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ORIGINAL PAPER

Optimal control of a linear unbranched chemical process with *n* steps: the quasi-analytical solution

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Abstract In this paper we present a method to solve a constrained optimal control problem to calculate the optimal enzyme concentrations in a chemical process by considering the minimization of the transition time. The method, based on Pontryagin's Minimum Principle, allows us to obtain the generalized solution of an n-step system with an unbranched scheme and bilinear kinetic models in an almost exclusively analytical way.

Keywords Optimal control · Chemical process · Pontryagin's principle

Mathematics Subject Classification 49J30 · 49M05 · 92E20 · 80A30 · 92C40

1 Introduction

This paper presents an optimal control problem which arises when metabolic chemical processes are considered. Within this context, one of the most important problems is the study of enzyme concentrations. Our work focuses on dynamic optimization, studying the problem of minimizing the transition time during which the substrate is converted into the product.

Let us consider the following (unbranched) reaction chain of n irreversible reaction steps converting substrate x_1 into product p:

$$x_1 \overset{u_1}{\to} x_2 \overset{u_2}{\to} x_3 \overset{u_3}{\to} \cdots \to x_{n-1} \overset{u_{n-1}}{\to} x_n \overset{u_n}{\to} p \tag{1}$$

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where x_1 is the substrate concentration (starting reagent), p the concentration of the final product, x_i $(i = 2, \ldots, n)$ the concentration of the intermediate compounds, and u_i $(i = 1, \ldots, n)$ the concentration of the enzyme catalyzing the i-th reaction.

For the dynamic case, the aim is to solve the problem analytically and numerically. An explicit solution for the simplest case, i.e. $n = 2$, can be found in [1]. For longer pathways, i.e. $n > 2$, the aforementioned authors solved the optimization problem numerically. An interesting study is presented in [2], in which the solution is obtained quasi-analytically, though with the constraint of considering only the case of $n = 3$ with two intermediate compounds. An interesting theoretical result is presented in [3] for the general case of n steps: the optimal enzyme concentration profile is of the "bang-bang" type (a well-known concept in the framework of optimal control which implies that the solution switches between 0 and the maximal level), except in the last interval. Other qualitative considerations of the solution are also presented, though not the analytical solution.

In this paper, we shall substantially extend the theoretical analysis of [2] and [3], presenting the quasi-analytical solution for the more general case of n steps. A fundamental difference with regard to the work presented in [3] is that, in said paper, the final steady-state enzyme levels are computed directly from an imposed final condition. In our study, leaving this condition free for the final interval will markedly complicate the development of the solution. The paper is organized as follows. Section 2 presents the statement of the problem. In Sect. 3, we carry out a calculation based on Pontryagin's Minimum Principle. Finally, we present the conclusions drawn.

2 Statement of the problem

The optimization of enzyme concentrations in metabolic pathways can be calculated using the optimality criterion of minimizing the time period during which an essential product is generated. Klipp et al. [1] and Bartl et al. [2] assumed bilinear (linear in the metabolite concentrations, x_i, and linear in the enzyme concentrations, u_i) and irreversible rate laws. Oyarzun et al. [3] used a more general model: the rate laws are only linear in the u_i, and some assumptions are made about the behaviour of the x_i. In this paper, we use a bilinear kinetic model to solve the problem analytically, likewise assuming that the enzymes can be switched on and off instantaneously. For the sake of simplicity, we employ normalized quantities. Enzyme levels are divided by the maximum total enzyme concentration, and substrate, intermediate and product levels by the initial substrate concentration.

Our goal is to convert substrate x_1 into product p as fast as possible. Several cost functions may be considered. In [3], combined optimization of the time taken to reach the new steady state and a measure of enzyme usage are considered:

$$\min_{u_1,\ldots u_n} \int_0^{t_f} (1 + \alpha^T \mathbf{u}(t))dt$$

where α is the vector of weights and u the vector of enzyme concentrations. If we choose $\alpha = 0$, then the minimization of the total operating time is considered:

$$\min_{u_1,\ldots u_n} \int_0^{t_f} dt$$

In this paper, we use the *transition time,* τ, as defined in [4] and [5], which is likewise used in [1] and [2]. In order to be converted into the product as fast as possible, substrate x_1 must follow the pathway of reactions x_i which lead to p within a minimum period of time. In metabolic analysis, this period of time is called the transition time. Thus, the objective function of the optimization problem may be defined as:

$$\min_{u_1,\ldots u_n} \tau = \min_{u_1,\ldots u_n} \int_0^{\infty} \frac{1}{x_1(0)}(x_1(0) - p(t))dt$$

Due to normalization, $x_1(0) = 1$, and the conservation relation:

$$x_1(t) + x_2(t) + \cdots + x_n(t) + p(t) = 1, \ \forall t \geq 0$$

the objective function can be written as:

$$\min_{u_1,\ldots u_n} \tau = \min_{u_1,\ldots u_n} \int_0^{\infty} (x_1(t) + x_2(t) + \cdots + x_n(t))dt \tag{2}$$

where concentrations $x_1, x_2, \ldots, x_n$ are the state variables (p is eliminated) and the enzyme concentrations $u_1, u_2, \ldots, u_n$ comprise the control variables.

The model of the reactions in (1) can then be described by the set of differential equations (see [1] and [2]):

$$\begin{cases} \dot{x}_1 = -k_1 u_1 x_1 & x_1(0) = 1, \ x_1(t) \geq 0 \\ \dot{x}_2 = k_1 u_1 x_1 - k_2 u_2 x_2 & x_2(0) = 0, \ x_2(t) \geq 0 \\ \dot{x}_3 = k_2 u_2 x_2 - k_3 u_3 x_3 & x_3(0) = 0, \ x_3(t) \geq 0 \\ \cdots & \\ \dot{x}_n = k_{n-1} u_{n-1} x_{n-1} - k_n u_n x_n & x_n(0) = 0, \ x_n(t) \geq 0 \end{cases} \tag{3}$$

where, for the sake of simplicity, we shall assume equal catalytic efficiencies of the enzymes ($k_i = 1$). As an initial condition, for $t = 0$, we shall consider the concentrations of the intermediate compounds and of the product to be equal to zero. Finally, we shall consider the concentrations of the compounds, x_i, as well as those of the enzymes, u_i, to be positive limited quantities and, after normalization, that the upper bound on the enzymatic concentration is 1. Hence, $(u_1(t), \ldots, u_n(t)) \in \Omega$, being:

$$\Omega = \{\mathbf{u} = (u_1(t), \ldots, u_n(t)) \in \mathbb{R}^n | u_1 \geq 0, \ldots u_n \geq 0; u_1 + \cdots + u_n \leq 1\} \tag{4}$$

We have thus stated an optimal control problem (OCP). Our standard Lagrange-type OCP can be mathematically formulated as follows:

$$\min_{\mathbf{u}(t)} I = \min_{\mathbf{u}(t)} \int_0^{t_f} F\,(t, \mathbf{x}(t), \mathbf{u}(t))\,dt$$

subject to satisfying:

$$\begin{aligned} &\dot{\mathbf{x}}(t) = f\,(t, \mathbf{x}(t), \mathbf{u}(t))\,;\ \mathbf{x}(0) = \mathbf{x}_0 \\ &\mathbf{u}(t) \in \Omega, 0 \le t \le t_f \end{aligned} \tag{5}$$

where I is the performance index, F is an objective function, $\mathbf{x} = (x_1(t), \ldots, x_n(t)) \in \mathbb{R}^n$ is the state vector, with initial conditions $\mathbf{x}_0$ $\mathbf{u} \in \mathbb{R}^n$ is the control vector, Ω denotes the set of admissible control values and t is the operating time that starts from 0 and ends at t_f. The state variables must satisfy the state equation (5) with given initial conditions. In this statement, we consider the final state to be free. Let H be the Hamiltonian function associated with the problem

$$H(t, \mathbf{x}, \mathbf{u}, \lambda) = F\,(t, \mathbf{x}, \mathbf{u}) + \lambda \cdot f\,(t, \mathbf{x}, \mathbf{u})$$

where $\lambda = (\lambda_1(t), \ldots, \lambda_n(t)) \in \mathbb{R}^n$ is called the *costate vector*. The classical approach involves the use of Pontryagin's Minimum Principle [6], which results in a two-point boundary value problem (TPBVP). In order for $\mathbf{u} \in \Omega$ to be optimal, a nontrivial function λ must necessarily exist, such that for almost every $t \in [0, t_f]$:

$$\begin{aligned} &\dot{\mathbf{x}} = H_\lambda; \mathbf{x}(0) = \mathbf{x}_0 \\ &\dot{\lambda} = -H_{\mathbf{x}}; \lambda(t_f) = \mathbf{0} \\ &\min_{\mathbf{u}\in\Omega} H(t, \mathbf{x}, \mathbf{u}, \lambda) \end{aligned} \tag{6}$$

Normally, the last optimality condition (6) is imposed as $H_{\mathbf{u}} = 0$ and the system of equations is solved for the control vector, $\mathbf{u}(t)$. However, if we consider control to appear linearly, (6), this leads to the minimization of a linear function of n variables of the following type:

$$\min_{\mathbf{u}\in\Omega} H = \min_{\mathbf{u}\in\Omega} \{-\mu_1 u_1 - \mu_2 u_2 - \cdots - \mu_n u_n\}$$

where the functions μ_i are called the *switching functions*. It is shown that control u_i will be activated when the switching function μ_i reaches its maximum value. If u_i switches between its upper and lower bounds only at isolated points in time, then the optimal control is said to be a *bang-bang type control* [7]. The times are called *switching times*.

3 Optimal solution

In this section, we present the solution to the optimal control problem defined in the previous section using Pontryagin's Minimum Principle [6]. The fundamental result to obtain may be summarized as follows:

Proposition 1 *There exists a set of switching times* $\{t_1, t_2, \ldots, t_{n-1}\}$, *(with* $0 < t_i < t_j$, *for* $i < j$ *) which partition the optimization interval as:*

$$[0, t_1) \cup [t_1, t_2) \cup \cdots \cup [t_{n-2}, t_{n-1}) \cup [t_{n-1}, \infty)$$

such that the optimal profile of the i *-th enzyme is of the bang–bang type and satisfies:*

$$u_i^*(t) = \begin{cases} 1 \ for \ t \in [t_{i-1}, t_i) \\ 0 \ for \ t \notin [t_{i-1}, t_i) \end{cases} ; \ i = 1, \ldots, n-1$$

with $t_0 = 0$. *In each interval* $[t_{i-1}, t_i)$, $i = 1, \ldots, n-1$, *the optimal metabolite concentration is given by:*

$$x_1(t) = \begin{cases} e^{-t} & i = 1 \\ e^{-t_1} & i > 1 \end{cases} \tag{7}$$

$$x_j(t) = \begin{cases} \prod_{h=1}^{j-1} (1 - e^{-(t_h - t_{h-1})}) \cdot e^{-(t_j - t_{j-1})} & j = 2, \ldots, i-1 \\ \prod_{h=1}^{j-1} (1 - e^{-(t_h - t_{h-1})}) \cdot e^{-(t - t_{i-1})} & j = i \\ \prod_{h=1}^{i-1} (1 - e^{-(t_h - t_{h-1})}) \cdot (1 - e^{-(t - t_{i-1})}) & j = i+1 \\ 0 & j = i+2, \ldots, n \end{cases} \tag{8}$$

In the last interval $(t \geq t_{n-1})$, *the solution is not of the bang–bang type.*

Proof In our case, as regards the control appearing linearly in the Hamiltonian H:

$$H = x_1 + x_2 + \cdots + x_n + \lambda_1(-u_1 x_1) + \lambda_2(u_1 x_1 - u_2 x_2) + \cdots + \lambda_n(u_{n-1} x_{n-1} - u_n x_n)$$

when H is minimized w.r.t. the control variables, we have that:

$$\min_{\mathbf{u} \in \Omega} H = \min_{\mathbf{u} \in \Omega} \{-\mu_1 u_1 - \mu_2 u_2 - \cdots - \mu_n u_n\}; \quad \begin{cases} \mu_1 = (\lambda_1 - \lambda_2) x_1 \\ \mu_2 = (\lambda_2 - \lambda_3) x_2 \\ \vdots \\ \mu_{n-1} = (\lambda_{n-1} - \lambda_n) x_{n-1} \\ \mu_n = \lambda_n x_n \end{cases} \tag{9}$$

where μ_i are the switching functions. From (9), we conclude that control u_i will be activated when the function μ_i reaches its maximum. Moreover, according to the optimality conditions:

$$\begin{cases} \dot{\lambda}_1 = -\frac{\partial H}{\partial x_1} \\ \dot{\lambda}_2 = -\frac{\partial H}{\partial x_2} \\ \vdots \\ \dot{\lambda}_{n-1} = -\frac{\partial H}{\partial x_{n-1}} \\ \dot{\lambda}_n = -\frac{\partial H}{\partial x_n} \end{cases} \Rightarrow \begin{cases} \dot{\lambda}_1 = (\lambda_1 - \lambda_2)u_1 - 1 \\ \dot{\lambda}_2 = (\lambda_2 - \lambda_3)u_2 - 1 \\ \vdots \\ \dot{\lambda}_{n-1} = (\lambda_{n-1} - \lambda_n)u_{n-1} - 1 \\ \dot{\lambda}_n = \lambda_n u_n - 1 \end{cases} \tag{10}$$

When control u_i is activated, the coefficient μ_i has to be positive: $\mu_i \geq 0$, $(\forall i = 1, \ldots, n)$ (otherwise $u_i = 0$). The following condition can thus be easily seen to hold:

$$\lambda_1 \geq \lambda_2 \geq \lambda_3 \geq \cdots \geq \lambda_n$$

We shall obtain the optimal solution constructively by intervals, starting from $t = 0$ and concatenating the results.

– First interval $[0, t_1]$. For $t = 0 \Rightarrow u_1 = 1, u_2 = 0, u_3 = 0, \cdots, u_n = 0$, since if $u_1 = 0$ from (3), $\dot{x}_1 = 0 \Rightarrow x_1(t) = 1, \forall t$ and the product will not be produced. Therefore, from (3), we have:

$$\begin{cases} \dot{x}_1 = -x_1 & x_1(0) = 1 \\ \dot{x}_2 = x_1 & x_2(0) = 0 \\ \dot{x}_3 = 0 & x_3(0) = 0 \\ \vdots & \\ \dot{x}_n = 0 & x_n(0) = 0 \end{cases} \Rightarrow \begin{cases} x_1(t) = e^{-t} \\ x_2(t) = 1 - e^{-t} \\ x_3(t) = 0 \\ \vdots \\ x_n(t) = 0 \end{cases}$$

Moreover, from (3), (9) and (10), the following holds:

$$\begin{cases} \dot{\lambda}_1 = \lambda_1 - \lambda_2 - 1 \\ \dot{\lambda}_2 = -1 \\ \dot{\lambda}_3 = -1 \\ x_3 = 0 \\ \vdots \\ x_n = 0 \end{cases} \Rightarrow \begin{cases} \dot{\mu}_1 = (\dot{\lambda}_1 - \dot{\lambda}_2)x_1 + (\lambda_1 - \lambda_2)\dot{x}_1 = \\ \qquad (\lambda_1 - \lambda_2)x_1 + (\lambda_1 - \lambda_2)(-x_1) = 0 \\ \dot{\mu}_2 = (\dot{\lambda}_2 - \dot{\lambda}_3)x_2 + (\lambda_2 - \lambda_3)\dot{x}_2 = \\ \qquad (\lambda_2 - \lambda_3)x_1 \geq 0 \\ \mu_3 = (\lambda_3 - \lambda_4)x_3 = 0 \\ \vdots \\ \mu_n = \lambda_n x_n = 0 \end{cases}$$

$$\Rightarrow \mu_1 = cte, \mu_2 = \text{increasing}, \ \mu_3 = 0, \ldots, \mu_n = 0$$

and we obtain the transition time for this interval:

$$\tau_1 = \int_0^{t_1} (x_1(t) + x_2(t) + x_3(t) + \cdots + x_n(t))\, dt = \int_0^{t_1} \left(e^{-t} + 1 - e^{-t} + 0 + \cdots + 0\right) dt = \int_0^{t_1} 1 dt = t_1$$

– Second interval $[t_1, t_2]$. For $t = t_1 \Rightarrow u_1 = 0, u_2 = 1, u_3 = 0, \cdots, u_n = 0$. Thus, from (3):

$$\begin{cases} \dot{x}_1 = 0 & x_1(t_1) = e^{-t_1} \\ \dot{x}_2 = -x_2 & x_2(t_1) = 1 - e^{-t_1} \\ \dot{x}_3 = x_2 & x_3(t_1) = 0 \\ \dot{x}_4 = 0 & x_4(t_1) = 0 \\ \vdots & \\ \dot{x}_n = 0 & x_n(t_1) = 0 \end{cases} \Rightarrow \begin{cases} x_1(t) = e^{-t_1} \\ x_2(t) = \left(1 - e^{-t_1}\right) e^{-(t-t_1)} \\ x_3(t) = \left(1 - e^{-t_1}\right)\left(1 - e^{-(t-t_1)}\right) \\ x_4(t) = 0 \\ \vdots \\ x_n(t) = 0 \end{cases}$$

Once again, using (3), (9) and (10), we have that:

$$\begin{cases} \dot{\lambda}_1 = -1 \\ \dot{\lambda}_2 = \lambda_2 - \lambda_3 - 1 \\ \dot{\lambda}_3 = -1 \\ \dot{\lambda}_4 = -1 \\ x_4 = 0 \\ \vdots \\ x_n = 0 \end{cases} \Rightarrow \begin{cases} \dot{\mu}_1 = (\dot{\lambda}_1 - \dot{\lambda}_2)x_1 + (\lambda_1 - \lambda_2)\,\dot{x}_1 = \\ \qquad -(\lambda_2 - \lambda_3)\,x_1 \le 0 \\ \dot{\mu}_2 = (\dot{\lambda}_2 - \dot{\lambda}_3)x_2 + (\lambda_2 - \lambda_3)\,\dot{x}_2 = \\ \qquad (\lambda_2 - \lambda_3)x_2 + (\lambda_2 - \lambda_3)\,(-x_2) = 0 \\ \dot{\mu}_3 = (\dot{\lambda}_3 - \dot{\lambda}_4)x_3 + (\lambda_3 - \lambda_4)\,\dot{x}_3 = \\ \qquad (\lambda_3 - \lambda_4)\,x_2 \ge 0 \\ \mu_4 = \lambda_4 x_4 = 0 \\ \vdots \\ \mu_n = \lambda_n x_n = 0 \end{cases}$$

$$\Rightarrow \mu_1 = \text{decreasing},\ \mu_2 = cte, \mu_3 = \text{increasing},\ \mu_4 = 0, \ldots, \mu_n = 0$$

The transition time for this interval is:

$$\begin{aligned} \tau_2 &= \int_{t_1}^{t_2} \left(e^{-t_1} + \left(1 - e^{-t_1}\right) e^{-(t-t_1)} + \left(1 - e^{-t_1}\right)\left(1 - e^{-(t-t_1)}\right) + \cdots + 0\right) dt \\ &= t_2 - t_1 \end{aligned}$$

The successive intervals up until the last but one are similarly obtained.

– *Interval* $\left[t_{n-2}, t_{n-1}\right]$. *For* $t = t_{n-2} \Rightarrow u_1 = 0, u_2 = 0, u_3 = 0, \ldots, u_{n-2} = 0, u_{n-1} = 1, u_n = 0$. From the state equations:

$$\begin{cases} \dot{x}_1 = 0 \\ \dot{x}_2 = 0 \\ \dot{x}_3 = 0 \\ \dot{x}_4 = 0 \\ \vdots \\ \dot{x}_{n-2} = 0 \\ \dot{x}_{n-1} = -x_{n-1} \\ \dot{x}_n = x_{n-1} \end{cases} \Rightarrow \begin{cases} x_1(t) = e^{-t_1} \\ x_2(t) = \left(1 - e^{-t_1}\right) e^{-(t_2-t_1)} \\ x_3(t) = \left(1 - e^{-t_1}\right)\left(1 - e^{-(t_2-t_1)}\right) e^{-(t_3-t_2)} \\ x_4(t) = \left(1 - e^{-t_1}\right)\left(1 - e^{-(t_2-t_1)}\right)(1 - e^{-(t_3-t_2)})e^{-(t_4-t_3)} \\ \vdots \\ x_{n-2}(t) = \left(1 - e^{-t_1}\right) \cdots (1 - e^{-(t_{n-3}-t_{n-4})})e^{-(t_{n-2}-t_{n-3})} \\ x_{n-1}(t) = \left(1 - e^{-t_1}\right) \cdots (1 - e^{-(t_{n-2}-t_{n-3})})e^{-(t-t_{n-2})} \\ x_n(t) = \left(1 - e^{-t_1}\right) \cdots (1 - e^{-(t_{n-2}-t_{n-3})})(1 - e^{-(t-t_{n-2})}) \end{cases}$$

And hence:

$$\tau_{n-1} = \int_{t_{n-2}}^{t_{n-1}} (x_1(t) + x_2(t) + x_3(t) + \cdots + x_n(t))\, dt = \int_{t_{n-2}}^{t_{n-1}} 1dt = t_{n-1} - t_{n-2}$$

– In the interval $[t_{n-1}, \infty)$, if it holds that $u_1 = 0$, $u_2 = 0$, $u_3 = 0$, $\ldots$, $u_n = 1$, we thus have that:

$$\begin{cases} \dot{x}_n = -x_n \\ \dot{\lambda}_n = \lambda_n - 1 \\ \mu_n = \lambda_n x_n \end{cases} \Rightarrow \dot{\mu}_n = \dot{\lambda}_n x_n + \lambda_n \dot{x}_n = (\lambda_n - 1)\, x_n + \lambda_n\, (-x_n) = -x_n \leq 0$$

$$\Rightarrow \mu_n = \text{decreasing}$$

and we will not have an interval in which to activate u_n. Therefore, in the last interval $(t \geq t_{n-1})$, the solution is not of the bang–bang type. □

The optimal solution have already been obtained analytically for the intervals $[0, t_1) \cup [t_1, t_2) \cup \cdots \cup [t_{n-2}, t_{n-1})$. The value of u_i and the values of concentrations $x_1, x_2, \ldots, x_n$ are given by Proposition 1. The following table presents the results developed from the formula (7) for ease of comprehension.

As we have just seen, u_n cannot be activated in the last interval $[t_{n-1}, \infty)$. Therefore, in order to calculate the solution in this last interval, we need to determine the minimum total transition time, τ. The result can be summarized in the following proposition.

Proposition 2 *The optimal values of* $x_1(t), x_2(t), \ldots, x_n(t)$ *are given by (7) in* $[t_{i-1}, t_i)$, $i = 1, \ldots, n-1$, *and by:*

$$x_j(t) = \sum_{h=1}^{j-1} \left[x_h(t_{n-1}) \prod_{k=h}^{j-1} u_k \left(\sum_{k=h}^{j} \prod_{\substack{i=h \\ i \neq k}}^{j} \frac{e^{-u_k(t-t_{n-1})}}{u_i - u_k} \right) \right] + x_j(t_{n-1}) e^{-u_j(t-t_{n-1})}$$

in the last interval $[t_{n-1}, \infty)$ *(with* $j = 1, \ldots, n$*).*

Proof To calculate the solution in the last interval, we consider the Hamiltonian:

$$H = x_1 + x_2 + \cdots + x_n - \mu_1 u_1 - \mu_2 u_2 - \mu_3 u_3 - \cdots - \mu_n u_n$$

As the optimality condition is independent of time, the following holds:

$$\dot{H} = \dot{x}_1 + \dot{x}_2 + \cdots + \dot{x}_n - \left(\dot{\mu}_1 u_1 + \dot{\mu}_2 u_2 + \cdots + \dot{\mu}_n u_n \right)$$
$$- \left(\mu_1 \dot{u}_1 + \mu_2 \dot{u}_2 + \cdots + \mu_n \dot{u}_n \right) = - \left(\mu_1 \dot{u}_1 + \mu_2 \dot{u}_2 + \cdots + \mu_n \dot{u}_n \right) = 0$$

thus:

$$\begin{cases} \dot{u}_1 = 0 \Rightarrow u_1 = cte \\ \dot{u}_2 = 0 \Rightarrow u_2 = cte \\ \dot{u}_3 = 0 \Rightarrow u_3 = cte \;\; ; \quad u_1 + u_2 + \cdots + u_n = 1 \\ \vdots \\ \dot{u}_n = 0 \Rightarrow u_n = cte \end{cases}$$

We shall now determine $x_1(t), x_2(t), \ldots, x_n(t)$ and the transition time in the last interval, $[t_{n-1}, \infty)$. Progressively solving the equations comprising the system of differential equations (3), we obtain the following expressions:

$$\begin{cases} x_1(t) = x_1(t_{n-1}) e^{-u_1(t-t_{n-1})} \\ x_2(t) = x_1(t_{n-1}) u_1 \left[\frac{1}{u_2-u_1} e^{-u_1(t-t_{n-1})} + \frac{1}{u_1-u_2} e^{-u_2(t-t_{n-1})} \right] \\ \qquad + x_2(t_{n-1}) e^{-u_2(t-t_{n-1})} \\ x_3(t) = x_1(t_{n-1}) u_1 u_2 \left[\frac{1}{u_2-u_1} \cdot \frac{1}{u_3-u_1} e^{-u_1(t-t_{n-1})} \right. \\ \qquad \left. + \frac{1}{u_1-u_2} \cdot \frac{1}{u_3-u_2} e^{-u_2(t-t_{n-1})} + \frac{1}{u_1-u_3} \cdot \frac{1}{u_2-u_3} e^{-u_3(t-t_{n-1})} \right] \\ \qquad + x_2(t_{n-1}) u_2 \left[\frac{1}{u_3-u_2} e^{-u_2(t-t_{n-1})} + \frac{1}{u_2-u_3} e^{-u_3(t-t_{n-1})} \right] \\ \qquad + x_3(t_{n-1}) e^{-u_3(t-t_{n-1})} \\ \cdots \end{cases} \tag{11}$$

which correspond to the general formula:

$$x_j(t) = \sum_{h=1}^{j-1} \left[x_h(t_{n-1}) \prod_{k=h}^{j-1} u_k \left(\sum_{k=h}^{j} \prod_{\substack{i=h \\ i \neq k}}^{j} \frac{e^{-u_k(t-t_{n-1})}}{u_i - u_k} \right) \right] + x_j(t_{n-1}) e^{-u_j(t-t_{n-1})}$$

Performing the appropriate operations, we thus obtain:

$$\begin{aligned} \int_{t_{n-1}}^{\infty} x_1(t)dt &= x_1(t_{n-1}) \frac{1}{u_1} \\ \int_{t_{n-1}}^{\infty} x_2(t)dt &= (x_1(t_{n-1}) + x_2(t_{n-1})) \frac{1}{u_2} \\ \int_{t_{n-1}}^{\infty} x_3(t)dt &= (x_1(t_{n-1}) + x_2(t_{n-1}) + x_3(t_{n-1})) \frac{1}{u_3} \\ &\vdots \end{aligned}$$

$$\int_{t_{n-1}}^{\infty} x_n(t)dt = (x_1(t_{n-1}) + x_2(t_{n-1}) + \cdots + x_n(t_{n-1}))\,\frac{1}{u_n}$$

Hence, the transition time for $[t_{n-1}, \infty)$ is:

$$\tau_n = \int_{t_{n-1}}^{\infty} (x_1(t) + \cdots + x_n(t))\,dt = x_1(t_{n-1})\left(\frac{1}{u_1} + \cdots + \frac{1}{u_n}\right)$$
$$+x_2(t_{n-1})\left(\frac{1}{u_2} + \cdots + \frac{1}{u_n}\right) + \cdots x_n(t_{n-1})\left(\frac{1}{u_n}\right)$$

And the total transition time will be:

$$\tau = \tau_1 + \tau_2 + \cdots \tau_{n-1} + \tau_n = t_1 + t_2 - t_1 + t_3 - t_2 + \cdots + t_{n-1} - t_{n-2} + \tau_n$$
$$= t_{n-1} + \tau_n = t_{n-1} + x_1(t_{n-1})\left(\frac{1}{u_1} + \cdots + \frac{1}{u_n}\right)$$
$$+x_2(t_{n-1})\left(\frac{1}{u_2} + \cdots + \frac{1}{u_n}\right) + \cdots + x_n(t_{n-1})\left(\frac{1}{u_n}\right)$$

where $x_i(t_{n-1})$ are known from Table 1. Thus, in order to calculate the solution in this last interval, we need to determine the minimum total transition time, $\tau(t_1, t_2, \ldots, t_{n-1}, u_1, u_2, \ldots, u_n)$. To minimize τ with the condition:

$$u_1 + u_2 + \ldots + u_n = 1$$

we apply the method of Lagrange multipliers to the augmented functional:

$$L(t_1, t_2, \ldots, t_{n-1}, u_1, u_2, \ldots, u_n, \beta) = \tau + \beta(u_1 + u_2 + \cdots + u_n - 1)$$

In order to do so, we have to solve the non-lineal system:

$$\frac{\partial L}{\partial t_1} = 0;\ \frac{\partial L}{\partial t_2} = 0;\ \cdots;\ \frac{\partial L}{\partial t_{n-1}} = 0;\ \frac{\partial L}{\partial u_1} = 0;\ \frac{\partial L}{\partial u_2} = 0;\ \cdots;\ \frac{\partial L}{\partial u_n} = 0;\ \frac{\partial L}{\partial \beta} = 0 \tag{12}$$

which may be done by means of any commonly used program. □

Remark 1 It is therefore in this last step when we truly determine the switching times: $t_1, t_2, \ldots, t_{n-1}$, and the values of $u_1, u_2, \ldots, u_n$ in the last interval, $[t_{n-1}, \infty)$ (in the other intervals, u_i is given by Proposition 1). The problem is now completely solved by calculating $x_1(t), x_2(t), \ldots, x_n(t)$. Finally, the concentration of product $p(t)$ can be easily calculated $\forall t$ using the conservation relation:

$$p(t) = 1 - (x_1(t) + x_2(t) + \cdots + x_n(t)), \quad \forall t \geq 0$$

Table 1 Metabolite concentration and transition time

Interval	Concentrations
$[0, t_1]$	$x_1(t) = e^{-t}$ $x_2(t) = 1 - e^{-t}$
$\tau = t_1$	$x_3(t) = 0; \ldots; x_n(t) = 0$
$[t_1, t_2]$	$x_1(t) = e^{-t_1}$ $x_2(t) = \left(1 - e^{-t_1}\right) e^{-(t-t_1)}$
$\tau = t_2 - t_1$	$x_3(t) = \left(1 - e^{-t_1}\right)\left(1 - e^{-(t-t_1)}\right)$ $x_4(t) = 0; \cdots; x_n(t) = 0$
$[t_2, t_3]$	$x_1(t) = e^{-t_1}$ $x_2(t) = \left(1 - e^{-t_1}\right) e^{-(t_2-t_1)}$ $x_3(t) = \left(1 - e^{-t_1}\right)\left(1 - e^{-(t_2-t_1)}\right) e^{-(t-t_2)}$
$\tau = t_3 - t_2$	$x_4(t) = \left(1 - e^{-t_1}\right)\left(1 - e^{-(t_2-t_1)}\right)(1 - e^{-(t-t_2)})$ $x_5(t) = 0; \cdots; x_n(t) = 0$
$\ldots$	$\ldots$
$\left[t_{n-2}, t_{n-1}\right]$	$x_1(t) = e^{-t_1}$ $x_2(t) = \left(1 - e^{-t_1}\right) e^{-(t_2-t_1)}$ $x_3(t) = \left(1 - e^{-t_1}\right)\left(1 - e^{-(t_2-t_1)}\right) e^{-(t_3-t_2)}$ $\vdots$
$\tau = t_{n-1} - t_{n-2}$	$x_{n-2}(t) = \left(1 - e^{-t_1}\right) \cdots (1 - e^{-(t_{n-3}-t_{n-4})}) e^{-(t_{n-2}-t_{n-3})}$ $x_{n-1}(t) = \left(1 - e^{-t_1}\right) \cdots (1 - e^{-(t_{n-2}-t_{n-3})}) e^{-(t-t_{n-2})}$ $x_n(t) = \left(1 - e^{-t_1}\right) \cdots (1 - e^{-(t_{n-2}-t_{n-3})})(1 - e^{-(t-t_{n-2})})$

We have thus solved the problem quasi-analytically; this last step, the calculation of the switching times, is the only one that is not carried out analytically or exactly. These two propositions provide an analytic justification of the behaviour described in [1] and observed experimentally in [8].

4 Example: Discussion of the results

Using the results presented in the previous section, we developed a program using the Mathematica® package that allows us to obtain the optimal solution. In Table 2, we present the optimal solution for the cases $n = 2, 3, 4, 5$. Let us see the switching times t_i $(i = 1, \ldots, n-1)$, the optimal profile of the i-th enzyme u_i $(i = 1, \ldots, n)$ in the last interval $[t_{n-1}, \infty)$, and the transition time τ. Remember that in the previous intervals, u_i is given by Proposition 1. Moreover, the substrate concentration, x_1, the concentrations of the intermediate compounds, $x_2, \ldots, x_n$, and the concentration of the final product, p, are immediately obtained in any interval using the presented formulae.

We shall now compare the results with those presented by other authors. Klipp et al. [1] present the analytical solution for the case $n = 2$. Compared to our solution, we have detected an error in the value they give to u_2, the correct value being $u_2 = 0.61803$. Figure 1 shows the optimal enzyme profile and the metabolite and product

Table 2 Optimal solution

n	t_1	t_2	t_3	t_4		
2	0.9624	–	–	–		
3	2.0061	2.9595	–	–		
4	2.7801	4.7452	5.7609	–		
5	3.3628	6.0746	8.0789	9.1759		
n	u_1	u_2	u_3	u_4	u_5	τ
2	0.38197	0.61803	–	–	–	3.5805
3	0.17882	0.33359	0.48758	–	–	7.1658
4	0.10439	0.18437	0.29208	0.41916	–	11.453
5	0.06989	0.11801	0.17623	0.26033	0.3755	16.267

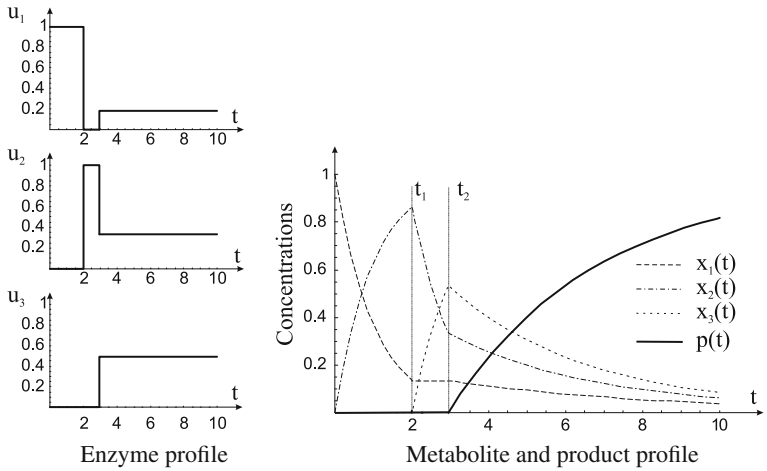

Fig. 1 Case $n = 3$

profile for the case $n = 3$. The solution obtained coincides with the one presented in [2].

Figure 2 shows the optimal solution for the case $n = 5$. An approximate solution for the case $n = 5$ is also presented in [1]. Compared to our solution, we have detected significant variations in the values of the switching times. The values given in [1] are: $t_1 = 3.08$, $t_2 = 5.28$, $t_3 = 6.77$, $t_4 = 7.58$. As the authors do not provide the values of u_i, we have not been able to check that the optimality equations are verified (12). However, the value of the transition time $\tau = 16.3(s)$ is similar to the one we obtained: $\tau = 16.267(s)$.

The results show a clear-cut chemical interpretation which we shall now elucidate in detail. During each of the first $n - 1$ intervals, only one enzyme is active and at its maximum value, namely u_i, corresponding to compound x_i, which we want to convert into x_{i+1}, $(i = 1, \ldots, n - 1)$. The solution is hence of the bang–bang type.

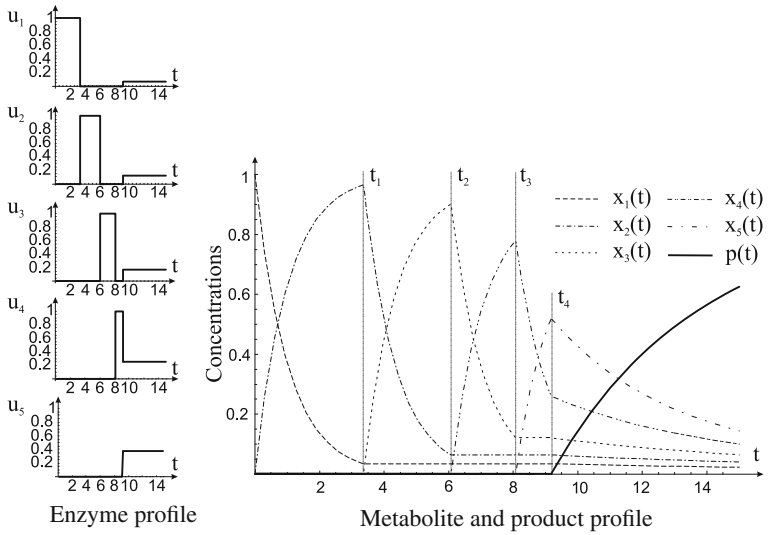

Fig. 2 Case $n = 5$

In these $n - 1$ intervals, the concentration of the metabolites varies as follows. In the first interval, starting from the initial value $x_1(0) = 1$, and using only enzyme u_1, substrate x_1 is converted into the intermediate compound x_2. Upon reaching the optimal value, the first switching time, t_1, appears. At this point, x_2 reaches its maximum value, $x_2(t_1)$, while x_1 takes on a constant value, $x_1(t_1)$, which it will maintain until the last interval. The process is repeated in the second interval, though now it is x_2 which, starting from this maximum value, $x_2(t_1)$, is converted into the intermediate compound x_3. Once the second switching time, t_2, has been reached, x_2 takes on a constant value, $x_2(t_2)$, which it will maintain as the optimal value until the instant t_{n-1}. The process is similarly repeated for all x_i.

Note that the maximum values obtained by metabolites $x_i(t_{i-1})$ become progressively lower as the process advances, whereas the constant values $x_i(t_i)$ that they maintain during a good part of the chain reaction increase progressively with increasing i. This is related to the fact that the intervals between switching times become progressively smaller as the chain reaction advances (see Fig. 2), with the subsequent decrease in the period of activation of each enzyme u_i.

Product p is only generated in the last interval $[t_{n-1}, \infty)$. As just stated, it is worth noting that the concentration of the substrates in this time period (without p) are ordered $x_i < x_{i+1}$. However, the most noteworthy fact is that a combination of all the enzymes u_i appears in which the enzyme concentrations are ordered $u_i < u_{i+1}$ (see Table 2; Fig. 2). Note that the last enzyme, u_n, only takes part in the last interval, and never does so at its maximum value of 1, because, along with the other enzymes, it must fulfil the condition (4).

Moreover, if we compare the solution obtained for different values of n, a number of conclusions may also be drawn. First, the minimal transition time logically increases as the number of intermediate compounds, n, increases. We can also see that the first

switching time is increasingly delayed and that the value in the last interval of the last enzyme, u_n, becomes progressively smaller with increasing n. Finally, it would appear paradoxical that the fastest possible conversion of the substrate into the final product is achieved when delaying (of course, in an appropriate manner) the appearance of intermediate compounds.

5 Conclusions

Our paper supposes the generalization of the optimal control problem that arises when considering a linear unbranched chemical process with n steps. We provide a quasi-analytical solution to the case of n steps by considering the minimization of the transition time. We show that the qualitative and quantitative description of the optimal solution provided by Proposition 1 considerably simplifies the computation of the optimal solutions, as we need only calculate the optimal switching times and the enzyme values in the last interval, seeing that the remaining unknowns are obtained analytically using the given formulas. We believe that the results obtained in this paper may be very useful to other researchers, serving as a benchmark for comparison with other approximate methods.

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