*Proceedings of the 14th International Conference*
*on Computational and Mathematical Methods*
*in Science and Engineering, CMMSE 2014*
*3–7July, 2014.*

# Sensitivity analysis of a linear unbranched chemical process with $n$ steps

**L. Bayón[1], J.A. Otero[1], M.M. Ruiz[1], P.M. Suárez[1] and C.Tasis[1]**

[1] *Department of Mathematics, University of Oviedo, EPI Gión, Spain*

emails: bayon@uniovi.es, jaurelio@uniovi.es, mruiz@uniovi.es, pedrosr@uniovi.es, ctasis@uniovi.es

**Abstract**

In this paper we present a quasi-analytical method to calculate the optimal enzyme concentrations in a chemical process by considering the minimization of the operation time. The resulting constrained optimal control problem is solved using Pontryagin's Minimum Principle. Our method allows us, first, to obtain the generalized solution of a $n$-step system with an unbranched scheme and bilinear kinetic models and with non-equal catalytic efficiencies of the enzymes. Second, we discuss in detail the sensitivity analysis of these catalytic parameters.

*Key words: Optimal Control, Chemical Process, Sensitivity Analysis*
*MSC 2000: 49J30, 49M05, 92E20, 80A30, 92C40*

## 1 Introduction

Let us consider an unbranched metabolic pathway composed of $n$ irreversible reaction steps converting substrate $x_1$ into product $p$. An explicit solution for the simplest case, i.e. $n = 2$, can be found in [1], while for longer pathways, the authors solved the optimization problem numerically. The solution is obtained quasi-analytically in [2], though with the constraint of considering only the case of $n = 3$ with two intermediate compounds. [3] present several theoretical results over qualitative properties of the solution for the general case of $n$ steps. These authors prove that the optimal enzyme concentration profile is of the "bang-bang" type, though they do not present the analytical solution. In a previous paper [4], we extended the theoretical analysis of [1], [2] and [3], presenting the quasi-analytical solution for the more general case of $n$ steps and assuming equal catalytic efficiencies of

the enzymes ($k_i = 1$). We considered the minimization of the transition time in [4]. This transition time is defined by a improper integral running until infinite time. Given that this model is somewhat unreal, in this paper we shall consider a more realistic situation in chemistry or biology. Moreover, we shall substantially extend the theoretical analysis of [4] to consider nonequal catalytic efficiencies $k_i$.

Sensitivity analysis (SA), on the other hand, investigates the relations between parameters of a model and a property of the outcome. Classically (see, for example, [5]), SA is performed by the partial derivatives of the outcome with respect to its parameters. When a closed-form equation describes the relationship between the independent variables and the dependent variable, this SA is easy to perform. This is precisely the major advantage of our method: it allows us to obtain the partial derivatives of the concentration of the compounds $x_i$ with respect to the catalytic efficiencies of the enzymes $k_i$.

## 2 Statement of the Problem

### 2.1 Model formulation

Let us consider the following unbranched metabolic pathway composed of $n$ irreversible reaction steps converting substrate $x_1$ into product $p$:

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

where $x_1(t)$ is the substrate concentration at time $t$, $p(t)$ the concentration of the final product at time $t$, $x_i(t)$ $(i = 2, \ldots, n)$ the concentration of the intermediate compounds at time $t$, and $u_i(t)$ $(i = 1, \ldots, n)$ the concentration at time $t$ of the enzyme catalyzing the $i$-th reaction. The model of the reactions in (1) can then be described by the set of differential equations:

$$\begin{cases} \dot{x}_1 = -k_1 u_1 x_1 & x_1(0) = 1, \quad x_1(t) \geq 0 \\ \dot{x}_2 = k_1 u_1 x_1 - k_2 u_2 x_2 & x_2(0) = 0, \quad x_2(t) \geq 0 \\ \dot{x}_3 = k_2 u_2 x_2 - k_3 u_3 x_3 & x_3(0) = 0, \quad x_3(t) \geq 0 \\ \cdots & \\ \dot{x}_n = k_{n-1} u_{n-1} x_{n-1} - k_n u_n x_n & x_n(0) = 0, \quad x_n(t) \geq 0 \end{cases} \tag{2}$$

In a previous paper [4], we assumed equal catalytic efficiencies of the enzymes ($k_i = 1$). In this paper, we shall substantially generalize the study to consider nonequal catalytic efficiencies.

### 2.2 Objective function

Our goal is to convert substrate $x_1$ into product $p$ as fast as possible and several cost functions may be considered. The *transition time*, $\tau$ (defined in [6]), is used in [1], [2] and

 ISBN: 978-84-616-9216-3

[4]. This transition time is defined by a time integral running until infinite time:

$$\min_{u_1,\ldots u_n} \tau = \min_{u_1,\ldots u_n} \int_0^\infty \frac{1}{x_1(0)}(x_1(0) - p(t))dt \tag{3}$$

In this paper, we shall consider a more realistic situation in biology where the product $p(t)$ need not be fully synthesized, but rather synthesized to a defined concentration. We therefore minimize the *operation time* (to distinguish it from the transition time) defined by specifying the final product concentration, e.g. $p(t_f) = 0.9$, with $t_f$ as the final time. The objective function of the optimization problem may thus be defined as:

$$\tau_{90} = \min_{u_1,\ldots u_n} t_f = \min_{u_1,\ldots u_n} \int_0^{t_f} dt \tag{4}$$

## 3 Optimal Solution

In this section, we present the solution to the optimal control problem (OCP) defined in the previous section:

$$\min_{\mathbf{u}(t)} \int_0^{t_f} F\left(t, \mathbf{x}(t), \mathbf{u}(t)\right) dt \tag{5}$$

subject to satisfying:

$$\dot{\mathbf{x}}(t) = f\left(t, \mathbf{x}(t), \mathbf{u}(t)\right) \tag{6}$$

$$\mathbf{x}(0) = \mathbf{x}_0 \tag{7}$$

$$\mathbf{u}(t) \in \Omega,\ 0 \le t \le t_f \tag{8}$$

where $F \equiv 1$ is the objective function, $\mathbf{x} = (x_1(t), ..., x_n(t)) \in \mathbb{R}^n$ is the state vector, with initial conditions $\mathbf{x}_0$, $\mathbf{u} \in \mathbb{R}^n$ is the control vector, $\Omega$ denotes the set of admissible control values and $t$ is the operating time, which starts from 0 and ends at $t_f$ (value to minimize). The state variables must satisfy the state equation (6) 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

$$H(t, \mathbf{x}, \mathbf{u}, \lambda) = F\left(t, \mathbf{x}, \mathbf{u}\right) + \lambda \cdot f\left(t, \mathbf{x}, \mathbf{u}\right) \tag{9}$$

where $\lambda = (\lambda_1(t), ..., \lambda_n(t)) \in \mathbb{R}^n$ is called the *costate vector*. The classical approach involves the use of Pontryagin's Minimum Principle [7], which results in a two-point boundary value problem (TPBVP). In order for $\mathbf{u} \in \Omega$ to be optimal, a nontrivial function $\lambda$ must necessarily exist, such that for almost every $t \in [0, t_f]$*:*

$$\dot{\mathbf{x}} = H_\lambda;\ \mathbf{x}(0) = \mathbf{x}_0 \tag{10}$$

$$\dot{\lambda} = -H_{\mathbf{x}};\ \lambda(t_f) = \mathbf{0} \tag{11}$$

$$\min_{\mathbf{u}\in\Omega} H(t, \mathbf{x}, \mathbf{u}, \lambda) \tag{12}$$

 ISBN: 978-84-616-9216-3

We now present the solution to the optimal control problem defined above using Pontryagin's Minimum Principle [7]. The fundamental result to obtain may be summarized as follows:

**Theorem 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:*

$$[0, t_1) \cup [t_1, t_2) \cup \cdots \cup [t_{n-2}, t_{n-1}) \cup [t_{n-1}, t_f] \tag{13}$$

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

$$u_i^*(t) = \begin{cases} 1 & for \quad t \in [t_{i-1}, t_i) \\ 0 & for \quad t \notin [t_{i-1}, t_i) \end{cases} \; ; \; i = 1, \ldots, n \tag{14}$$

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

$$x_1(t) = \begin{cases} e^{-k_1 t} & i = 1 \\ e^{-k_1 t_1} & i > 1 \end{cases} \tag{15}$$

$$x_j(t) = \begin{cases} \prod_{h=1}^{j-1} (1 - e^{-k_h(t_h - t_{h-1})}) \cdot e^{-k_j(t_j - t_{j-1})} & j = 2, \ldots, i-1 \\ \prod_{h=1}^{j-1} (1 - e^{-k_h(t_h - t_{h-1})}) \cdot e^{-k_j(t - t_{i-1})} & j = i \\ \prod_{h=1}^{i-1} (1 - e^{-k_h(t_h - t_{h-1})}) \cdot (1 - e^{-k_i(t - t_{i-1})}) & j = i+1 \\ 0 & j = i+2, \ldots, n \end{cases} \tag{16}$$

We have thus solved the problem quasi-analytically. The optimal solution has been obtained analytically for all the intervals $[0, t_1) \cup [t_1, t_2) \cup \cdots \cup [t_{n-1}, t_f]$. The calculation of the switching times $t_1, t_2, \ldots, t_{n-1}$ and the value of $t_f$ is the only one that is not carried out analytically or exactly.

## 4 Examples

Using the results presented in the previous section, we developed a program using the Mathematica package that allows us to obtain the optimal solution.

### 4.1 Example 1: Optimal solution

Let us consider the following values for the nonequal catalytic efficiencies $k_i$:

$$k_1 = 10; \; k_2 = 10; \; k_3 = 9; \; k_4 = 9; \; k_5 = 8; \; k_6 = 7; \; k_7 = 5; \; k_8 = 3; \; k_9 = 12 \tag{17}$$

In Table I, we present the optimal solution for the cases $n = 3, \ldots, 9$. Let us see the switching times $t_i$ $(i = 1, \ldots, n)$, and the operation time $\tau = t_n$. Remember that $u_i$ is given

by 1 in all the intervals (when it is active). 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 formulas presented in Theorem 1. Figure 1 shows the optimal solution for the case $n = 9$.

Table I. Switching times and operation time of the optimal solution.

| $n$ | $t_1$ | $t_2$ | $t_3$ | $t_4$ | $t_5$ | $t_6$ | $t_7$ | $t_8$ | $t_9$ |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 0.3401 | 0.6803 | 1.0469 | - | - | - | - | - | - |
| 4 | 0.3702 | 0.7404 | 1.1404 | 1.5404 | - | - | - | - | - |
| 5 | 0.3958 | 0.7917 | 1.2201 | 1.6485 | 2.1160 | - | - | - | - |
| 6 | 0.4188 | 0.8376 | 1.2915 | 1.7453 | 2.241 | 2.7898 | - | - | - |
| 7 | 0.4440 | 0.8880 | 1.3698 | 1.8516 | 2.3792 | 2.9633 | 3.7150 | - | - |
| 8 | 0.4755 | 0.9510 | 1.4677 | 1.9845 | 2.5512 | 3.1801 | 3.9942 | 5.1845 | - |
| 9 | 0.4821 | 0.9642 | 1.4883 | 2.0124 | 2.5874 | 3.2257 | 4.0529 | 5.2648 | 5.6817 |

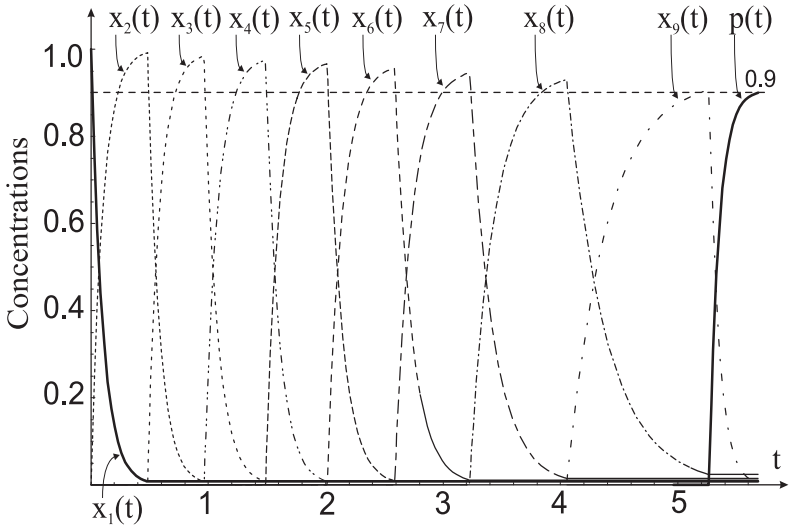


Figure 1. Metabolite and product profile. Case $n = 9$.

## 4.2 Example 2: Differential SA

Sensitivity analysis (SA) investigates the effect of parameter change on the solution of mathematical models, with more than a dozen SA techniques having been reported ([5]). *Differential SA* will be employed in the present paper. In this case, the sensitivity coefficient, $\phi_i$, for a particular independent variable can be calculated from the partial derivative of the dependent variable with respect to the independent variable. When an explicit algebraic equation describes the relationship, the differential SA is easy to perform.

 ISBN: 978-84-616-9216-3

Let us now see how the Differential SA of our problem can be performed immediately, employing analytic formulas to do so (16). The sensitivity coefficient, $\phi_{ij}$, defined from the partial derivative of the dependent variable $x_i$ $(i = 1, \ldots, n)$ with respect to $k_j$ $(i = 1, \ldots, i)$ :

$$\phi_{ij} = \frac{dx_i}{k_j} \tag{18}$$

was calculated using the Mathematica package. A summary of the results is shown in Figure 2.

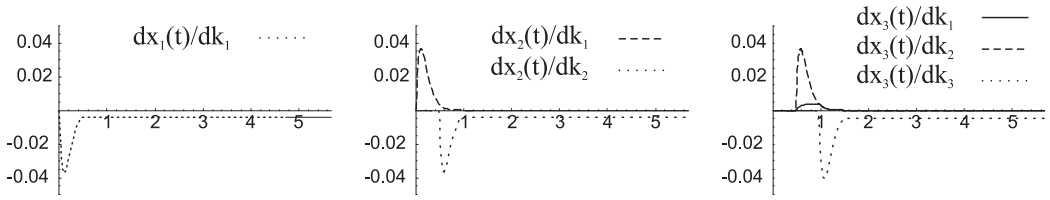


Figure 2. Sensitivity coefficients.

## 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 operation time and non-equal catalytic efficiencies of the enzymes. Using our closed-form equation for the optimal solution, the sensitivity analysis is very easy to perform.

## 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] L. Bayon, J.M. Grau, M.M. Ruiz, P.M. Suarez, *Optimal control of a linear unbranched chemical process with steps: the quasi-analytical solution*, J. Math. Chem. **52(4)**, (2014) 1036-1049.

[5] T. Turanyi, *Sensitivity analysis of complex kinetic systems. Tools and applications*, J. Math. Chem. **5(3)** (1990) 203-248.

[6] 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.

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

 ISBN: 978-84-616-9216-3