation is used in place of that in [7,8].

The Lagrange polynomials for the approximation of state and control variables are:

$$z^j_{n,K+1}(\theta) = \sum_{i=0}^{K} z^j_{n,i}\varphi_i(\theta), \quad j = 1, \ldots, \mathrm{NS},\ n = 1, \ldots, \mathrm{NE} \tag{2a}$$

where

$$\varphi_i(\theta) = \prod_{k=0, k\neq i}^{K} \frac{\theta - \theta_k}{\theta_i - \theta_k}, \quad i = 0, \ldots, K \tag{2b}$$

$$u^m_{n,K}(\theta) = \sum_{i=1}^{K} u^m_{n,i}\psi_i(\theta), \quad m = 1, \ldots, \mathrm{NC},\ n = 1, \ldots, \mathrm{NE} \tag{3a}$$

where

$$\psi_i(\theta) = \prod_{k=1, k\neq i}^{K} \frac{\theta - \theta_k}{\theta_i - \theta_k}, \quad i = 1, \ldots, K \tag{3b}$$

Thus, every state profile is approximated by $(K+1)$th order polynomials (one in every element), and the control profiles by Kth order polynomials, allowing to represent discontinuities in control and non-differentiabilities in states profiles, as shown in Fig. 1.

In (2a) and (3a), $z^j_{n,i}$ and $u^m_{n,i}$ are polynomial coefficients, which correspond to the optimization variables. Functions φ_i and ψ_i (polynomial building blocks) depend only on the location of the collocation points. With the polynomial approximation, the jth DAE can be written in the form of a set of residual equations, one for every collocation point i and element n, as follows:

$$R^j(t_{n,i}) = \frac{\mathrm{d}z^j_{n,K+1}(\theta_i)}{\mathrm{d}\theta}\frac{\mathrm{d}\theta}{\mathrm{d}t} - F^j[z^1_{n,i}, \ldots, z^{\mathrm{NS}}_{n,i}, u^1_{n,i}, \ldots, u^{\mathrm{NC}}_{n,i}, t_{n,i}] = 0, \quad j = 1, \ldots, \mathrm{NS},\ n = 1, \ldots, \mathrm{NE},\ i = 1, \ldots, K \tag{4}$$

Rice and Do [19] proposed a vectorial notation for the derivatives of the Lagrange polynomials at the collocation points:

$$\frac{\mathrm{d}z^j_{n,K+1}(\theta)}{\mathrm{d}\theta} = \underline{A}\cdot z^j_n, \quad z^j_n = [z^j_n(\theta_0), z^j_n(\theta_1), \ldots, z^j_n(\theta_K)]^{\mathrm{T}}, \quad j = 1, \ldots, \mathrm{NS},\ n = 1, \ldots, \mathrm{NE} \tag{5}$$

In (5), $\underline{A}$ is a square matrix of dimension $K+1$ that is calculated from θ_i, and z^j_n the vector of values for the jth variable in element n. From (1) yields:

$$\frac{\mathrm{d}\theta_i}{\mathrm{d}t_{n,i}} = \frac{1}{t_f(\alpha_{n+1} - \alpha_n)} \tag{6}$$

Substitution of (5) and (6) into (4) yields a set of algebraic residual equations:

$$R^j(t_{n,i}) = \underline{A}\cdot z^j_n \frac{1}{t_f(\alpha_{n+1} - \alpha_n)} - F^j[z^1_{n,i}, \ldots, z^{\mathrm{NS}}_{n,i}, u^1_{n,i}, \ldots, u^{\mathrm{NC}}_{n,i}, t_{n,i}] = 0, \quad j = 1, \ldots, \mathrm{NS},\ n = 1, \ldots, \mathrm{NE},\ i = 1, \ldots, K \tag{7}$$

Other constraints must be added to guarantee the continuity of the state profiles at the element limits. Therefore, the polynomials are extrapolated to generate the initial point of the next element. With the orthogonal collocation approach, the OCP turns into an NLP problem:

$$\begin{aligned}
&\min_{u^m_{n,i}, z^j_{n,i}, \alpha_n} \Phi[z^j_{n,i}, u_{n,i}, t_f]\\
&\text{s.t. } R^j(t_{n,i}) = \underline{A}\cdot z^j_n \frac{1}{t_f(\alpha_{n+1} - \alpha_n)} - F^j[z^1_{n,i}, \ldots, z^{\mathrm{NS}}_{n,i}, u^1_{n,i}, \ldots, u^{\mathrm{NC}}_{n,i}, t_{n,i}] = 0\\
&h[z^1_{n,i}, \ldots, z^{\mathrm{NS}}_{n,i}, u^1_{n,i}, \ldots, u^{\mathrm{NC}}_{n,i}] = 0\\
&g[z^1_{n,i}, \ldots, z^{\mathrm{NS}}_{n,i}, u^1_{n,i}, \ldots, u^{\mathrm{NC}}_{n,i}] \leq 0\\
&z^j_{1,0} = Z^j_0\\
&z^j_{n,0} = z^j_{n-1,K+1} = \textstyle\sum_{i=0}^{K} z^j_{n-1,i}\varphi_i(\theta = 1), \quad n = 2, \ldots, \mathrm{NE}\\
&u^m_{n,0} = \textstyle\sum_{i=1}^{K} u^m_{n,i}\psi_i(\theta = 0), \quad n = 2, \ldots, \mathrm{NE}\\
&u^m_{n,K+1} = \textstyle\sum_{i=1}^{K} u^m_{n,i}\psi_i(\theta = 1)\\
&U^{m\mathrm{L}} \leq u^m_{n,i} \leq U^{m\mathrm{U}}, \quad i = 0, \ldots, K+1\\
&Z^{j\mathrm{L}} \leq z^j_{n,i} \leq Z^{j\mathrm{U}}
\end{aligned}$$

In NLP unless specified, the indexes are denoted by $j = 1, \ldots, \mathrm{NS}$; $m = 1, \ldots, \mathrm{NC}$; $n = 1, \ldots, \mathrm{NE}$ and $i = 1, \ldots, K$. The optimization variables are the polynomial coefficients ($z^j_{n,i}$, $u^m_{n,i}$) and the element limits (α_n) that predict non-smooth points on the profiles.

2.2. Control of the approximation error by direct enforcement

The polynomial approximation of the state profiles brings errors to the DAE solution. Vasantharajan and Biegler [22] present two strategies for error control: equidistribution and direct enforcement. The former reformulates the problem to find a solution with alternation in error sign, whereas in the latter constraints are added to reduce the error in non-collocation (nc) points. The second approach is more straightforward and allows a direct control of the approximation error value, but it is important to choose a sufficient number of elements to satisfy the error tolerance and to obtain feasible solutions. Nevertheless, both formulations provide criteria for defining the location of the element limits.

In this work, the direct enforcement is the selected strategy. Denoting the nc points as θ_{nc}, added constraints for each one are as follows:

$$-\xi \leq CR^j(t_{n,\mathrm{nc}}) \leq \xi, \quad j = 1, \ldots, \mathrm{NS},\ n = 1, \ldots, \mathrm{NE} \tag{8}$$

where ξ is the tolerance on the absolute error, $R^j(t_{n,\mathrm{nc}})$ the residue on jth variable estimate at time $t_{n,\mathrm{nc}}$. The constant C (which penalizes the error at nc points by their proximity to the collocation points) is calculated for each point nc as follows:

$$C = \frac{1}{A}\int_0^{\theta_{\mathrm{nc}}} \prod_{i=1}^{K} (s - \theta_i)\,\mathrm{d}s, \quad A = \prod_{i=1}^{K} (\theta_{\mathrm{nc}} - \theta_i) \tag{9}$$

Approximation residues at nc points are obtained by differentiating the interpolation polynomials and computing the analytical derivatives (DAE) with the values of state and control profiles from (2a) and (3a) as follows:

$$R^j(t_{n,\mathrm{nc}}) = \frac{\mathrm{d}z^j_{n,K+1}(\theta_{\mathrm{nc}})}{\mathrm{d}\theta}\frac{\mathrm{d}\theta}{\mathrm{d}t} - F^j[z^1_{n,K+1}(\theta_{\mathrm{nc}}), \ldots, z^{\mathrm{NS}}_{n,K+1}(\theta_{\mathrm{nc}}), u^1_{n,K}(\theta_{\mathrm{nc}}), \ldots, u^{\mathrm{NC}}_{n,K}(\theta_{\mathrm{nc}}), t_{n,\mathrm{nc}}],$$
$$j = 1, \ldots, \mathrm{NS},\ n = 1, \ldots, \mathrm{NE} \tag{10}$$

Therefore, constraints (8) and (10) must be added to NLP for each nc point, the errors (approximation residues) at nc points characterize the approximation quality and are considered as a basis for the selection of the number of finite elements and collocation points for the approximation.

3. Application examples

This section presents two application examples of orthogonal collocation for the optimization of dynamic bioprocesses. The first one is a simplified model for the penicillin biosynthesis [8], which was chosen due to the fact that it has been addressed by several approaches, thus allowing the assessment of the performance of the collocation approach. The second problem deals with a model for the fermentative production of PHAs [10], which is a complex model with multiple control variables that was not completely solved by a sequential approach [17]. Both examples were solved on a Pentium II 450 MHz personal computer running GAMS 2.5 [4] as modeling environment and CONOPT2 [9], that is an implementation of the generalized reduced gradient method.

3.1. The penicillin biosynthesis problem

The optimal control problem for penicillin biosynthesis has been solved by various approaches: analytically [13], by dynamic programming [14] and by an evolutionary approach (EA) [20], which only shows the suggested control profile. The process is modeled by four differential equations on the following states: volume (V), concentrations of biomass (X), product (P) and substrate (S). To allow the comparison among the three approaches, the substrate feed rate (U) is maintained as the control variable, and the feed concentration is constant (S_{F}). The problem is defined by (OCP1) as follows:

$$\min_{U(t),t_f} \Phi = -P(t_f)V(t_f)$$

$$\text{s.t. } \dot{X}(t) = \mu(X,S)X - \left(\frac{X}{S_{\mathrm{F}}V}\right)U$$

$$\dot{P}(t) = \rho(S)X - K_{\mathrm{deg}}P - \left(\frac{P}{S_{\mathrm{F}}V}\right)U$$

$$\dot{S}(t) = -\mu(X,S)\left(\frac{X}{Y_{X/S}}\right) - \rho(S)\left(\frac{X}{Y_{P/S}}\right) - \left(\frac{m_S S}{K_m + S}\right)X + \left(1 - \frac{S}{S_{\mathrm{F}}}\right)\frac{U}{V}$$

$$\dot{V}(t) = \frac{U}{S_{\mathrm{F}}}$$

$$\mu(X,S) = \mu_{\max}\left(\frac{S}{K_X X + S}\right)$$

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

$$X^{\mathrm{L}} \leq X(t) \leq X^{\mathrm{U}}$$

$$S^{\mathrm{L}} \leq S(t) \leq S^{\mathrm{U}}$$

$$V^{\mathrm{L}} \leq V(t) \leq V^{\mathrm{U}}$$

$$U^{\mathrm{L}} \leq U(t) \leq U^{\mathrm{U}}$$

$$t^{\mathrm{L}} \leq t_f \leq t^{\mathrm{U}}$$

Table 1
Bounds and initial variable values for penicillin biosynthesis

Variable	Bounds		Initial value
	Lower	Upper	
X (g/l)	0	40	1.5
P (g/l)	0	–	0.0
S (g/l)	0	100	0.0
V (l)	0	10	7.0
U (g/h)	0	50	–
t_f (h)	72	200	–

where $\mu(X, S)$ is the specific biomass growth rate (h^{-1}) and $\rho(S)$ the specific penicillin production rate (g P/g X h). Bounds and initial variable values are shown in Table 1, whereas parameter definitions and values are in Table 2.

The number of collocation points is an important parameter to attain satisfactory approximation. Cuthrell and Biegler [8] demonstrated that the profiles can be approximated with suitable accuracy using low-order polynomials (e.g. $K+1 < 5$). Moreover, Riascos and Pinto [18] suggested that four collocation points are enough for each element, that good approximation is generated employing two finite elements, and that error control is need to obtain satisfactory results. An important result from our previous work is that satisfactory approximation can only be attained with finite elements and error control, even with the use of polynomials of high order ($K = 20$). Moreover, it was observed that the percent error (Eq. (11)) is more suitable than the absolute error (Eq. (10)) to evaluate the approximation, and that a satisfactory approximation is attained for percent error tolerance values of 1%.

In [8] and [18] it was observed that the problem is relatively insensitive to the initial part of the control profile, i.e. 0–30 h. Furthermore, it is suggested that the optimal control profile before the singular arc may be non-unique; hence, this part is not reproducible.

The optimal profiles obtained by each methodology are presented in Fig. 2. The analytical solution suggests a maximum flow rate period (0–11.2 h), a batch period (11.2–28.8 h) and a singular flow rate period (28.8 h-t_f) for the control profile. Dynamic programming (IDP) and EA generate control profiles with large differences for the two initial periods compared to the analytical solution, as well as the proposed methodology, but these strategies did not provide a good estimate for the discontinuity of the control profiles (Table 3 and Fig. 2b). The value of the process end

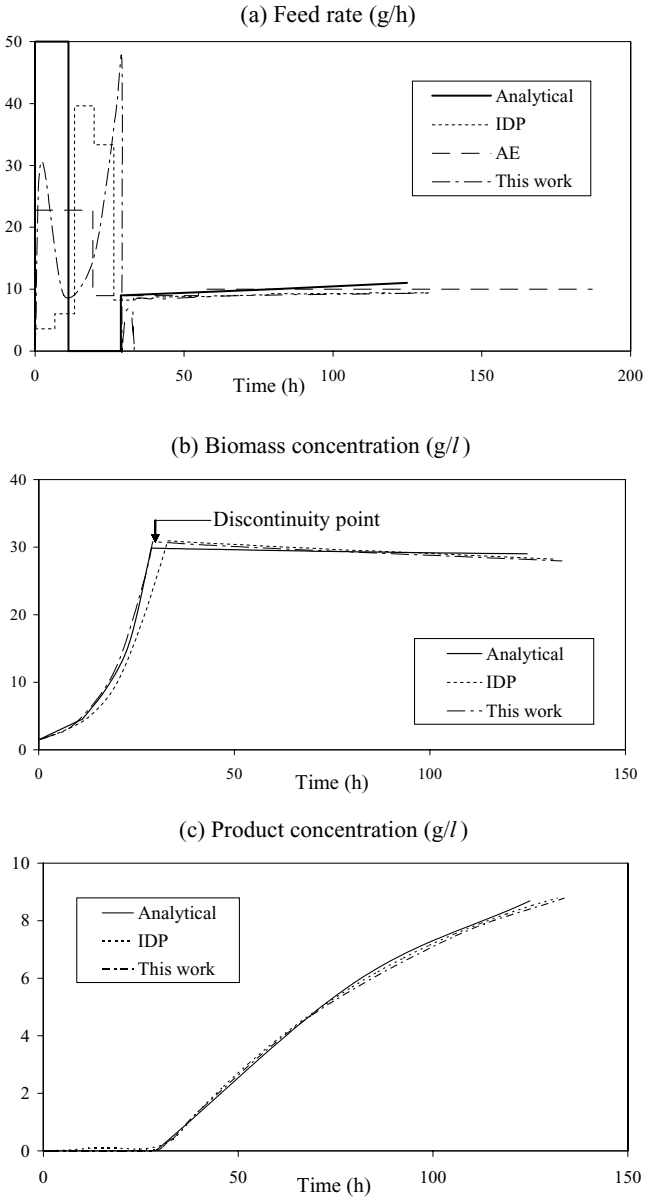

Fig. 2. Optimal profiles for penicillin biosynthesis.

Table 2
Parameters of penicillin biosynthesis model

Parameter	Definition	Value
μ_{max}	Maximum specific biomass growth rate (h^{-1})	0.11
ρ_{max}	Maximum specific production rate (g P/g X h)	0.0055
K_X	Saturation parameter for biomass growth (g S/g X)	0.006
K_P	Saturation parameter for production (g S/l)	0.0001
K_{in}	Inhibition parameter for production (g S/l)	0.1
K_{deg}	Product degradation rate (h^{-1})	0.01
K_m	Saturation parameter for maintenance consumption (g S/l)	0.0001
m_S	Maintenance consumption rate (g S/g X h)	0.029
$Y_{X/S}$	Yield factor for substrate to biomass (g X/g S)	0.47
$Y_{P/S}$	Yield factor for substrate to product (g P/g S)	1.2
S_F	Feed concentration (g S/l)	500

Table 3
Results for penicillin biosynthesis

Methodology	Discontinuities (h)	Objective function (g P)	t_f (h)
Analytical	11.2, 28.8	86.9	124.9
IDP	33.0	87.9	132.0
EA	–	85.4	187.1
This work	29.1	87.9	133.8

time is slightly better for IDP, whereas orthogonal collocation provides a better estimation of the time in which the discontinuity takes place.

The variance in control trajectories, for all methods, in the first 30 h is due to model insensitivity. During this period the control condition is to have a sufficient substrate concentration to support the biomass growth at maximum specific rate. Moreover, in the end of this period a small substrate concentration is necessary to bring the penicillin production to the next period. Thus, the first discontinuity of the control profile (11.2 h) is not reproducible.

For biomass concentration, collocation generates better results. A more thorough evaluation of the impact of the number of collocation points and finite elements, and error tolerance on the algorithm performance and solution quality; and a comparison with a sequential approach for this application example are shown in [18]. Finally, the authors studied the productivity as objective function, so to maximize product in the smallest possible time.

3.2. Model for the fermentative production of PHAs

The model for optimizing the production of poly(β-hydroxybutyrate) (PHB) and poly(β-hydroxybutyrate-co-β-hydroxyvalerate) (P(HB-co-HV)) by *Alcaligenes eutrophus* (shown in Appendix A) is based on the model initially proposed by Ferraz et al. [10], and updated from the experimental results of Piccoli [17]. The model has 11 states and from 2 to 4 control profiles. Due to the structure of the model, the natural control variables, i.e. the feed rates, are selected as control variables since it is not possible to simplify the problem solution by the choice of other control variables (e.g., singular to non-singular). Therefore, the optimization problem can be written in the OCP form of Section 2.1.

3.3. Optimization of PHB production

The optimization of PHB production employs two control variables, as in [17]. The case studies are defined in Table 4, results and statistics are shown in Table 5 and percent approximation errors in state variables at nc points are illustrated in Table 6. Values in Table 6 represent the average and maximum percent errors in each profile, which are calculated as follows:

$$PR^j(t_{n,\mathrm{nc}}) = 100\frac{R^j(t_{n,\mathrm{nc}})}{F^j[z^1_{n,K+1}(\theta_{\mathrm{nc}}),\ldots,z^{\mathrm{NS}}_{n,K+1}(\theta_{\mathrm{nc}}),u^1_{n,K}(\theta_{\mathrm{nc}}),\ldots,u^{\mathrm{NC}}_{n,K}(\theta_{\mathrm{nc}}),t_{n,\mathrm{nc}}]},\quad j=1,\ldots,\mathrm{NS},\ n=1,\ldots,\mathrm{NE} \tag{11}$$

In (11), $R^j(t_{n,\mathrm{nc}})$ denotes the residue on jth variable estimate at time $t_{n,\mathrm{nc}}$. In Table 4, three groups of case studies are presented. The first one (PHB1–PHB4) that handles two control variables aims at comparing the simultaneous with the sequential approach and selects the same control variables as those from [17]. As for the production of P(HB-co-HV), two other groups of case studies are selected. The first (PHV1 and PHV2) relaxes the simplification imposed by Piccoli [17], for which the sugar concentration values were fixed in order to reduce the number of control variables, by adding the two substrates separately. Finally, in cases PHV3 and PHV4 the strategy is taken to the limit by considering all possible control variables.

Table 4
Case features for PHAs production

Case	Control variables	No. of elements/no. of points	Error control
PHB1	2 (F_1, F_2)	3/4	No
PHB2	2 (F_1, F_2)	3/4	Yes
PHB3	2 (F_1, F_2)	3/5	Yes
PHB4	2 (F_1, F_2)	4/4	Yes
PHV1	3 (F_1, F_2, F_3)	4/4	Yes
PHV2	3 (F_1, F_2, F_3)	4/4	Yes (iterative)
PHV3	4 (F_{1f}, F_{1g}, F_2, F_3)	4/4	Yes (iterative)
PHV4	4 (F_{1f}, F_{1g}, F_2, F_3)	4/4	Yes (iterative)

Table 5
Results and statistics for PHAs production

Case	Statistics		Results	
	Iterations	CPU time (min:s)	t_f (h)	Φ (g/l h)
Piccoli			32.45	3.28
PHB1	759	0:47	28.8	3.79
PHB2	657	1:31	28.2	2.43
PHB3	1579	4:17	29.0	3.46
PHB4	1405	6:11	29.7	3.62
Piccoli			35.0	2.56
PHV1	3786	13:50	35.0	2.84
PHV2	4990	14:10	33.5	2.98
PHV3	8133	30:26	34.7	2.92
PHV4	9450	20:34	32.7	2.99

Case PHB1 was solved without error control and clearly requires improvement of the approximation. The results and error values for cases PHB2–PHB4 show that the number of elements is very important to obtain a satisfactory solution, and on the other hand that a large number of collocation points in every element is not required.

To verify the efficiency of the error control strategy, the approximation error was calculated (no constrained) at two additional points in every element (verification points). These error values (Table 7) suggest that the approximation is improved over the complete profiles.

In case PHB4, the relative errors were sufficiently small and the productivity was 10% higher than in [17]; the state and control profiles are shown in Fig. 3.

Table 6
Errors in nc points for PHB production

Case	Average and maximum relative errors in each profile							
	X_r	P_1	S_1	S_2	S_3	S_4	E_1	E_2
PHB1	6.7×10^3	8.3×10^3	118	47	4.1	9.6	4.7	0.4
	1.1×10^4	1.2×10^4	214	100	6.1	10.1	7.0	0.6
PHB2	0.7	1.2	0.5	0.7	0.5	7.3	0.5	0.1
	1.5	4.7	1.4	1.5	1.8	9.1	1.9	0.4
PHB3	1.4	0.7	1.1	1.0	1.6	6.1	8.4	22.6
	2.9	2.5	2.3	2.3	5.1	6.1	41.3	109.7
PHB4	0.2	0.1	0.3	0.3	0.3	3.2	0.5	0.1
	0.6	0.5	0.8	0.8	0.8	3.6	1.9	0.5

3.4. Optimization of P(HB-co-HV) production

This problem involves three control variables. In [17], due to model size and complexity, the sequential algorithm was unable to solve it. Hence, the sugar concentration values were fixed in order to reduce the number of control variables and problem complexity. In this work, the original problem is solved for all control variables and two cases are considered (see Table 4). Case PHV1 is similar to PHB4, and case PHV2 incorporates a procedure to auto-correct the tolerance values, which starts by solving the optimization problem with non-rigorous tolerances; then, it reduces the values on variables that show unacceptable approximation, and solves the problem from the previous solution; the procedure is repeated until the solution satisfies the required relative errors on all variables.

The simultaneous optimization of this complex model is satisfactory and the computed productivity is 16% higher than in the sequential optimization approach of Piccoli, with a reasonable computational effort (Table 5). This suggests that by freeing the sugar concentrations, it becomes possible to achieve a better operating policy (with higher productivity).

Errors in nc points (Table 8) are small for both cases, and the CPU times indicate that the computational effort does not increase significantly when the tolerance auto-correction is implemented. Fig. 4 presents the state profiles for case PHV2, from which it can be observed that, as well as in the production of PHB, the rate of biomass growth is improved and the production phase is anticipated.

In two other cases, fructose and glucose substrates were fed independently. This proposed strategy gives rise to an even more complex problem. In run PHV3, the starting point

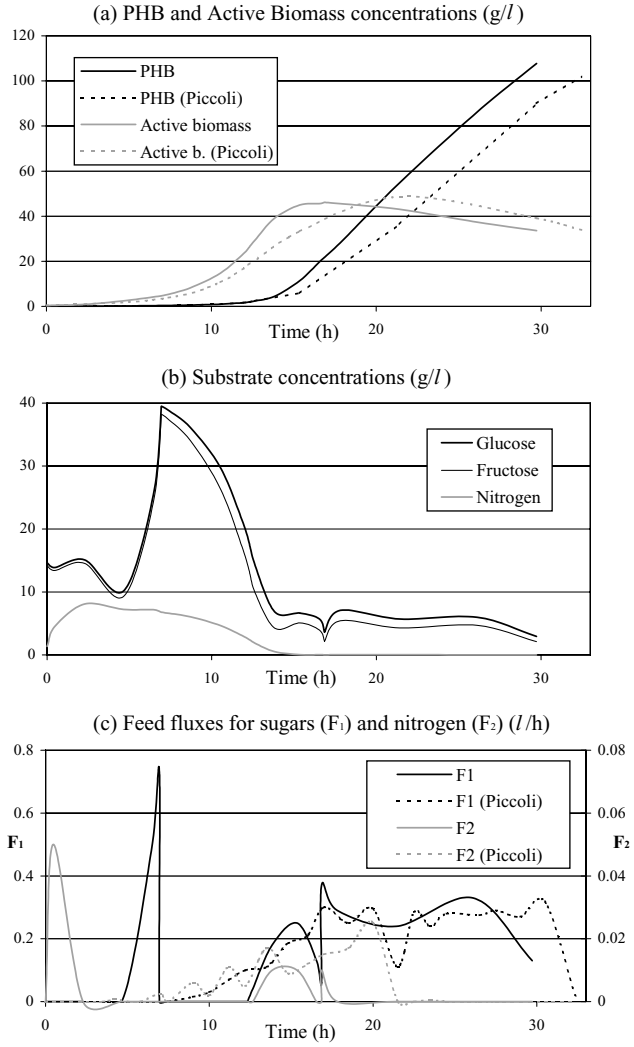

Fig. 3. Optimal state and control profiles for PHB production.

Table 7
Errors in verification points for PHB production

Case	Average and maximum relative errors in each profile							
	X_r	P_1	S_1	S_2	S_3	S_4	E_1	E_2
PHB2	1.1	2.7	0.3	0.3	0.2	5.8	0.8	0.3
	4.8	8.7	0.6	0.6	0.6	11.4	3.9	1.3
PHB3	8.2	37.1	29.0	22.5	5.5	195	4.5	1.2
	31.2	175	136	105	17.0	531	17.7	4.6
PHB4	0.2	0.2	0.1	0.2	0.1	3.4	0.6	0.2
	0.7	0.4	0.4	0.4	0.3	11.4	3.9	1.3

Table 8
Errors in nc points for P(HB-co-HV)

Case	Average and maximum relative errors in every profile									
	X_r	P_1	P_2	S_1	S_2	S_3	S_4	S_5	E_1	E_2
PHV1	0.3	0.2	0.3	0.4	0.5	0.1	0.6	0.5	0.4	0.1
	0.7	0.3	0.5	0.9	0.9	0.4	0.6	0.5	1.4	0.2
PHV2	0.1	0.2	0.5	0.2	0.3	0.1	0.9	0.9	0.4	0.1
	0.3	0.4	0.8	0.6	0.7	0.2	0.9	1.0	2.0	0.4
PHV3	0.2	0.2	0.4	0.1	0.2	0.2	0.9	0.9	0.3	0.1
	0.6	0.8	0.9	0.1	0.7	0.4	0.9	0.9	2.0	0.3
PHV4	0.3	0.1	0.3	0.2	0.2	0.2	0.8	0.9	0.6	0.1
	0.8	0.7	0.9	1.0	0.7	0.5	0.8	0.9	2.0	0.4

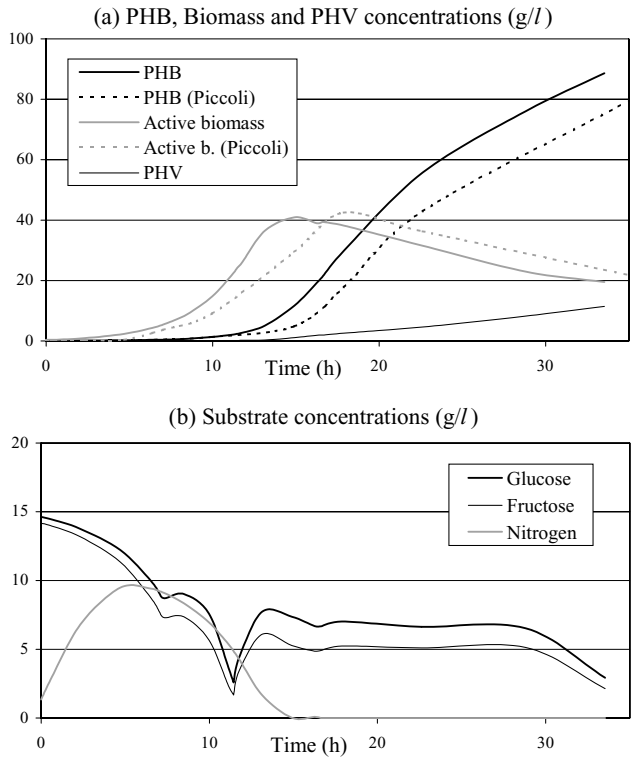

Fig. 4. Optimal state profiles for P(HB-co-HV) production.

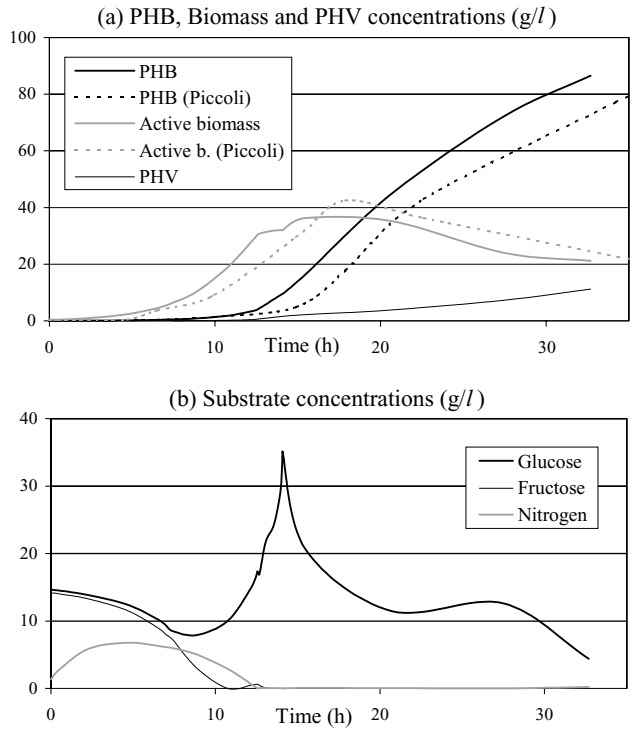

Fig. 5. Optimal state profiles for P(HB-co-HV) production with four control variables.

for the optimization is the result from a simulation with constant flow rates, as all previous cases; whereas in run PHV4 the optimization started from the result of case PHV2. In both runs the iterative error control procedure was applied.

In case PHV4, CPU time and number of iterations include the solution of case PHV2 for the generation of the initial point. From Table 5, it can be noted that despite the significant increase in the number of iterations for case PHV4, CPU time reduces when compared to that of run PHV3.

Fig. 5 presents the state profiles obtained in case PHV4. The biomass and product profiles are similar to those obtained in case PHV2, whereas sugar concentrations present considerable differences when compared to those of run PHV2. An interesting feature is that the glucose and fructose concentration profiles have different forms (Fig. 5b).

4. Conclusions

A simultaneous approach for solving OCPs was investigated and applied to biotechnological processes that operate in fed-batch mode. The impossibility to estimate discontinuities in the control profile with global collocation motivates the incorporation of finite elements. The approximation of the control and state profiles by orthogonal polynomials brings errors, which are satisfactory reduced when an error control strategy is used, with a small increment in computational effort. The computed errors at unconstrained points suggest that error control improves the approximation over the entire profiles.

Two case studies were developed. The first one relied on a simplified model previously solved by analytical approach, IDP and an evolutionary algorithm; the results show that orthogonal collocation founds the discontinuity points and identifies singular arcs in the optimal control profiles, doing a better estimation of state profiles. The second case study is based on a complex model for the production of PHAs, which was solved for three scenarios, composed of two, three and four control variables. The first has been previously solved with a sequential strategy that was, however, unable to deal with the second; whereas to solve the last, a sequential strategy is unconceivable. Despite the fact that small approximation errors are originated, results show that the relative errors for the simultaneous approach are acceptable, that the number of elements is very important to obtain a satisfactory solution, and that a large number of collocation points in every element is not needed.

The optimization of P(HB-co-HV) production is satisfactory and shows that this methodology efficiently solves dynamic problems with several control variables that are unsolvable by sequential strategies. The second solved scenario shows that productivity improvements can be obtained by freeing control variables, whereas the increase in productivity achieved from manipulating independently sugar substrates (third scenario) is marginal and probably does not substantiate its practical implementation.

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Appendix A. PHAs production model

This appendix describes the dynamic model for the production of PHAs from *Alcaligenes eutrophus*. This model was partially proposed in [10] and further updated and validated in [17]. The main process features and assumptions represented in the model are the following:

- Glucose, fructose and propionic acid are limiting and inhibitory substrates in biomass and PHB generation, whereas in PHV production propionic acid is the only limiting and inhibitory substrate.
- Nitrogen is a limiting substrate in biomass generation, because it takes part in protein synthesis.
- Oxygen is limiting in biomass generation, and limiting and inhibitory in polymer production.
- Accumulation of polymers may inhibit their production.
- Biomass growth shows a *lag* phase.

The model is composed by the following set of equations:

$$\frac{dV}{dt} = F \tag{A.1}$$

$$F = F_1 + F_2 + F_3 - \text{Evap} \tag{A.2}$$

$$\frac{dX_r}{dt} = -\frac{F}{V}X_r + R_1 v_1 \tag{A.3}$$

$$R_1 = \mu_1 E_1 \left[\frac{t^{K_0}}{t^{K_0} + K_1}\right]\left[\frac{S_C}{K_{1C} + S_C + (S_C^2/K_{1Ci})}\right] \times \left[\frac{S_3}{K_{13} + S_3}\right]\left[\frac{S_4}{K_{14} + S_4}\right][\exp(-K_{15i}S_5^{n15i})]X_r \tag{A.4}$$

$$S_C = S_1 + S_2 + S_5 \tag{A.5}$$

$$\mu_1 = \frac{\mu_{1,\max}(\mu_{1,\max} + \beta_1)}{u_1^*\alpha_1 + \alpha_1^*} \tag{A.6}$$

$$\frac{dP_1}{dt} = -\frac{F}{V}P_1 + R_2 v_2 \tag{A.7}$$

$$R_2 = \mu_2 E_2 \left[\frac{S_C}{K_{2C} + S_C + (S_C^2/K_{2Ci})}\right] \times \left[\frac{S_4}{K_{24} + S_4 + (S_4^{n24}/(K_{24i} + S_4))}\right] \times \left[\frac{1}{(K_P((P_1 + P_2)/X_t))^{np} + 1}\right] \times [\exp(-K_{25i}S_5^{n25i})]X_r \tag{A.8}$$

$$\mu_2 = \frac{\mu_{2,\max}(\mu_{2,\max} + \beta_2)}{\alpha_2 + \alpha_2^*} \tag{A.9}$$

$$\frac{dP_2}{dt} = -\frac{F}{V}P_2 + R_3 v_2 \tag{A.10}$$

$$R_3 = \mu_3 E_2 \left[\frac{S_5}{K_{35} + S_5 + (S_5^2/K_{35i})}\right] \times \left[\frac{S_4}{K_{34} + S_4 + (S_4^{n34}/(K_{34i} + S_4))}\right] \times \left[\frac{1}{K_P((P_1 + P_2)/X_t)^{np} + 1}\right]X_r \tag{A.11}$$

$$\mu_3 = \frac{\mu_{3,\max}(\mu_{3,\max} + \beta_2)}{\alpha_2 + \alpha_2^*} \tag{A.12}$$

$$X_t = X_r + P_1 + P_2 \tag{A.13}$$

$$\frac{dS_1}{dt} = \frac{F_1}{V}S_{1e} - \frac{F}{V}S_1 - \frac{1}{Y_{X_rS_1}}R_1\frac{S_1}{S_C}v_1 - \frac{1}{Y_{P_1S_1}}R_2\frac{S_1}{S_C}v_2 - \frac{1}{Y_{P_2S_1}}R_3\frac{S_1}{S_C}v_2 - \frac{m_{S_1}S_1}{K_{m_{S_1}} + S_1}X_r \tag{A.14}$$

$$\frac{dS_2}{dt} = \frac{F_1}{V}S_{2e} - \frac{F}{V}S_2 - \frac{1}{Y_{X_rS_2}}R_1\frac{S_2}{S_C}v_1 - \frac{1}{Y_{P_1S_2}}R_2\frac{S_2}{S_C}v_2 - \frac{1}{Y_{P_2S_2}}R_3\frac{S_2}{S_C}v_2 - \frac{m_{S_2}S_2}{K_{m_{S_2}} + S_2}X_r \tag{A.15}$$

$$\frac{dS_3}{dt} = \frac{F_2}{V}S_{3e} - \frac{F}{V}S_3 - \frac{1}{Y_{X_rS_3}}R_1 v_1 - \frac{m_{S_3}S_3}{K_{m_{S_3}} + S_3}X_r \tag{A.16}$$

$$\frac{dS_4}{dt} = \frac{F_1+F_2+F_3}{V}S_4^* - \frac{F}{V}S_4 - \frac{1}{Y_{X_rS_4}}R_1 v_1 - \frac{1}{Y_{P_1S_4}}R_2 v_2 - \frac{1}{Y_{P_2S_4}}R_3 v_2 - \frac{m_{S_4}S_4}{K_{m_{S_4}} + S_4}X_r + k_L a(S_4^* - S_4) \tag{A.17}$$

$$\frac{dS_5}{dt} = \frac{F_3}{V}S_{5e} - \frac{F}{V}S_5 - \frac{1}{Y_{X_rS_5}}R_1\frac{S_5}{S_C}v_1 - \frac{1}{Y_{P_1S_5}}R_2\frac{S_5}{S_C}v_2 - \frac{1}{Y_{P_2S_5}}R_3 v_2 - \frac{m_{S_5}S_5}{K_{m_{S_5}} + S_5}X_r \tag{A.18}$$

$$\frac{dE_1}{dt} = r_{E_1}u_1 - \beta_1 E_1 - \mu E_1 + \alpha_1^* \tag{A.19}$$

$$\frac{dE_2}{dt} = r_{E_2}u_2 - \beta_2 E_2 - \mu E_2 + \alpha_2^* \tag{A.20}$$

$$\mu = \frac{1}{X_r + P_1 + P_2}\left[\frac{dX_r}{dt} + \frac{dP_1}{dt} + \frac{dP_2}{dt}\right] \tag{A.21}$$

Table A.1
Variables of PHAs production model

	Description	Initial values
State variables		
V	Volume (l)	5.0
X_r	Active biomass concentration (g/l)	0.404
P_1	PHB concentration (g/l)	0.806
P_2	PHV concentration[a] (g/l)	0.0
S_1	Glucose concentration (g/l)	14.62
S_2	Fructose concentration (g/l)	14.16
S_3	Nitrogen concentration (g/l)	1.341
S_4	Oxygen dissolved concentration (mg/l)	7.0
S_5	Propionic acid concentration[a] (g/l)	0.0
E_1	Growth enzyme concentration (g/g)	0.027519
E_2	Accumulation enzyme concentration (g/g)	0.16353
Control variables		
F_1	Feed flow rate of sugars (l/h)	
F_{1g}, F_{1f}	Feed flow rates of glucose and fructose[b] (l/h)	
F_2	Feed flow rate of NH_4OH for pH control (l/h)	
F_3	Feed flow rate of propionic acid[a] (l/h)	
Auxiliary variables		
r_{E_1}, r_{E_2}	Specific rate of enzymes E_1 and E_2 synthesis (g/g h)	
u_1, u_2	Cybernetic variables for synthesis control of E_1 and E_2	
v_1, v_2	Cybernetic variables for activity control of E_1 and E_2	
X_t	Total biomass (g/l)	
R_1, R_2, R_3	Growth, PHB and PHV production rate (g/l h)	
μ_1, μ_2, μ_3	Specific growth, PHB and PHV production rate (g/g h)	
μ	Specific total biomass production rate (h^{-1})	
S_C	Total concentration of carbon sources (g/l)	
F	Total feed rate (l/h)	

[a] Variables for production of P(HB-co-HV) only.
[b] These fluxes replace F_1 in runs PHV3 and PHV4.

$$r_{E_1} = \frac{\alpha_1 S_3 S_C S_4}{(K^E_{13} + S_3)(K^E_{1C} + S_C)(K^E_{14} + S_4)} \quad (A.22)$$

$$r_{E_2} = \frac{\alpha_2 S_C S_4}{(K^E_{2C} + S_C)(K^E_{24} + S_4)} \quad (A.23)$$

$$u_1 = \frac{R_1}{R_1 + R_2}, \qquad u_2 = \frac{R_2}{R_1 + R_2} \quad (A.24)$$

$$v_1 = \frac{R_1}{\max_k(R_k)}, \qquad v_2 = \frac{R_2}{\max_k(R_k)} \quad (A.25)$$

Eqs. (A.1), (A.3), (A.7), (A.10) and (A.14)-(A.20) define the dynamics of the state variables and conform the DAE system; the other ones define the auxiliary variables, and are algebraic equality constraints into the OCP. The variables are given in Table A.1 and the operational and model parameters are given in Tables A.2 and A.3.

For cases PHV3 and PHV4, the feed flow rate of sugars (F_1) must be replaced and the Eqs. (A.2), (A.14), (A.15) and (A.17) are rewritten as:

$$F = F_{1g} + F_{1f} + F_2 + F_3 - \text{Evap} \quad (A.26)$$

$$\frac{dS_1}{dt} = \frac{F_{1g}}{V} S_{1e} - \frac{F}{V} S_1 - \frac{1}{Y_{X_r S_1}} R_1 \frac{S_1}{S_C} v_1 - \frac{1}{Y_{P_1 S_1}} R_2 \frac{S_1}{S_C} v_2 - \frac{1}{Y_{P_2 S_1}} R_3 \frac{S_1}{S_C} v_2 - \frac{m_{S_1} S_1}{K_{m_{S_1}} + S_1} X_r \quad (A.27)$$

$$\frac{dS_2}{dt} = \frac{F_{1f}}{V} S_{2e} - \frac{F}{V} S_2 - \frac{1}{Y_{X_r S_2}} R_1 \frac{S_2}{S_C} v_1 - \frac{1}{Y_{P_1 S_2}} R_2 \frac{S_2}{S_C} v_2 - \frac{1}{Y_{P_2 S_2}} R_3 \frac{S_2}{S_C} v_2 - \frac{m_{S_2} S_2}{K_{m_{S_2}} + S_2} X_r \quad (A.28)$$

Table A.2
Operational parameters for PHAs production

Parameter	Definition	PHB	PHV1, PHV2	PHV3, PHV4
S_{1e}	Glucose concentration in F_1 or F_{1g} (g/l)	300	400	700
S_{2e}	Fructose concentration in F_1 or F_{1f} (g/l)	300	400	700
S_{3e}	Nitrogen concentration in F_2 (g/l)	533.65	266.8	266.8
S_{5e}	Propionic acid concentration in F_3 (g/l)	0	120	120
$k_L a$	Oxygen volumetric transfer coefficient (h^{-1})	1600	1600	1600
Evap	Evaporation rate (l/h)	0	0	0

Table A.3
Parameters of PHAs production model

Parameter	Definition	Value
$Y_{P_1S_1}$	Stoichiometric factor for glucose to PHB conversion (g/g)	0.62991
$Y_{P_1S_2}$	Stoichiometric factor for fructose to PHB conversion (g/g)	0.56498
$Y_{P_1S_4}$	Stoichiometric factor for oxygen to PHB conversion (g/mg)	0.0013472
$Y_{P_1S_5}$	Stoichiometric factor for propionic acid to PHB conversion (g/g)	1.7714
$Y_{P_2S_1}$	Stoichiometric factor for glucose to PHV conversion (g/g)	0.66587
$Y_{P_2S_2}$	Stoichiometric factor for fructose to PHV conversion (g/g)	0.51778
$Y_{P_2S_4}$	Stoichiometric factor for oxygen to PHV conversion (g/mg)	0.00024102
$Y_{P_2S_5}$	Stoichiometric factor for propionic acid to PHV conversion (g/g)	0.6231
$Y_{X_rS_1}$	Yield factor for glucose to active biomass conversion (g/g)	0.6458
$Y_{X_rS_2}$	Yield factor for fructose to active biomass conversion (g/g)	0.52755
$Y_{X_rS_3}$	Yield factor for nitrogen to active biomass conversion (g/g)	4.8157
$Y_{X_rS_4}$	Yield factor for oxygen to active biomass conversion (g/g)	0.0014052
$Y_{X_rS_5}$	Yield factor for propionic acid to active biomass conversion (g/g)	0.26817
K_0	Lag phase parameter	5.168
K_1	Lag phase parameter	0.031658
K_{13}	Saturation parameter for growth rate by nitrogen (g/l)	0.030421
K_{14}	Saturation parameter for growth rate by oxygen (mg/l)	0.08115
K_{15i}	Inhibition parameter for growth rate by propionic acid	0.5
K_{1C}	Saturation parameter for growth rate by carbon (g/l)	0.18824
K_{1Ci}	Inhibition parameter for growth rate by carbon (mg/l)	199.99
K_{13}^E	Saturation parameter for enzyme E_1 production rate by nitrogen (g/l)	0.045287
K_{14}^E	Saturation parameter for enzyme E_1 production rate by oxygen (mg/l)	0.037416
K_{1C}^E	Saturation parameter for enzyme E_1 production rate by carbon (g/l)	0.79559
K_{24}	Saturation parameter for PHB production rate by oxygen (mg/l)	0.026069
K_{24i}	Inhibition parameter for PHB production rate by oxygen (mg/l)	16.73
K_{25i}	Inhibition parameter for PHB production rate by propionic acid (g/l)	0.022492
K_{2C}	Saturation parameter for PHB production rate by carbon (g/l)	1.3293
K_{2Ci}	Inhibition parameter for PHB production rate by carbon (g/l)	78.212
K_{2C}^E	Saturation parameter for enzyme E_2 production rate by carbon (g/l)	1.0231
K_{24}^E	Saturation parameter for enzyme E_2 production rate by oxygen (mg/l)	0.26075
K_{34}	Saturation parameter for PHV production rate by oxygen (mg/l)	0.028876
K_{35}	Saturation parameter for PHV production rate by propionic acid (g/l)	0.011517
K_{34i}	Inhibition parameter for PHV production rate by oxygen (mg/l)	1.6055
K_{35i}	Inhibition parameter for PHV production rate by propionic acid (g/l)	25.765
K_P	Inhibition parameter for PHB and PHV production rate by intracellular polymer (g/g)	0.52507
$K_{m_{S_1}}$	Saturation parameter for glucose maintenance consumption rate (g/l)	0.0001
$K_{m_{S_2}}$	Saturation parameter for fructose maintenance consumption rate (g/l)	0.0001
$K_{m_{S_3}}$	Saturation parameter for nitrogen maintenance consumption rate (g/l)	0.0001
$K_{m_{S_4}}$	Saturation parameter for oxygen maintenance consumption rate (mg/l)	0.0001
$K_{m_{S_5}}$	Saturation parameter for propionic acid maintenance consumption rate (g/l)	0.0001
m_{S_1}	Glucose maintenance consumption rate (g/g h)	0.041893
m_{S_2}	Fructose maintenance consumption rate (g/g h)	0.072086
m_{S_3}	Nitrogen maintenance consumption rate (g/g h)	0.0010473
m_{S_4}	Oxygen maintenance consumption rate (g/g h)	81.269
m_{S_5}	Propionic acid maintenance consumption rate (g/g h)	0.055095
$n15i$	Inhibition parameter for growth rate by propionic acid	2.0
$n24$	Inhibition parameter for PHB production rate by oxygen	2.0
$n34$	Inhibition parameter for PHV production rate by oxygen	2.0
$n25i$	Inhibition parameter for PHB production rate by propionic acid	5.3174
np	Inhibition parameter for PHB and PHV production rate by intracellular polymer	32.975
u_1^*	Maximum value of cybernetic variable for control of enzyme E_1 synthesis	0.63408
S_4^*	Equilibrium concentration of dissolved oxygen (mg/l)	7.0
α_1	Maximum specific synthesis rate of enzyme E_1 (h^{-1})	0.010568
α_1^*	Basal specific synthesis rate of enzyme E_1 (h^{-1})	0.00031009
α_2	Maximum specific synthesis rate of enzyme E_2 (h^{-1})	0.00038715
α_2^*	Basal specific synthesis rate of enzyme E_2 (h^{-1})	0.089967
β_1	Denaturation rate of enzyme E_1 (h^{-1})	0.32154
β_2	Denaturation rate of enzyme E_2 (h^{-1})	0.23842
$\mu_{1,max}$	Maximum specific growth rate (h^{-1})	0.34087
$\mu_{2,max}$	Maximum specific PHB production rate (h^{-1})	0.21644
$\mu_{3,max}$	Maximum specific PHV production rate (h^{-1})	0.061262

$$\frac{dS_4}{dt} = \frac{F_{1g} + F_{1f} + F_2 + F_3}{V} S_4^* - \frac{F}{V} S_4 - \frac{1}{Y_{X_r S_4}} R_1 v_1 - \frac{1}{Y_{P_1 S_4}} R_2 v_2 - \frac{1}{Y_{P_2 S_4}} R_3 v_2 - \frac{m_{S_4} S_4}{K_{m_{S_4}} + S_4} X_r + k_L a(S_4^* - S_4) \quad \text{(A.29)}$$

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