Proceedings of the 15th International Conference
on Computational and Mathematical Methods
in Science and Engineering, CMMSE 2015
3–7July, 2015.

Solving linear unbranched pathways with Michaelis-Menten kinetics using the Lambert W-Function

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Abstract

In this paper, an n-step, linear and unbranched pathway with Michaelis-Menten kinetics is solved in a quasi-analytical way. The method, based on the Optimal Control theory, calculates the optimal enzyme concentrations, while minimizing the operation time. In the computation of the solution, the Lambert W-Function plays a fundamental role, due to the presence of a non-linear kinetic model. Our method allows us to obtain the generalized solution and the sensitivity analysis of the catalytic parameters.

Key words: Optimal Control, Michaelis-Menten kinetic, Lambert W-Function
MSC 2000: 49J30, 49M05, 80A30

1 Introduction

This paper presents a method for obtaining the generalized solution of an n-step system with an unbranched scheme and non-linear kinetic models in an almost exclusively analytical way. Most of the previous papers use a bilinear (linear in the metabolite concentrations, x_i, and linear in the enzyme concentrations, u_i) kinetic model for the solution. For example, an explicit solution for $n = 2$, can be found in [1], while, for $n = 5$, the authors solved the optimization problem numerically. The solution for $n = 3$ is obtained quasi-analytically in [2]. In a previous paper [3], we addressed the minimization of the transition time, and generalized the works of [1], [2], presenting the quasi-analytical solution for the general case of n steps, but under the assumption of equal catalytic efficiencies of the enzymes ($k_i = 1$). Later, in [4], and addressing the minimization of the operation time, we extend the theoretical analysis of [3], considering unequal catalytic efficiencies, k_i.

 ISBN: 978-84-617-2230-3

There are few works dealing with nonlinear models in x_i. Among these, [5] used the Michaelis-Menten (MM) model [6], though for a particular case ($n = 4$). In [7], a metabolic control analysis is used to obtain the optimal behavior both in the setting of an unbranched linear pathway and one of MM type. A mathematical model of an unbranched reaction chain obeying MM kinetics is used in [8] for $n = 3$. Another numerical example with a three-step pathway and reversible MM kinetics is shown in [9]. Besides these numerically solved examples, [10] derives analytic equations but for a very simple example, modeling a single enzyme that follows MM kinetics and operates in the middle of an unbranched metabolic pathway.

Focusing on the kinetics models, the MM model has proven to be a powerful approach for describing enzyme processes. Due to difficulties to obtain closed form solutions for this model, several papers based upon effective scaling and singular perturbation techniques have been written, giving fairly accurate solutions [11]. A closed form solution to the MM equation was found, by the first time, in [12], using the Lambert W-function. A generalization that is still valid when the initial substrate concentration is close to that of the enzyme was recently presented in [13]. In [14] the Lambert W-function is employed to estimate the catalytic parameters. In this paper we present both the solution for the general case of n steps and a sensitivity analysis of the catalytic parameters (the K_m and k_{cat} constants). Using optimal control techniques, a functional that takes into account the operation time is minimized. We prove that the optimal enzyme concentration profile (in a quasi-closed form) is of "bang-bang" type.

2 Theoretical Foundations

2.1 Kinetic Model

The kinetics of the Michaelis-Menten (MM) model [6] describes the velocity (rate) of lots of enzymatic reactions. This model assumes a simple 2-step reaction: step 1 (Binding), when the enzyme E interacts with the substrate S to form the enzyme-substrate complex ES; step 2 (Catalysis), decomposition ES to regenerate the free enzyme E and the new product P.

$$E + S \underset{bind.}{\overset{k_1}{\underset{k_{-1}}{\rightleftarrows}}} [ES] \overset{k_2=k_{cat}}{\underset{cat.}{\rightarrow}} E + P \tag{1}$$

The rate equation of the MM kinetic model is:

$$V_0 = \frac{d[P]}{dt} = \frac{V_{\max}.[S]}{K_M + [S]} = \frac{k_2.[S]}{K_M + [S]}[E_T] \tag{2}$$

where $d[P]/dt$ or V_0 is the initial rate of product generation, $V_{\max}$ is the maximum rate and $[E_T]$ is the total enzyme concentration. The following ratio of rate constants is called

 ISBN: 978-84-617-2230-3

the MM constant, K_m:

$$K_m = \frac{k_{-1} + k_2}{k_1} \tag{3}$$

The MM equation (2) shows how the initial reaction rate V_0 depends on the substrate concentration, $[S]$. From (2) follows that K_m can also be defined as the substrate concentration at which the rate $V_{\max}/2$ is reached. Several simplifying assumptions are required to derive the MM equation:

(1) The binding step is fast and the catalytic step is slower.
(2) At an early stage, when the initial velocity (V_0) is measured, $[P] \approx 0$.
(3) ES reaches steady state immediately, so that $[ES]$ is constant.
(4) $[S]$ is constant at early times.
(5) The total enzyme concentration $[E_T]$ is: $[E_T] = [E] + [ES]$.

2.2 The Lambert W-Function

The Lambert W-function, $W(z)$ is a set of functions which are the branches of the inverse of the function:

$$z = f(W) = We^W \tag{4}$$

where W is any complex number. In this paper we focus on real-valued $W(x)$, which is defined only for $x \geq -1/e$ and is double-valued on $(-1/e, 0)$.

Adding the condition $W \geq -1$, we get a single-valued function $W_0(x)$ which is the principal branch of the W-function. In this case, $W_0(0) = 0$ and $W_0(-1/e) = -1$. For $W \leq -1$, one gets the lower branch, denoted $W_{-1}(x)$, which is decreasing from $W_{-1}(-1/e) = -1$ to $W_{-1}(0-) = -\infty$.

We refer the reader to [15] for a survey on existing results on this function. For example, by implicit differentiation, one proves easily that all branches of W satisfy:

$$\frac{dW}{dx} = \frac{W(x)}{x(1 + W(x))};\ x \notin \{0, -1/e\} \tag{5}$$

In [12], a closed solution to the equation (2) is given:

$$[S](t) = K_m W\left[\frac{[S_0]}{K_m} \exp\left(\frac{-V_{\max} t + [S_0]}{K_m}\right)\right] \tag{6}$$

which we are going to use extensively in this work for an n-step system with an unbranched scheme.

 ISBN: 978-84-617-2230-3

2.3 Pontryagin's Minimum Principle

We provide a summary of Optimal Control Theory in this section. More specifically, we state Pontryagin's Minimum Principle (PMP). An optimal control problem, in the multidimensional case, with free end-time t_f and free end state $\mathbf{x}(t_f)$ can be stated as the following equation:

$$\min_{t_f,\mathbf{u}(t)} J = \int_0^{t_f} F(\mathbf{x}(t),\mathbf{u}(t),t)dt + B[t_f,\mathbf{x}(t_f)] \tag{7}$$

subject to:

$$\dot{x}_i(t) = f_i(\mathbf{x}(t),\mathbf{u}(t),t);\ x_i(0) = x_{i0};\ i = 1,...,n \tag{8}$$

$$\mathbf{u}(t) \in U(t),\ 0 \le t \le t_f \tag{9}$$

with $\mathbf{x}(t) = (x_1(t),...,x_n(t)) \in \mathbb{R}^n$ the state vector, and $\mathbf{u}(t)$= $(u_1(t),...,u_n(t)) \in \mathbb{R}^n$ the control vector. The optimal t_f^* is unknown and to be determined. The following hypotheses are assumed: (i) F and $\mathbf{f} = (f_1(t),...,f_n(t))$ are continuous. (ii) F and $\mathbf{f}$ have partial first derivatives with respect to continuous t and $\mathbf{x}$. They may not have a continuous derivative in $\mathbf{u}$. (iii) The control variable, $\mathbf{u}(t)$, may not be continuous, it only needs to be piecewise continuous. (iv) The state variable, $\mathbf{x}(t)$, is continuous, but its derivative only needs to be piecewise continuous ($\mathbf{x}(t)$ admits corner points). And (v) B has continuous partial first derivatives. The set of admissible controls, U, is often compact and convex. The Hamiltonian is defined as:

$$H(\mathbf{x}(t),\mathbf{u}(t),\lambda(t),t) = F(\mathbf{x}(t),\mathbf{u}(t),t) + \lambda(t)\mathbf{f}(\mathbf{x}(t),\mathbf{u}(t),t) \tag{10}$$

where $\lambda(t) = (\lambda_1(t),\ldots,\lambda_n(t))$ is the costate vector. The following theorem [16] establishes the necessary conditions for optimality for the problem being addressed here:

Theorem 1. Pontryagin's Minimum Principle (PMP)

Let $\mathbf{u}^*(t)$ be the optimal piecewise control path, and $\mathbf{x}^*(t)$, the optimal associated state path, defined in the interval $[0,t_f]$. There is a continuous function, $\lambda^*(t)$, which has piecewise continuous first derivatives, such that for each $t \in [0,t_f]$, the following conditions are verified, for each $i = 1,...,n$:

$$\begin{aligned}
&\text{(i)} \quad \dot{\lambda}_i^*(t) = -\frac{\partial H(\mathbf{x}^*(t),\mathbf{u}^*(t),\lambda^*(t),t)}{\partial x_i};\ \lambda_i^*(t_f^*) = \frac{\partial B[t_f^*,\mathbf{x}^*(t_f^*)]}{\partial x_i}\\
&\text{(ii)} \quad H(\mathbf{x}^*(t),\mathbf{u}^*(t),\lambda^*(t),t) \le H(\mathbf{x}^*(t),\mathbf{u}(t),\lambda^*(t),t);\ \mathbf{u}(t) \in U(t)\\
&\text{(iii)} \quad \dot{x}_i^*(t) = f_i(\mathbf{x}^*(t),\mathbf{u}^*(t),t);\ x_i^*(0) = x_{i0}\\
&\text{(iv)} \quad H(\mathbf{x}^*(t_f^*),\mathbf{u}^*(t_f^*),\lambda^*(t_f^*),t_f^*) + \frac{\partial B[t_f^*,\mathbf{x}^*(t_f^*)]}{\partial t_f} = 0
\end{aligned} \tag{11}$$

 ISBN: 978-84-617-2230-3

The solution may not be interior so that minimizing the Hamiltonian does not necessarily imply $\partial H/\partial \mathbf{u} = \mathbf{0}$. If the dynamic function, $\mathbf{f}$, and the integrand, F, have no explicit time-dependence, the problem is said to be autonomous. In this case, $H_t \equiv 0$, which implies that the Hamiltonian is constant throughout said solution:

$$H(\mathbf{x}^*(t), \mathbf{u}^*(t), \lambda^*(t)) = const. \tag{12}$$

When the control $\mathbf{u}$ appears linearly in $F(\mathbf{x}(t), \mathbf{u}(t), t)$ and in $\mathbf{f}(\mathbf{x}(t), \mathbf{u}(t), t)$, then:

$$H(\mathbf{x}(t), \mathbf{u}(t), \lambda(t), t) = \nu(\mathbf{x}(t), \lambda(t), t) - \mu(\mathbf{x}(t), \lambda(t), t)\mathbf{u} \tag{13}$$

As we shall eventually see, in our specific case the optimality condition (ii) leads to the minimization of a linear function of n variables of the following type:

$$\min_{\mathbf{u}\in U} H = \min_{\mathbf{u}\in U} \left\{ -\sum_{i=1}^{n} \mu_i u_i \right\} \tag{14}$$

where the functions $\mu_i = -\partial H/\partial u_i$ are called the switching functions. Minimizing H with respect to u_i leads to:

$$u_i^*(t) = \begin{cases} u_{i\,\max} & \text{if} \quad \partial H/\partial u_i < 0 \\ u_{\text{sing}} & \text{if} \quad \partial H/\partial u_i = 0 \\ u_{i\,\min} & \text{if} \quad \partial H/\partial u_i > 0 \end{cases} \tag{15}$$

If u_i switches between its upper and lower limits only at isolated points in time, then the optimal control is said to be a *bang-bang type control*. Those times are called the *switching times*. If $\partial H/\partial u_i = 0$ for every t in some open subinterval, then the original problem is called a singular control problem and the corresponding trajectory, a singular arc u_{sing}.

3 Statement of the Problem and Optimal Solution

We are going to focus on unbranched metabolic pathways with MM kinetics as described below. Consider the following unbranched metabolic pathway composed of n irreversible reactions converting substrate x_1 into product p:

$$x_1 \overset{u_1}{\to} x_2 \overset{u_2}{\to} x_3 \overset{u_3}{\to} \cdots \to x_{n-1} \overset{u_{n-1}}{\to} x_n \overset{u_n}{\to} p \tag{16}$$

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 each intermediate compound at time t, and $u_i(t)$ $(i = 1, \ldots, n)$ the concentration at time t of the enzyme catalyzing the i-th reaction. For the sake of simplicity, we use normalized quantities: the u_i are divided by the maximum total enzyme concentration, and the x_i and p are divided by $x_1(0)$. Using (2) we get:

$$v_i(x_i(t), u_i(t)) = \frac{k_i x_i(t)}{K_{mi} + x_i(t)} u_i(t) \tag{17}$$

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where v_i is the rate of the i-th reaction ($i = 1, \ldots, n$), and the dynamical model for the pathway shown in (16) is given by conservation of mass:

$$\dot{x}_i(t) = v_{i-1}(x_{i-1}(t), u_{i-1}(t)) - v_i(x_i(t), u_i(t)); \ (i = 1, \ldots, n) \tag{18}$$

So, the reactions in (16) can then be modeled by the set of differential equations:

$$\begin{cases} \dot{x}_1 = -\dfrac{k_1 x_1}{K_{m1} + x_1} u_1 & x_1(0) = 1 \\ \dot{x}_2 = \dfrac{k_1 x_1}{K_{m1} + x_1} u_1 - \dfrac{k_2 x_2}{K_{m2} + x_2} u_2 & x_2(0) = 0 \\ \ldots & \\ \dot{x}_n = \dfrac{k_{n-1} x_{n-1}}{K_{mn-1} + x_{n-1}} u_{n-1} - \dfrac{k_n x_n}{K_{mn} + x_n} u_n & x_n(0) = 0 \end{cases} \tag{19}$$

with $x_i(t) \geq 0$. Due to normalization, we have $x_1(0) = 1$, and:

$$x_1(t) + x_2(t) + \ldots + x_n(t) + p(t) = 1, \ \forall t \geq 0 \tag{20}$$

Our goal is to convert transform x_1 into product p as fast as possible. Thus, we shall minimize the operation time, which is defined in terms of the concentration of the final product, $p(t_f)$, with t_f as the final time. In the case of an exhaustible initial substrate, x_1, from (20), and imposing $p(t_f) = C_f$ ($0 < C_f < 1$), we obtain:

$$x_1(t_f) + x_2(t_f) + \ldots + x_n(t_f) = 1 - C_f \tag{21}$$

So that the optimization problem may thus be defined as the following control problem (Pr):

$$\begin{array}{ll} \text{(Pr):} & \tau_{C_f} = \min\limits_{u_1, \ldots u_n} \displaystyle\int_0^{t_f} dt = \min\limits_{u_1, \ldots u_n} t_f \\ \text{subject to:} & (19), (21), \text{ and:} \\ & U(t) = \{\mathbf{u} \in \mathbb{R}^n \mid u_1 \geq 0, \ldots u_n \geq 0; \ u_1 + \ldots + u_n \leq 1\} \end{array} \tag{22}$$

Using PMP, we get the following solution to (Pr):

Theorem 2. **Optimal Solution**

The optimal i-enzyme profile is of bang-bang type and satisfies:

$$u_i^*(t) = \begin{cases} 1 & for \quad t \in [t_{i-1}, t_i) \\ 0 & for \quad t \notin [t_{i-1}, t_i) \end{cases} \ ; \ i = 1, \ldots, n \tag{23}$$

where $\{t_0, t_1, t_2, ..., t_n\}$ *are the switching times, with* $t_0 = 0$ *and* $t_n = t_f$. *If we denote by* $x_{ji}(t)$ *the optimal j-th metabolite concentration in the i-th interval* $[t_{i-1}, t_i]$, $i = 1, \ldots, n$,

 ISBN: 978-84-617-2230-3

with $x_{10}(t_0) = 1$, *then the optimal solution is:*

$\mathbf{x_{j1}(t)}$	*for*	**j**
$K_{m1}W\left(\frac{x_{10}(t_0)}{K_{m1}}e^{\frac{x_{10}(t_0)}{K_{m1}}}e^{-\frac{k1}{K_{m1}}(t-t_0)}\right)$		1
$x_{10}(t_0) - x_{11}(t)$		2
0		$3, \ldots, n$

(24)

$\mathbf{x_{ji}(t)}$	*for*	**j**
$x_{jj}(t_j)$		$1, \ldots, i-1$
$K_{mi}W\left(\frac{x_{ii-1}(t_{i-1})}{K_{mi}}e^{\frac{x_{ii-1}(t_{i-1})}{K_{mi}}}e^{-\frac{k_i}{K_{mi}}(t-t_{i-1})}\right)$		i
$x_{ii-1}(t_{i-1}) - x_{ii}(t)$		$i+1$
0		$i+2, \ldots, n$

(25)

$\mathbf{x_{jn}(t)}$	for	**j**
$x_{jn}(t_j)$		$1, \ldots, n-1$
$K_{mn}W\left(\frac{x_{nn-1}(t_{n-1})}{K_{mn}}e^{\frac{x_{nn-1}(t_{n-1})}{K_{mn}}}e^{-\frac{k_n}{K_{mn}}(t-t_{n-1})}\right)$		n

(26)

4 Conclusions

We have presented in this paper for the first time the quasi-analytical solution of an n-step linear unbranched pathway with Michaelis-Menten kinetics. As objective function we minimize the operation time, defined by specifying the final concentration of the product. Traditionally, kinetics with non-linear equations, like Michaelis-Menten, have only been solved approximately. The closed-form formulae of Theorem 2 allow finding the solution for problems of arbitrary dimension, with the only already stated limitation of solving the nonlinear system. With the proposed iterative method of progressively finding the solution for increasing values of n, we have verified that the solution of the system poses no special difficulty from the numerical point of view. The reason is that on each step n, the starting seeds for unknowns $1, \ldots, n-1$ can be estimated to high precision taking those of the previous step and the value of the new unknown can also be easily estimated. All the issues related to convergence of numerical processes, frequent in other methods, are thus prevented.

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