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Analysis of the dynamical behavior for enzyme-catalyzed reactions with impulsive input

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Previous work has concentrated on the nature and validity of this reactions. In the paper, the dynamical behavior of Michaelis–Menten type kinetics for enzyme-catalyzed biochemical reactions is studied. Under the practical background, we investigate the effects of impulsive substrate-input.

KEY WORDS: enzymatic-reactions, impulsive input, dissipation

AMS subject classification: 34A37

1. Introduction

It is well known that enzymes are fundamental to life and with prior knowledge of the behavior of the enzyme most chemists, physicists, and chemical engineers entered the realm of bio-reactions and have extensively studied their functions within plants, animals, and microorganisms [1–4]. One of the greatest value works is the simple yet powerful model which Michaelis and Menten, [5] 1913 produced to describe a single substrate plus enzyme to product reaction. This isolated chemical reaction has been researched from diverse aspects in [6–9]. Man and its environment are all open systems, however, and have exchange for substance and energy in between. There are all kinds of energy input such as constant input or periodic input. The model of constant input simulates this simple process of enzyme reaction that a living system can take substance from its circumstances and release products to them [10]; that of periodic input describes plant photosynthesis depend on light intensity and the process of absorbing carbon resources is periodic fluctuations in ideal [11]. Therefore, almost all enzymatic reaction in a living system should include substrate input and product removal. But it is not suitable of such two class of inputs to elucidate the manner of drugs into the body. We know that for some diseases human body doesn't

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need the same dose of drugs in the whole day and will produce the resistance to drugs in reverse. In fact, drugs metabolism is the reaction of drugs and enzymes in the liver. So, it is very great value of impulsive differential equation [12] to picture this process of drugs *in vivo*. An understanding of the impulsive differential model (see equation (3.1)) requires some familiarity with the elementary enzyme reaction and the impulsive theory. The former is as follows; the latter will be discussed in section 2.

Based on experiments, Michaelis and Menten [5] proposed the basic enzymatic reaction which takes the following form:

$$S + E \rightleftharpoons C(ES) \longrightarrow E + P$$

Figure 1. The basic enzyme-substrate reaction.

where $S, E, C(ES)$, and P denote, respectively, the free substrate, free enzyme, enzyme-substrate complex, and the product concentrations.

According to figure 1, Menten wrote the following differential equations to study the chemical reaction of the single substrate with enzyme:

$$\begin{aligned} \dot{e} &= -k_1 es + (k_{-1} + k_2)c, \\ \dot{s} &= -k_1 es + k_{-1}c, \\ \dot{c} &= k_1 es - (k_{-1} + k_2)c, \\ \dot{p} &= k_2 c, \end{aligned} \tag{1.1}$$

where s, e, c, and p denote, respectively, the free substrate, free enzyme, enzyme-substrate complex, and the product concentrations. The parameters k_1, k_{-1}, k_2 are positive rate constants for each reaction.

In fact, only the second and third equations need thinking because they have no relation with others in model (1.1).

Let e_0, s_0, and c_0 denote, respectively, the initial values of e, s, and c. Adding the first and third equation of system (1.1), we get

$$\dot{e} + \dot{c} = 0.$$

That is

$$e(t) + c(t) = \text{constant} = e_0 + c_0.$$

Namely,

$$e(t) = e_0 + c_0 - c(t). \tag{1.2}$$

Our reaction system can be described completely by equation (1.3):

$$\begin{aligned} \dot{s} &= -k_1(e_0 + c_0 - c)s + k_{-1}c, \\ \dot{c} &= k_1(e_0 + c_0 - c)s - (k_{-1} + k_2)c. \end{aligned} \tag{1.3}$$

So, we think over equation (1.3) instead of equation (1.1).

In the paper, we will first consider the enzyme reaction of constant input and prove that state-steady is global stabilization with Dulac's function [6] in section 2. Section 3 prove the model of impulsive input is dispersive [7] and we simulate periodic solutions in matlab in section 4 followed by a short conclusion (section 5).

2. The model of constant input

First, we introduce three kinds of basic models, that is

$$\dot{u} = r_1 - r_2 u, \quad u(0) = u_0 \tag{2.1}$$

and

$$\begin{array}{ll} \dot{u} = -ru, & t \neq n\tau, \\ u(t^+) = u(t) + p, & t = n\tau, \\ u(0^+) = u_0 & \end{array} \tag{2.2}$$

and

$$\begin{array}{ll} \dot{v}(t,x) \leqslant g(t, v(t,x)), & t \neq n\tau, \\ v(t, x(t^+)) \leqslant \psi_n(v(t, x(t))), & t = n\tau. \end{array} \tag{2.3}$$

For equations (2.1)–(2.3), we have the following conclusions.

Lemma 2.1. System (2.1) has a positive equilibrium u^* and for every solution u of equation (2.1)

$$|u - u^*| \to 0, \quad \text{as } t \to \infty,$$

where $u^* = \frac{r_1}{r_2}$.

Lemma 2.2. [13]. System (2.2) has a positive periodic solution $u^*(t)$ and for every solution u(t) of equation (2.2)

$$|u(t) - u^*(t)| \to 0, \quad \text{as } t \to \infty,$$

where $u^*(t) = \frac{pe^{-(r(t-n\tau))}}{1-e^{-r\tau}}, t \in (n\tau, (n+1)\tau], n \in N$.

Lemma 2.3. [13]. Let $v \in v_0$. Assume that system (2.3)

$$\begin{array}{ll} D^+V(t,x) \leqslant g(t, V(t,x)), & t \neq n\tau, \\ V(t, x(t^+)) \leqslant \psi_n(V(t, x(t))), & t = n\tau, \end{array}$$

where g: $R_+ \times R_+ \longrightarrow R$ satisfies (H) and ψ_n: $R_+ \to R_+$ is non-decreasing. (H) g is continuous in $(n\tau, (n+1)\tau] \times R$, and for $x \in R_+, n \in N$,

$$\lim g(t, y) = g(n\tau^+, x), \quad \text{as } (t, y) \to (n\tau^+, x).$$

Let $r(t)$ be the maximal solution of the scalar impulsive differential equation

$$\begin{aligned} &\dot{u} = g(t, u), \quad t \neq n\tau, \\ &u(t^+) = \psi_n(u(t)), \quad t = n\tau. \\ &u(0^+) = u_0. \end{aligned}$$

Then $v(0^+, x_0) \leqslant u_0$ implies $v(t, x(t)) \leqslant r(t)$, $t \geqslant 0$, where $x(t)$ is any solution of (3.1).

The process of enzyme reaction with constant input is shown in figure 2:

$$I(t) \to S + E \rightleftharpoons C(ES) \to E + P$$

Figure 2. The enzyme-substrate reaction with substrate input.

So, the model of constant input is:

$$\begin{aligned} \dot{s} &= I_0 - k_1(e_0 + c_0 - c)s + k_{-1}c, \\ \dot{c} &= k_1(e_0 + c_0 - c)s - (k_{-1} + k_2)c. \end{aligned} \tag{2.4}$$

For this model (2.4), we demonstrate its dissipative in the plane.

2.1. *The boundary of the model*

Using the differential inequality theory, we will prove this system (2.4) is boundary in the quadrant.

Theorem 2.1. $R^2_{0+} = (x, y)|x \geqslant 0, y \geqslant 0$ is an invariant domain of equation (2.4).

Proof. We know that

$$\dot{s}|_{s=0} = I_0 + k_{-1}c > 0 \quad \text{for all } c > 0$$

and

$$\dot{c}|_{c=0} = k_1(e_0 + c_0)s > 0 \quad \text{for all } s > 0.$$

So, if the arbitrary initial point $p_0(s_0, c_0) \in R^2_{+0}$, the cure described by equation (2.4) still belongs to this region. □

Theorem 2.2. If $e_0 + c_0 > I_0/k_2$, this system (2.4) has only one equilibrium and no limit cycle in the plane.

Proof. Let the right of equation (2.4) equal to zeros and get its equilibrium (s^*, c^*), namely

$$(s^*, c^*) = \left(\frac{(k_{-1} + k_2)c^*}{k_1(e_0 + c_0 - c^*)}, \frac{I_0}{k_2}\right).$$

We will study the behavior of this equilibrium in the quadrant and firstly make it move the origin point through the following transition:

$$x = s + s^*, \qquad y = c + c^*.$$

We get

$$\begin{aligned} \dot{x} &= -k_1(e_0 + c_0 - y)x + k_{-1}y, \\ \dot{y} &= k_1(e_0 + c_0 - y)x - (k_{-1} + k_2)y. \end{aligned} \tag{2.5}$$

The secular equation of this systems is

$$\lambda^2 + [k_1(e_0 + c_0 - c^*) + k_1 s^* + (k_{-1} + k_2)]\lambda + k_1 k_2(e_0 + c_0 - c^*) = 0.$$

Obviously, all its eigenvalues are negative. By the eigenvalue theory so that this equilibrium (s^*, c^*) is locally stable in the plane.

We will conclude that system (2.4) has no limit cycle by the Dulac's function. Let

$$\begin{aligned} \dot{s} &= I_0 - k_1(e_0 + c_0 - c)s + k_{-1}c \doteq P, \\ \dot{c} &= k_1(e_0 + c_0 - c)s - (k_{-1} + k_2)c \doteq Q \end{aligned}$$

and

$$B(s, c) = s^{\alpha-1}c^{\beta-1},$$

where the parameters α and β are integers.

We compute

$$\begin{aligned} D &= \frac{\partial(BP)}{\partial s} + \frac{\partial(BQ)}{\partial c} \\ &= s^{\alpha-2}c^{\beta-2}[(\alpha - 1)cI_0 - k_1\alpha(e_0 + c_0 - c)sc + (\alpha - 1)k_{-1}c^2 \\ &\quad + k_1(e_0 + c_0)(\beta - 1)s^2c - k_1\beta s^2c - \beta(k_{-1} + k_2)sc]. \end{aligned}$$

Choose $\alpha = 0, \beta = 1$, we get

$$D = s^{-2}c^{-1}[-cI_0 - k_{-1}c^2 - k_1s^2c - (k_{-1} + k_2)sc] < 0.$$

So, by the Dulac's theorem, we can reach the conclusion that this equilibrium (s^*, c^*) is globally stable in the plane.

Theorem 2.3. System (2.4) is permanent.

Proof. First we consider the inequality below and compute the minimum of $s(t)$ in the quadrant. Because of $c > 0$, we get

$$\dot{s} > I_0 - k_1(e_0 + c_0)s \quad \text{for all } t > 0.$$

Using lemma (2.1), from the above inequality we obtain the minimum $s(t)$ of system (2.4), that is,

$$s_{\min} = \frac{I_0}{k_1(e_0 + c_0)}.$$

For some $t^* \in [t_0, \infty)$, if $c(t^*) > (e_0 + c_0)$, we compute

$$\dot{c} < 0.$$

So, there must exist T_1, when $t > T_1$, $c(t) < e_0 + c_0$.

That is

$$c_{\max} < e_0 + c_0, \quad \text{for all } t \in [T_1, \infty).$$

According to above reasoning, we know that

$$c(t) < c_{\max}, \quad \text{for all } t > T_1$$

and deduce

$$\dot{s} < I_0 - k_1(e_0 + c_0)s + k_1 c_{\max} s + k_{-1} c_{\max}.$$

By lemma (2.1), solving this inequality, one can get the maximum

$$s_{\max} = \frac{I_0 + k_{-1} c_{\max}}{k_1(e_0 + c_0) - k_1 c_{\max}}.$$

Similarly, there exists a T_2, so that

$$s_{\min} < s(t) < s_{\max} \quad \text{for all } t > T_2.$$

Therefore, we have the following inequality

$$\dot{c} > k_1(e_0 + c_0)s_{\min} - k_1 c s_{\max} - (k_{-1} + k_2)c \quad \text{for all } t > T_2.$$

By lemma (2.1), we get this conclusion, that is,

$$c_{\min} = \frac{k_1(e_0 + c_0)s_{\min}}{k_1 s_{\max} + (k_{-1} + k_2)} \quad \text{for all } t > T_3.$$

This completes proof of theorem 2.3. □

3. The model of impulsive input

With an impulse perturbation, the above reaction rate equation (2.4) become:

$$\begin{aligned} &\dot{s} = I_0 - k_1(e_0 + c_0 - c)s + k_{-1}c, \quad t \neq n\tau, \\ &\dot{c} = k_1(e_0 + c_0 - c)s - (k_{-1} + k_2)c, \\ &s(t^+) = s(t) + \epsilon I_0, \quad t = n\tau, \end{aligned} \tag{3.1}$$

similarly, where s, e, c, and p denote, respectively, the free substrate, free enzyme, enzyme-substrate complex, and the product concentrations. The parameters k_1, k_{-1}, k_2 are positive rate constants for each reaction. The e_0, s_0, and c_0 denote, respectively, the initial concentration of e, s, and c. The ϵ $(0 < \epsilon < 1)$ is perturbation factor of impulsive equation (3.1) and also positive constant. In the same manner, we conclude R^+ is the invariant manifold of equation (3.1).

Lemma 3.1. For the solution $s(t)$ of equation (3.1), there exists a $T_1 > 0$, such that

$$s(t) > m_1, \quad \text{as } t > T_1,$$

where m_1 is a positive constant.

Proof. For all t since $c(t) \geqslant 0$, we get

$$\dot{s} > I_0 - k_1(e_0 + c_0)s.$$

By lemmas 2.2 and 2.3, we have

$$s(t) \geqslant x(t) \quad \text{and} \quad x(t) \to \overline{x}(t), \ \text{as } t \to \infty,$$

where $x(t)$ is the solution of

$$\begin{aligned} &\dot{x} = I_0 - k_1(e_0 + c_0)x, \quad t \neq n\tau, \\ &x(t^+) = x(t) + \epsilon I_0, \quad t = n\tau \end{aligned}$$

and $\overline{x}(t) = \frac{I_0}{k_1(e_0+c_0)} - \frac{\epsilon I_0 e^{k_1(e_0+c_0)(t-n\tau)}}{1-e^{k_1(e_0+c_0)}\tau}$, for $t \in (n\tau, (n+1)\tau]$.

For $t \in (n\tau, (n+1)\tau]$, $\overline{x}(t)$ is a monotonic decreasing function of time t and has a minimum value m_1 at $t = (n+1)\tau$, that is,

$$m_1 = \frac{I_0}{k_1(e_0 + c_0)} - \frac{\epsilon I_0 e^{k_1(e_0+c_0)\tau}}{1 - e^{k_1(e_0+c_0)}\tau}.$$

So, there must exist a $T_1 > 0$, such that

$$s(t) \geqslant x(t) \geqslant \overline{x}(t) = m_1, \quad \text{as } t > T_1.$$

This completes proof of lemma 3.1. □

Lemma 3.2. For the solution $c(t)$ of equation (3.1), there exists a $T_2 > 0$, such that

$$c(t) < M_1, \quad \text{as } t > T_2,$$

where M_1 is a positive constant.

Proof. For some $t^* \in [t_0, \infty)$, if $c(t^*) > (e_0 + c_0)$, we compute

$$\dot{c} < 0.$$

So, there must exist T_2, when $t > T_2, c(t) < M_1 = e_0 + c_0$.

Lemma 3.3. For the solution $s(t)$ of equation (3.1),there exists a $T_3 > T_2 > 0$, such that

$$s(t) < m_2, \quad \text{as } t > T_3,$$

where m_2 is a positive constant.

Proof. As just mentioned,

$$c(t) < M_1, \quad \text{as } t > T_2.$$

We get

$$\dot{s} < I_0 - k_1(e_0 + c_0)s + k_1 s M_1 + k_{-1} M_1.$$

By lemmas 2.2 and 2.3, we have

$$s(t) \leqslant y(t) \quad \text{and } y(t) \to \overline{y(t)}, \ \text{ as } t \to \infty,$$

where $y(t)$ is the solution of

$$\begin{aligned} &\dot{y} = I_0 + k_{-1} M_1 + k_1 M_1 y - k_1(e_0 + c_0)y, \quad t \neq n\tau, \\ &y(t^+) = y(t) + \epsilon I_0, \quad t = n\tau, \\ &y(0^+) = s_0 > 0 \end{aligned}$$

and $\overline{y(t)} = \frac{I_0 + k_{-1} M_1}{k_1(e_0 + c_0 - M_1)} - \frac{\epsilon I_0 e^{k_1(e_0 + c_0 - M_1)(t - n\tau)}}{1 - e^{k_1(e_0 + c_0 - M_1)\tau}}$, for $t \in (n\tau, (n+1)\tau]$.

For $t \in (n\tau, (n+1)\tau]$, $\overline{y}(t)$ is a monotonic decreasing function of time t and has a minimum value m_2 at $t = (n+1)\tau$, that is,

$$m_2 = \frac{I_0 + k_{-1} c_{\max}}{k_1(e_0 + c_0 - c_{\max})} - \frac{\epsilon I_0 e^{k_1(e_0 + c_0 - c_{\max})\tau}}{1 - e^{k_1(e_0 + c_0 - c_{\max})\tau}}.$$

So, there must exist a $T_3 > T_2 > 0$, such that

$$s(t) \leqslant m_2 \leqslant y(t), \quad \text{as } t > T_3.$$

This completes proof of lemma 3.3. □

Lemma 3.4. For the solution $c(t)$ of equation (3.1), there exists a $T_4 > 0$, such that

$$c(t) > M_2, \quad \text{as } t > T_4,$$

where M_2 is a positive constant.

Proof. By lemmas 3.1 and 3.3, we know

$$m_1 \leqslant s(t) \leqslant m_2, \quad \text{as } t > \max\{T_1, T_3\}.$$

Therefore, when $t > \max\{T_1, T_3\}$, we get

$$\dot{c} > k_1(e_0 + c_0)m_1 - k_1 m_2 c - (k_{-1} + k_2)c.$$

By lemmas 2.1 and 2.3, we have

$$c(t) \geqslant z(t), \; z(t) \to z^*, \quad \text{as } t \to \infty,$$

where $z(t)$ is the solution of

$$\begin{aligned} &\dot{z} = k_1(e_0 + c_0)m_1 - k_1 m_2 cz - (k_{-1} + k_2)z, \\ &z(0) = c_0 > 0 \end{aligned}$$

and $z^* = k_1(e_0 + c_0)m_1/(k_1 m_2 + k_{-1} + k_2)$.
So, there must exist a $T_4 \geqslant \max\{T_1, T_3\}$, such that

$$c(t) \geqslant z^*$$

namely

$$c(t) \geqslant M_2, \quad \text{as } t > T_4.$$

This completes proof of lemma 3.4 (Figure 3).

4. Graphs of periodic solutions

Figure 3 shows the graphs of periodic solutions with the same initial conditions for figure 2.

5. Conclusion

This work has examined the dissipation and global behavior of enzymatic reactions with impulsive input. Almost all beings in our planet depend on enzymes to complete metabolize, respectively. In the chemical reaction, the form of substrate input is various and it has actual background for impulsive input. Our results better explain the problem with the process of using drugs *in vivo* [9].

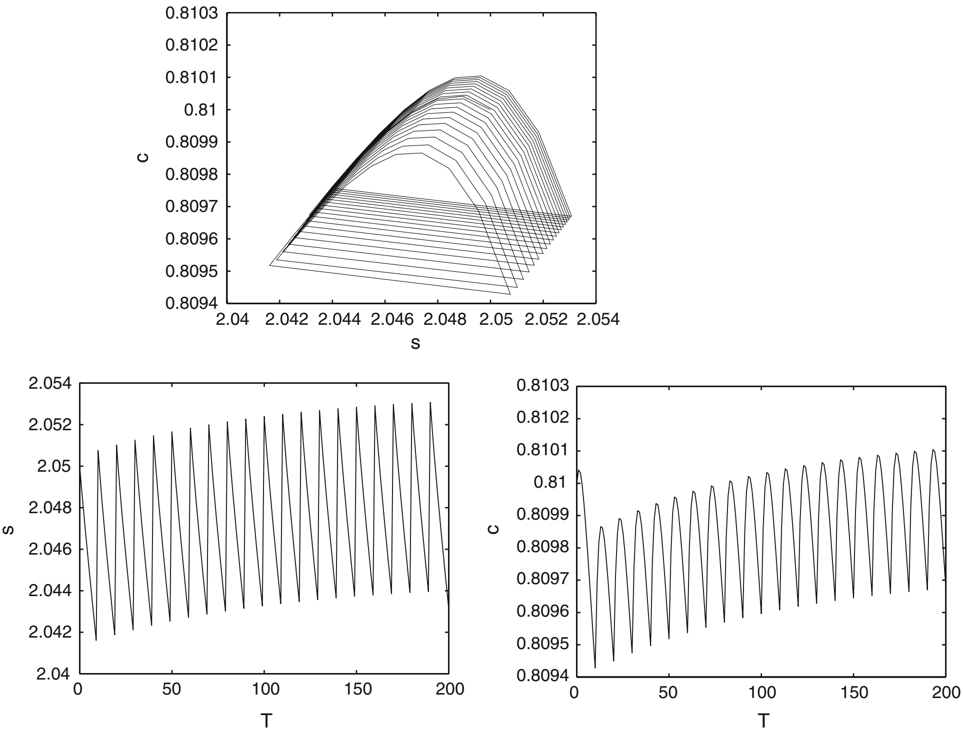

Figure 3. The three graphs are those of reactants x–y plane and time series, respectively. Initial conditions is the same with figure 2. At fixed $a = 1.3$ for $75 \leqslant t \leqslant 100$.

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