Proceedings of the 13th International Conference
on Computational and Mathematical Methods
in Science and Engineering, CMMSE 2013
24-27 June, 2013.

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

L. Bayón, J.M. Grau, M.M. Ruiz and P.M. Suárez

Department of Mathematics, University of Oviedo, Spain
e-mails: bayon@uniovi.es, grau@uniovi.es, mruiz@uniovi.es, pedrosr@uniovi.es

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 Maximum Principle, allows us to obtain, in an almost exclusively analytical way, the generalized solution of an n-step system with an unbranched scheme and bilinear kinetic models.

Key words: Optimal Control, Chemical Process, Pontryagin's Principle

MSC 2000: 49J30, 49M05, 92E20, 80A30, 92C40.

1 Introduction

In this paper we present an optimal control problem that 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 reactions steps converting substrate x_1 into product p:

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

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, but 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. The paper is organized as follows. Section 2 presents the statement of the problem. In Section 3 we carry out a calculation based on Pontryagin's Maximum 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. [1] and [2] assumed bilinear (linear in the metabolite concentrations, x_i, and linear in the enzyme concentrations, u_i) and irreversible rate laws. [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 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 simplicity's sake, 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 is considered. In this paper, we use the *transition time,* τ, as defined in [4], which is likewise used in [1] and [2]. 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:

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

the objective function can be written as:

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

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

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

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

where, for the sake of simplicity, we shall assume equal catalytic efficiencies of the enzymes ($k_i = k = 1$). 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, $(u_1(t), ..., u_n(t)) \in \Omega$, being:

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

We have thus stated an optimal control problem.

3 Optimization

In this section we present the solution to the optimal control problem defined in the previous section using Pontryagin's Minimum Principle (PMP) [5]. In our case, as regards the control appearing linearly in the Hamiltonian function 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:

$$\min_{\mathbf{u}} H = \min_{\mathbf{u} \in \Omega} \{-\mu_1 u_1 - \mu_2 u_2 - \cdots - \mu_n u_n\}; \quad \begin{cases} \mu_1 = (\lambda_1 - \lambda_2) x_1 \\ \mu_2 = (\lambda_2 - \lambda_3) x_2 \\ \vdots \\ \mu_{n-1} = (\lambda_{n-1} - \lambda_n) x_{n-1} \\ \mu_n = \lambda_n x_n \end{cases} \tag{5}$$

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. The times are called *switching times*. We shall obtain the optimal solution constructively by intervals, starting from $t = 0$ and concatenating the results. The fundamental result to obtain may be summarized as follows:

Proposition 1. *There exists a set of switching times* $\{t_1, t_2, ..., t_{n-1}\}$, *(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 satisfies:*

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

with $t_0 = 0$. *In the last interval* $(t \geq t_{n-1})$, *the solution is not of the bang-bang type.*

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

(6)

The optimal solution is 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 is given by Proposition 1, while the values of the concentrations $x_1, x_2, \ldots, x_n$ are given by (6). The transition times τ_i are defined by:

$$\tau_i = \int_{t_{i-1}}^{t_i} \left(x_1(t) + x_2(t) + x_3(t) + \cdots + x_n(t)\right) dt; \; i = 1, \ldots, n-1$$

In the last interval, $[t_{n-1}, \infty)$, it is observed that u_n cannot be activated. Therefore, in order to calculate the solution in this last interval, we need to determine the minimum total transition time, τ. It can be seen that $\tau(t_1, t_2, \ldots, t_{n-1}, u_1, u_2, \ldots, u_n)$

is given by:

$$\tau = t_{n-1} + x_1(t_{n-1}) \left(\frac{1}{u_1} + \cdots + \frac{1}{u_n} \right) + x_2(t_{n-1}) \left(\frac{1}{u_2} + \cdots + \frac{1}{u_n} \right) + \cdots + x_n(t_{n-1}) \left(\frac{1}{u_n} \right)$$

where $x_i(t_{n-1})$ are known from (6).

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:

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

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

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

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

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 completely solved by calculating $x_1(t), x_2(t), \cdots, x_n(t)$ in $[t_{n-1}, \infty)$ by means of the following equations:

$$\begin{cases} x_1(t) = x_1(t_{n-1}) e^{-u_1(t-t_{n-1})} \\ x_2(t) = x_2(t_{n-1}) e^{-u_2(t-t_{n-1})} \\ + \frac{u_1}{u_2-u_1} x_1(t_{n-1}) \left(e^{-u_1(t-t_{n-1})} - e^{-u_2(t-t_{n-1})} \right) \\ x_3(t) = x_3(t_{n-1}) e^{-u_3(t-t_{n-1})} + \frac{u_2}{u_3-u_2} x_2(t_{n-1}) e^{-u_2(t-t_{n-1})} \\ + \frac{u_2 u_1}{u_2-u_1} x_1(t_{n-1}) \left(\frac{e^{-u_1(t-t_{n-1})}}{u_3-u_1} - \frac{e^{-u_2(t-t_{n-1})}}{u_3-u_2} \right) \\ - \frac{u_2}{u_3-u_2} x_2(t_{n-1}) e^{-u_3(t-t_{n-1})} \\ - \frac{u_2 u_1}{u_2-u_1} x_1(t_{n-1}) (\frac{1}{u_3-u_1} - \frac{1}{u_3-u_2}) e^{-u_3(t-t_{n-1})} \\ \vdots \end{cases}$$

We have thus solved the problem quasi-analytically; this last step, the calculation of the switching times, being the only one that is not carried out analytically or exactly.

4 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.

References

[1] E. Klipp, R. Heinrich, H.G. Holzhutter, *Prediction of temporal gene expression. Metabolic optimization by re-distribution of enzyme activities*, Eur. J. Biochem. **269 (22)**, (2002) 5406–5413.

[2] M. Bartl, P. Li, S. Schuster, *Modelling the optimal timing in metabolic pathway activation-Use of Pontryagin's Maximum Principle and role of the Golden section*, BioSystems **101** (2010) 67–77.

[3] D. Oyarzun, B. Ingalls, R. Middleton, D. Kalamatianos, *Sequential activation of metabolic pathways: a dynamic optimization approach*, Bull. Math. Biol. **71(8)** (2009) 1851–1872.

[4] M. Llorens, J.C. Nuno, Y. Rodriguez, E. Melendez-Hevia, F. Montero, *Generalization of the theory of transition times in metabolic pathways: a geometrical approach*, Biophys. J. **77(1)** (1999) 23–36.

[5] R. Vinter, *Optimal Control, Systems & Control: Foundations & Applications*, Birkhäuser Boston, Inc., Boston, MA, 2000.