Shahid Chamran University of Ahvaz

Journal of Advanced Mathematical Modeling
ISSN (print): 2251-8088, ISSN (on-line): 2645-6141
Vol. x No. x (2024), pp. xx-xx.
DOI: x No.

A NEW APPROACH TO KINETIC ANALYSIS AND MATHEMATICAL MODELING ANALYSIS OF BASIC ENZYME RETRACTION: REACTION KINETICS IN ENZYMATIC T-CELL PROLIFERATION

M.H. RAHMANI DOUST*, M. SARAJ AND S. SAMARGHANDIAN

Communicated by:

Abstract. Chemical reactions have main impact in processes of any alive organism. Their mechanisms have complexity naturally. To do so, development of a simplifying model is essential to understand the governing hypothesis. Our aim is to present mathematical models for enzymes reactions to show how these models represent biochemical phenomena. The catalytic process is important in the present research. We study the comprehensive mathematical modeling framework for basic enzyme kinetics, focusing on catalytic reactions including influence of activators and inhibitors. We start with the second order basic enzyme reaction, which governs essential features of a broad class of biochemical processes. We then extend it to another reactions, investigate and apply the biologically relevant systems such as T-cell proliferation reactions. We modify governing systems of ordinary differential equations by help of non-dimensionalization method, allowing for new insight into kinetic reactions. Initial value problems are formulated based on realistic biological conditions, and the resulting models are analyzed to reveal concentration profiles of key reactants over time. We adequate the our results by MATLAB software simulation.

MSC(2020): 34D20, 80A30, 92B05, 92C40, 92C45.

Keywords: T-cell Proliferation, Mass Action Law, Enzyme Reaction, Logistic Growth.

Received: dd mmmm yyyy, Accepted: dd mmmm yyyy.

*Corresponding author.

1. Introduction

We begin with nomenclature table consisting needful symbols and abbreviations, then present background and applications of mathematics in multidisciplinary sciences such as biology and biochemistry historically. After presenting preliminaries, we approach to mathematical modeling of chemical kinetics for enzyme reactions, and finally investigate solutions of obtained models and their behavior that describes the reactant.

Table 1. Nomenclature table

.

Symble	**Meaning**	**Abbrivation**	**Meaning**
$\rightleftharpoons$	Reversible reaction	*BER*	Basic enzyme reaction
$\rightharpoonup$	Reaction only one way	*LMA*	Law of mass action
$\Longrightarrow$	Imply	*QSSA*	Qsiua-steady-state approximation
$\longrightarrow$	Tend	*IVP*	Initial value problem
$\forall$	Universal quantifier	*ODEs*	Ordinary differential equations
$\exists$	Existential quantifier	T-cell	Thymus (or T-lymphocytes) cell
$\approx$	Nearly equal	APCs	Antigen-presenting cells
$\ll$	Less than so much	SODEs	system of ordinary differential equations
[ ]	Reactant concentration	O	Order of magnitude
$\mathbb{R}$	Real numbers set	k_m	Michaelis constant

Obviously, biochemical reactions and mathematical application has main role in processes of alive organism. Nearly, all of sciences branches especially biochemistry, biology for their continuing have to not only use mathematics but also involve with the mathematics more than last centuries. And so, all of scientists: mathematicians, chemists, physicists, physicians, physiologists have to take help from each other. Practical application of mathematical models to help of unravel the underlying mechanisms involved in the chemical and biological process is so important. Chemical kinetics play the key role in all processes of living organisms such as: biology, ecology, environmental sciences even physiological area.

In the process of mathematical modeling, depending of independent variables, a differential equation or system of differential equations may be appeared. For more details on

this subject one can refer to [22] and [36]. Most of the biochemical reactions are catalyzed by enzymes, each enzyme being highly specific for one type of reaction. Also enzymes are important in regulating biological process such as activators or inhibitors in a reaction. In 1835, Berzelius suggested that most of the biochemical reactions could occur under the influence of a new force which he calls catalytic. In 1878, Kihne coined the term enzyme for this catalytic force, from a Greek word. For more details on enzyme reactions, enzyme kinetics and theories of chemical reactions rates one may refer to the text book such as [1], [10], and [39]. Kinetics is one of the four branches of physical chemistry. To understand and predict the behavior of chemical systems, one should not only consider kinetics but also go to it deeply. Chemical kinetics, in some text references is called as reaction kinetics. Topics such as "chemical kinetics and reaction mechanisms", "rates and mechanisms of chemical reactions", "chemical kinetics","kinetics and mechanisms", may be referred to [4], [5], [11] and [18] respectively. To see a nice text book for who wants go deeply on physical chemistry one may refer to [13]. In 1902, Brown suggested that the enzyme, E, combines with its substrate, S, to form an intermediate complex which then decomposes into the product, P, and E. In 1913, one of the most basic enzyme reactions (abbreviated by *BERs*) introduced by Michaelis and Menten [17]. This model indeed mirror a large number of real reactions and phenomena. The enzyme indeed has catalysis role in these reactions to form a complex matter which in turn is converted into a product with and enzyme. The enzymes effectiveness is reflected in small concentrations needed in their relations in compared with the concentration of the substrates involved. One for going into the subjects such as "enzyme reactions" may refer to [12], [20], [21], [37], [38] and [40]. The models also incorporate regulatory effects through activators and inhibitors, enhancing their biological relevance. To study the subjects such as activation or inhibition in which play the feedback controls role on *BER*, one may see that a problem is led to differential equation that describes the logistic growth model. Verhulst (1838-1845) proposed that a self-limiting process should operate when a population becomes too large. He was the first who introduce the logistic growth. More related references in which the applications of single species with exponential or logistic growth rate are studied may be seen in [6], [9], and [36].

After 1920, V. Volterra proposed a system of ordinary differential equations to exhibit the population dynamics of two interacting species including a prey and predator. He

made some predicts such as increasing in predator fish and decreasing in its prey in the Adriatic sea [42]. Independently, same equations are studied independently by A.J. Lotka to describe a hypothetical chemical reaction in which the chemical concentrations oscillate in the united states [15] on 1925. this leads to the famous problem known as nonlinear system of Lotka-Volterra predator-prey equations employed in biochemical reactions so much. Some of the systems of Lotka- Volterra equations and their applications in biological models related to biochemistry are investigated in [7], [23], [24], [**?**], [25], [26], [27], [28], [29], [30], [31], [32], [33], [34]and [35]. An online tool for analyzing enzyme initial rate data and teaching enzyme kinetics is investigated in [16]. The singular perturbation methods, quasi steady state approximation (abbreviated by $QSSA$) to obtain a uniformly valid asymptotic solution studied by Borghans in [2] on 1996. Control of T-cell activation and signaling by aminoacidic catabolizing enzymes is studied in [3]. One to see a review of the literature on mathematical models of tumor cell proliferation may refer to [8]. Review of T-cell proliferation regulatory factors in treatment and prognostic prediction for solid tumors is studied in [14] on 2023. Mathematical modeling of immunological reactions is investigated in [19]. A review article on T-cells in health and disease may be seen in [41] on 2023. We use reaction mechanisms which are plausible biochemically. Before modeling, we present next definitions needful later.

Definition 1.1. Membranes where enzymes are physically confined and localized in a certain region of space with retention of their catalytic activities, and where enzymes can be used repeatedly and continuously, are called **immobilized enzyme system**.

Definition 1.2. As regarding an enzyme is concerned to be present in small amount compared with the substrate, the assumption is that the substrate concentration does not change during this initial transit stage. This state is called as **quasi-steady state approximation(*QSSA*)**.

Definition 1.3. The process that removes units from equations by converting variables into dimensionless forms using characteristic scales is called **nondimensionalization**.

Definition 1.4. The characteristic time over which certain processes occur is called **timescale** or **transient time** in a chemical reaction.

Definition 1.5. If a substrate that binds at one site increases the binding activity at another site then the substrate is called **activator**; if it decreases the activity it is called **inhibitor**.

Definition 1.6. T-cells (or T-lymphocytes) are crucial for are the major cell components of the adaptive immune system, cell-based immune responsible immune functions to maintain host healthy and prevent various types of diseases and cancer.

2. Modeling and Discussion

The second order reversible biochemical reaction mechanism known as the *BER* in which an enzyme plays as catalysis role. This model is too complicated biochemical model. Because it is qualitative understanding, models of models are first steps. The first model which will be analyzed is the second order reversible having the enzyme as catalysis. This reaction is starting point to the present work. We model and investigate some of the biochemical sequence of consecutive reactions in which having catalytic mechanism mathematically. We will analyze some of the reactions having catalytic process including consequence steps only. The solutions behavior that describes the reactant concentrations is main purpose.

The *BER* is a reaction cycle model. Assume that firstly there are two reactants enzyme and substrate which are denoted by E and S respectively. Moreover, consider one molecule of S combines with a molecule of E to form one molecule of SE. Finally produce molecule of P and one molecule of E. In fact, there is a sequence of reactions where the first reaction is reversible, while the second one is irreversible. The following reaction, therefore, may be obtained:

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} SE \xrightarrow{k_2} P + E \tag{2.1}$$

k_2. All of parameters are considered positive.

The Michaelis constant in the *BER* (2.1) is given by

$$k_m = \frac{k_{-1} + k_2}{k_1} \tag{2.2}$$

Now, we describe the concentrations and reactants as follows:

c $s = [S]$, $e = [E]$, $c = [SE]$ and $p = [P]$ show the reactant concentrations in the *BER* (2.1);

- The letters S, E, SE and P are considered to show reactants matters as: substrate; enzyme, complex obtained matter and product respectively;
- The constant parameters associated with the rates of reactions are denoted by k_1, k_{-1} and k_2. All of parameters are considered positive.
- Time unite and reactant concentration are assumed as second and milligram/milliliter, respectively. However, using dimensionless method these units may omitted.

By considering the above statements and the initial concentration for existing reactants in the *BER* (2.1), one may obtain the following IVP:

$$\begin{cases} \frac{ds}{dt} = -k_1 es + k_{-1} c, & \frac{de}{dt} = -k_1 es + (k_{-1} + k_2) c, \\ \frac{dc}{dt} = k_1 es - (k_{-1} + k_2) c, & \frac{dp}{dt} = k_2 c, \\ s(0) = s_0, \quad e(0) = e_0, & c(0) = p(0) = 0 \end{cases} \tag{2.3}$$

The four equations in the above system exhibit the following mechanisms:

- The first equation statements that the change rate of concentration$[S]$is made up of decreasing rate of $[S][E]$and rate proportional to$[SE]$.
- The second one statements that the change rate of concentration$[E]$is made up of a loos rate of $[S][E]$ and again rate proportional to$[C]$.
- The third one statements that the change rate of concentration$[C]$is made up of increasing rate of$[S][E]$ and decreasing rate proportional to$[C]$.
- The last equation statements that change rate of concentration$[P]$is made up just increasing rate of $[C]$. we also see that this equation is uncoupled from the first three equations.

T-cells are a white blood cell type playing crucial role in the immune system. They are developed from bone marrow derived thymocyte progenitors in the thymus. These cells are the major cell components of the adaptive immune function and system, responsible for protecting, mediating cell-based immune responses to keep the host healthy and prevent various types of diseases and cancer. Types and their jobs are given in Table 2.

T-cell proliferation indeed is regulated by a complex interplay of signals, including the activation of intracellular signaling pathways and the production of cytokines. These processes are initiated by interactions between T-cells and *APCs*. Key enzymes involved in T-cell proliferation include those that degrade amino acids. T-cell proliferation is a complex process involving various enzyme-mediated reactions. These enzymes regulate

TABLE 2. Kinds of T-cell

T-cell Name	**T-cell Duty**
Helper	Direct other immune cells to fight infection
Cytotoxic	Kill or destroy infected cells
Regulatory	Control immune responses and Prevent excessive inflammation and autoimmune reactions
Memory	Provide long-term protection and Initial rapid immune responses upon re-exposure

amino acid availability, glucose metabolism, calcium signaling, ultimately influencing the expansion and function of T-cells in the immune response. Mathematical modeling of T-cell proliferation mediated by enzyme reactions typically involves capturing the complex biological processes by which T-cells grow, divide, and respond to external stimuli such as antigens, cytokines, or co-stimulatory signals. Similarity to the *BER* Michaelis-Menten, applying the *BER* principles to T-cell proliferation in response to an antigen can be approached using mathematical modeling, particularly by combining enzyme kinetics with cell population dynamics. This occurs in various enzyme reactions but arises in a quite different situation involving T-cell proliferation in response to an antigen. By replacing all of reactants components in the *BER* (2.1) as table (3), we obtain the following reactions kinetics:

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \xrightarrow{k_2} E + 2S \tag{2.4}$$

The above reaction kinetics is an automatically enzyme system. In fact, it is not standard Michaelis-Menten, because the product is two molecules of substrate rather than a different product P. Behavior mimics logistic or exponential proliferation in early stages. Biological Interpretation (T-cell Proliferation) The model captures T-cell activation where cytokines bind receptors (enzyme-substrate complex), triggering signal transduction and release of more cytokines, enhancing the signal. It embodies positive feedback: one active complex yields two substrates, which can re-enter the cycle. This explains the explosive expansion of T-cells upon activation. This reaction indeed is based on standard the *BER*

TABLE 3. Reactants Components in the *BER*(2.1) and T-cell Proliferation (2.4)

Components of *BRE*	**Components of T-cell Proliferation**
Subtract (S)	T-cell (proliferating cell)
Enzyme (E)	Site on the antigen-presenting cell (APC)
Complex (SE)	Bound T-cell and antigen-presenting cell complex
Final Product (P)	2 T-cells (original + new proliferated cell)

enzyme kinetics (2.1). Paying attention to the (2.4), we are able to interpret it biologically as follows:

- A T-cell (S) binds to a site on an *APC* (E) to form a complex (C),
- The complex then triggers T-cell proliferation, producing an extra T-cell, and the APC is free again to engage more T-cells,
- The *APC* is not consumed and so behaves like an enzyme,
- This process changes the dynamics and analytical approach since *APCs* may be present in excess,

By simple comparison between the *BER* and T-cell proliferation, we carry out the following two key points:

- In the *BER* (2.1), $\varepsilon = e_0/s_0 \ll 1$, that is the enzyme amount is small quantity,
- In T-cell proliferation, we reverse this: *APC* sites (enzyme analog) may be in excess, so the small parameter is now $\varepsilon = s_0/e_0 \ll 1$.

After replacing the substrate, s-equation in reduced system (**??**), we take the following variables variation:

$$\bar{s}(t) = s(t) + c(t). \tag{2.5}$$

We now add the first and third equations in (2.3) as the equation for the total substrate. It leads to the following equation:

$$\frac{d\bar{s}}{dt} = -k_2 c \tag{2.6}$$

And so, we obtain

$$\frac{dc}{dt} = k_1(e_0 s - sc) - (k_{-1} - k_2)c$$
$$\Rightarrow \frac{dc}{dt} = k_1(e_0 - c)s - \frac{k_{-1} + k_2}{k_1}c$$

By considering Michaelis constant in (2.2), we get the concentration rate for reactant c as follows:

$$\frac{dc}{dt} = k_1[(e_0 - c)(-s - c) - k_m c] \tag{2.7}$$

The above equation which is obtained is this equation for $\bar{s}(t)$ and the third of (2.3) written in terms of c and $\bar{s}$, together with the initial concentrations. Therefore, the following *IVP* becomes:

$$\begin{cases} \frac{d\bar{s}}{dt} = -k_2 c \\ \frac{dc}{dt} = k_1[(e_0 - c)(\bar{s} - c) - k_m c] \\ \bar{s}(0) = s_0, c(0) = 0 \end{cases} \tag{2.8}$$

The qualitative behavior for reactant concentrations of dimensionless IVP (2.8) initial concentrations have been exhibited in Figure 1 and Figure 2.

2.1. **Non-dimensionalization.** It is obvious that the above solutions are implicit functions, and so it is impossible to find out the reactant's concentration as function of t. Thus we should study solution behavior. The analysis of the above model is same the previous case nearly. They derive conditions for an equivalent *QSSA*. The application of the *BER* models combined with differential equations for population dynamics, provides a powerful framework to study and simulate T-cell proliferation in response to antigen stimulation. In fact, by translating the *BER* to a T-cell proliferation, we find out the following matters:

(1) Obtaining mathematical flexibility using the *BER* kinetics;
(2) Leading the reversal of assumptions (enzyme in excess) to different dynamics and asymptotic behavior;
(3) Having predictability model how T-cell expansion is influenced by *APC* availability and binding kinetics.

This approach is useful for not only modeling of immune responses under vaccination or infection but also guiding therapeutic interventions like T-cell immunotherapy. Also it

help us to understand thresholds and saturation in immune activation. After constructing related systems of equations, we go to their interpretation. Paying to system of separable *ODEs* (2.8), we see that the first equation substrate depletion exhibits that the non-dimensionalization substrate concentration $\bar{s}(t)$ is decreasing over time as the enzyme-substrate complex $c(t)$ persists. The constant k_2 represents the rate of product formation from the complex, in standard Michaelis-Menten kinetics. The second equation complex concentration describes that this expression links time to the integral over a rational function of c, possibly derived from solving the differential equation for $c(t)$ in terms of t. Taking variables variation $a = -e_0 - \bar{s} - k_m$ and $b = -e_0\bar{s}$ and after substituting and using initial conditions c_0 and s_0, one can solve the reduced system (2.8).

$$\begin{cases} \bar{s}(t) = -k_2 \int c(t)\, dt \\ k_1 t = -\int \dfrac{1}{c^2 + ac - b}\, dc \end{cases} \tag{2.9}$$

The appeared integral in the 2^{nd} may be reach to the following integral:

$$\int \frac{1}{c^2 + ac - b}\, dc = \int \frac{1}{(c + \frac{a}{2})^2 - (\frac{a^2}{4} + b)}\, dc$$

Therefore, the solution of the above system may be found out as the above. Thus, one is able to determine the long-time behavior of $c(t)$ and $\bar{s}(t)$ may be determined; and sensitivity to parameter changes (k_m and e_0). Regarding the above solutions are implicit functions, we are going to dimensionless the *IVP* (2.8). We first take the variables $\bar{s}(t), c(t)$ and $e(t) = e_0 - c(t)$ to denote the substrate (T-cells), the complex and the effector (or enzyme) respectively. Then we take parameters k_1, k_{-1}, k_2 as rate constants, k_m to denote the Michaelis constant and finally we assume that s_0, e_0 as initial concentrations.

$$Variables \quad Variations \begin{cases} Variables : \tau = k_1 e_0 t, \quad u = \dfrac{\bar{s}}{s_0}, \quad v = \dfrac{c}{e_0} \\ Parameters : \alpha = \frac{k_2}{k_1 e_0}, \quad \beta = \frac{k_m}{k_1 e_0}, \quad \sigma = \frac{s_0}{e_0} \end{cases} \tag{2.10}$$

To find out $\frac{du}{d\tau}$ and $\frac{dv}{d\tau}$, we use the chain rule in derivatives. Starting with the first equation in the *IVP* (2.8), we get

$$\begin{aligned} \tfrac{du}{d\tau} &= \frac{du}{ds} \cdot \frac{ds}{dt} \cdot \frac{dt}{d\tau} = \frac{1}{s_0} \cdot (-k_2 c) \cdot \frac{1}{k_1 e_0} \\ &= \frac{1}{s_0} \cdot (-k_2 e_0 v) \cdot \frac{1}{k_1 e_0} = -\tfrac{k_2}{k_1 s_0} v = -\tfrac{\alpha}{\sigma} v \end{aligned}$$

Thus, the first dimensionless equation is as follow:

$$\frac{du}{d\tau} = -\frac{\alpha}{\sigma}v \tag{2.11}$$

We now continue this process for the second equation similarly:

$$\frac{dv}{d\tau} = \frac{dv}{dc}\cdot\frac{dc}{dt}\cdot\frac{dt}{d\tau} = \frac{1}{e_0}\cdot\left(k_1\left[(e_0-c)(\bar{s}-c)-k_m c\right]\right)\cdot\frac{1}{k_1 e_0}$$
$$= \frac{1}{e_0}\cdot\left(k_1\left[(e_0-e_0v)(e_0u-e_0v)-k_m e_0 v\right]\right)\cdot\frac{1}{k_1 e_0} = (1-v)(\sigma u - v) - \beta v$$

Thus, the second dimensionless equation is as follows:

$$\frac{dv}{d\tau} = (1-v)(\sigma u - v) - \beta v \tag{2.12}$$

Therefore, the dimensional less system may obtain is given by:

$$\begin{cases} \frac{du}{d\tau} = -\frac{\alpha}{\sigma}v \\ \frac{dv}{d\tau} = (1-v)(\sigma u - v) - \beta v \\ u(0) = 1, \quad v(0) = 0 \end{cases} \tag{2.13}$$

This non-dimensionalization and analytical solution strategy help us to simplify and study biochemical kinetics systems same as Michaelis-Menten equations, the *BER*, T-cell metabolic regulation (in an immunological context). We are going to analyze how substrate depletion due to enzyme activity affects T-cell proliferation, where $c(t)$ is a critical intermediate (as complex). The qualitative behavior for reactant concentrations of last system associated to the (2.13) for different parameters have been exhibited in Figure 3 and Figure 4.

2.2. **Transient Times.** We are interested to estimate, the transient timescale, time required for the system to reach quasi-steady-state or a significant shift in substrate/enzyme dynamics. In fact, timescale is typically the time t_{trans} it takes for the system one of the following processes:

(1) To reach to the *QSSA* for the complex reactant $c(t)$,
(2) To exhibit a significant change in the substrate or complex concentrations,
(3) To separate fast dynamics from slow dynamics.

We should define characteristic times for complex formation which is governed by enzyme-substrate binding kinetics, and substrate depletion or regeneration(governed by

catalytic turnover). The timescale for the complex means that time that takes $c(t)$ to build up, which may be carried out by the following equation:

$$\tau_c \equiv \frac{1}{k_1 s_0 + k_{-1} + k_2} \tag{2.14}$$

and so, assuming $\varepsilon = \frac{e_0}{s_0}$, we obtain

$$\frac{d\bar{c}}{d\tau} = (1 - \bar{c})(\bar{s} - \varepsilon\bar{c}) - k_m\bar{c} \tag{2.15}$$

This form is standard for singular perturbation and we get following estimations:

(1) Fast transient for $c(t)$ in which timescale $\tau_c \cong 1$,
(2) Slow change in $\bar{s}$ in which timescale $\tau_s \cong \frac{1}{\varepsilon}$.

The complex builds up rapidly, after which substrate dynamics and autocatalysis dominate. We would like to classify the timescales into three following classes:

(1) Early phase (fast); this means that the complex $c(t)$ rapidly approaches a quasi-steady level,
(2) Mid phase (slower); this means that the substrate $\bar{s}(t)$ increases due to $2S$ production,
(3) Late phase; this possible runaway substrate increase or saturation depending on system closure.

Therefore, the transient timescale for complex τ_c in (2.14) is so short time due to high k_1, and then system evolves slowly due to substrate regeneration. Finally, the value of small parameter $\varepsilon = \frac{e_0}{s_0}$, enables to *QSSA*. Now we want to analyze the *QSSA* for $c(t)$. The *QSSA* implies that to occur $\frac{dc}{dt} \approx 0$, that is the complex equilibrates rapidly compared to substrate and product. After solving $e_0\bar{s} - e_0 c - \bar{s}c + c^2 = k_m c$, we get

$$c^2 - (e_0 + \bar{s} + k_m)c + e_0\bar{s} = 0 \tag{2.16}$$

Using the following quadratic formula, we can find the roots of the above equation:

$$c(\bar{s}) = \frac{1}{2}\left[e_0 + \bar{s} + k_m \pm \sqrt{(e_0 + \bar{s} + k_m)^2 - 4e_0\bar{s}}\quad\right] \tag{2.17}$$

Choosing the above minus root, we will be ensured $c(\bar{s}) \leq \min(e_0, \bar{s})$ and therefore, the final *QSSA* may be find out by following formula:

$$c(\bar{s}(t)) = \frac{1}{2}\left[e_0 + \bar{s}(t) + k_m \pm \sqrt{(e_0 + \bar{s}(t) + k_m)^2 - 4e_0\bar{s}(t)} \quad \right] \tag{2.18}$$

This expresses $c(t)$ as a function of substrate concentration. And so,

$$\frac{d\bar{s}}{dt} = -k_2 c(\bar{s}(t)) \tag{2.19}$$

Therefore, we may conduct that it reduces the system to a single *ODE* in base of $\bar{s}$, greatly simplifying analysis and moreover, it works well when $e_0 \ll s_0$.

The complete model is given by (2.8). Assuming $dc/dt \approx 0$ complex forms and decays quickly, and regarding to (2.18), we get the following closed-form single *ODE*:

$$\frac{d\bar{s}}{dt} = -k_2 \cdot \frac{1}{2}\left[e_0 + \bar{s} + k_m \pm \sqrt{(e_0 + \bar{s} + k_m)^2 - 4e_0\bar{s}} \quad \right] \tag{2.20}$$

This is the first-order nonlinear *ODE* for $\bar{s}(t)$, suitable for integration and analysis of phase plane and prediction the long-term behavior (such as steady state). Now we see that the value of $\bar{s}(t)$ increases over time due to autocatalysis, and so the sign of *ODE* should be:

$$\frac{d\bar{s}}{dt} = +k_2 c(\bar{s}(t)). \tag{2.21}$$

We thus get the following *IVP*:

$$\begin{cases} \frac{d\bar{s}}{dt} = \frac{k_2}{2}\left[e_0 + \bar{s} + k_m \pm \sqrt{(e_0 + \bar{s} + k_m)^2 - 4e_0\bar{s}} \right] \\ \bar{s}(0) = s_0 \end{cases} \tag{2.22}$$

Now, we nondimensionalize the *ODE* (2.22) for substrate concentration $\bar{s}(t)$, derived from your autocatalytic enzyme kinetics under the *QSSA*:

$$Variables \quad Variations \begin{cases} Variables : \tau = k_2 t, \quad \bar{s}(t) = s_0 \cdot \hat{s}(\tau) s(t) \\ Parameters : \varepsilon = \frac{e_0}{s_0}, \quad \kappa = \frac{k_m}{s_0} \end{cases} \tag{2.23}$$

Substitute into the *ODE* (2.22), we compute:

$$\frac{d\bar{s}}{dt} = \frac{ds_0\hat{s}}{dt} = s_0\frac{d\hat{s}}{dt} = s_0 \cdot k_2 \cdot \frac{d\hat{s}}{d\tau} \tag{2.24}$$

So the *ODE* (2.22) becomes as follow:

$$\frac{d\bar{s}}{dt} = s_0 \cdot k_2 \cdot \frac{d\hat{s}}{d\tau} = \frac{k_2}{2}\left[e_0 + s_0\hat{s} + k_m \pm \sqrt{(e_0 + s_0\hat{s} + k_m)^2 - 4e_0s_0\hat{s}}\right] \tag{2.25}$$

By simplification for k_2 and s_0, we get the following dimensionless *IVP*:

$$\begin{cases} \frac{d\hat{s}}{d\tau} = \frac{1}{2}\left[\varepsilon + \hat{s} + \kappa \pm \sqrt{(\varepsilon + \hat{s} + \kappa)^2 - 4\varepsilon\hat{s}}\right] \\ \hat{s}(0) = 1 \end{cases} \tag{2.26}$$

The above *IVP* describes dimensionless substrate buildup over dimensionless time. Behavior depends critically on ε (enzyme-to-substrate ratio) and κ (Michaelis constant scale). By help of simulation method, we have studied the solutions behavior of implicit functions $\bar{s}(t)$ and $c(t)$. Their behavior are described in diagram which are drawn in Figure 5.

We finally summarize T-cell proliferation kinetics as follows:

Two main questions in T-cell proliferation kinetics may be asked as: how fast do T-cells begin expanding after antigen stimulation and how long to reach peak or steady-state The model T-cell population $T(t)$ usually may lead to the following growth (or decay) of logistic equations,

$$\frac{dT}{dt} = \alpha T - \beta T^2 \tag{2.27}$$

Two timescales concepts are become as follow:

(1) For exponential growth model, time to reach initial activation time or initial growth time is given by $\tau_c = t_{\text{growth}} \sim \frac{1}{\alpha}$
(2) For logistic growth model or density-limited model, time to approach steady state (or carrying capacity of the environment) is given by $\tau_s = t_{\text{logistic}} \sim \frac{1}{\beta T_0}$.

In timescale and dimensionless process, one may reduce the system, design experimental estimate the parameters which are so important. In the mechanism of model reduction, we are able to find out fast variables can be assumed to equilibrate (QSSA), allowing simpler models. While the experimental design helps to determine how long to run an assay or collect data. By estimating the existing parameters, we are able to find out the

characteristic times in which help us to fit obtained model to data more robustly. We are able to compare timescale of reaction kinetics in the *BER* (2.1) and enzymatic T-cell proliferation (2.4) as follow: The timescale in the *BER* is that time to form complex or deplete substrate which is $\frac{1}{k_1(s_0+k_m)}$ while the timescale in T-cell proliferation is that time for significant expansion or approach to steady state which is $\frac{1}{\alpha}$ or $\frac{1}{\beta T_0}$.

3. Numerical Simulation

The obtained results are adequate to chemical reactions kinetics by MATLAB software. In fact, simulation conducted using MATLAB, demonstrate the system behavior under various parameter regimes. All of obtained solutions graphs have been drawn after each related IVP. The details of parameters, initial concentrations of reactants and time have been becoming after each graph. In fact, each drawn graph exhibits the behavior of reactant concentrations, and so it helps us to interpret, analyze and predict the behavior of reaction mechanism.

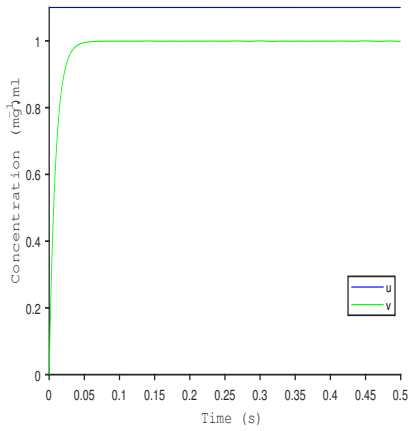


Figure 1. The Diagram of Solution Behavior of IVP (2.8) Associated to The T-Cell Prolifreaction Rraction (2.4); Note: Regarding in the IVP (2.8) e_0 is shown as parameter. So does in this figure. Constant Parameters of Reactions Rtae: $k_2 = k_1 = 10^{-1}, e_0 = 5$; Initial Concentration of Reatants: $s(0) = 1.1, c(0) = 0$; Time: $\tau \in [0, 5]$

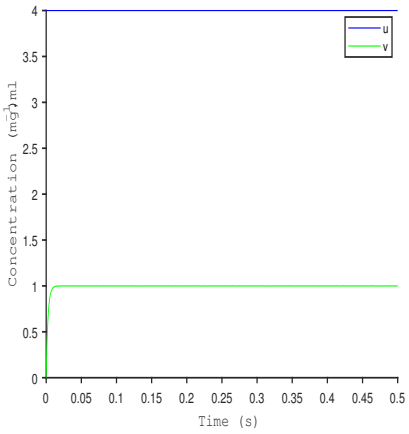


FIGURE 2. The Diagram of Solution Behavior of IVP (2.8) Associated to The T-Cell Proliferation Reaction (2.4);Note: Regarding in the IVP (2.8) e_0 is shown as parameter. So does in this figure. Constant Parameters of Reactions Rate: $k_2 = k_1 = 10^{-1}, e_0 = 5$; Initial Concentration of Reactants: $s(0) = 4, c(0) = 0$; Time: $\tau \in [0, 5]$

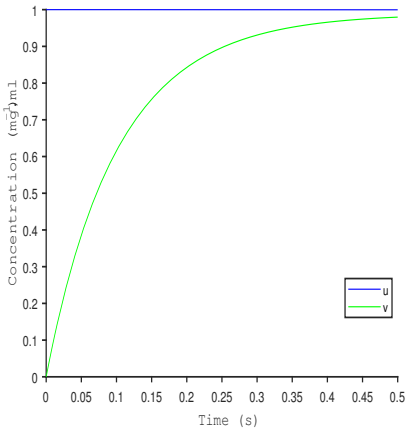


FIGURE 3. The Diagram of Solution Behavior of Dimensionless IVP (2.13); Constant Parameters of Reactions Rate: $\alpha = 10^{-2}, \beta = 10^{-1}, \sigma = 10$; Initial Concentration of Reactant: $u(0) = 1, v(0) = 0$; Time: $\tau \in [0, 1]$

4. CONCLUSION

The biochemical reactions have received conspicuous attention in the multidisciplinary sciences area because of playing the key role in all processes of living organisms. Modeling of these reactions, what we want from a model is some understanding of the underlying dynamics and mechanisms governing the phenomena. The first step therefore is to find a biologically reasonable model which qualitatively describes the phenomena behavior. In

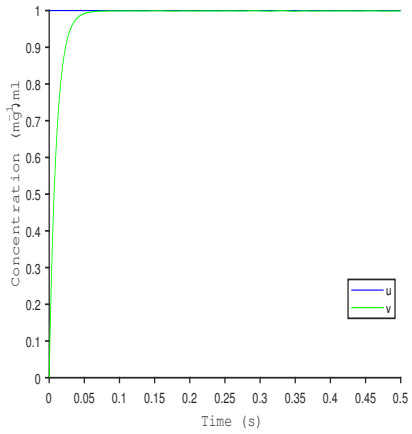


FIGURE 4. The Diagram of Solution Behavior of Dimensionless IVP (2.13); Constant Parameters of Reactions Rate: $\alpha = 10^{-2}, \beta = 10^{-1}, \sigma = 100$; Initial Concentration of Reactant: $u(0) = 1, v(0) = 0$; Time: $\tau \in [0, 1]$

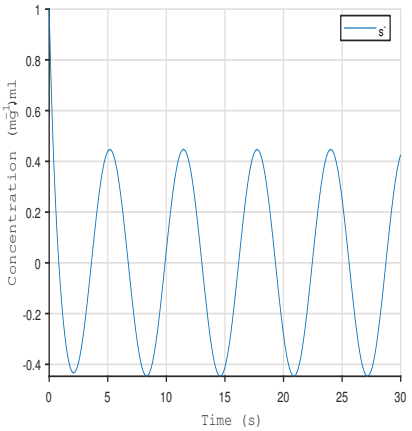


FIGURE 5. The Diagram of Solution Behavior of IVP (2.8) Associated to The T-Cell Proliferation Reaction (2.4);Note:Regarding in the IVP (2.8) e_0 is shown as parameter. So does in this figure. Constant Parameters of Reactions Rate:$k = 10^{-1}, \varepsilon = 10$; Initial Concentration of Reactants:$s^-(0) = 1$; Time:$\tau \in [0, 30]$

this regard we focused on modeling, analyzing and interpreting the *BER* and its extensions in various aspects. The aforementioned investigated reactions are suicidal substrate and cooperative mechanisms which having practical applications in biology. Mathematical models of T-cell proliferation, especially when incorporating enzyme kinetics, are powerful tools in medicine. These models help to clinicians, immunologists, and pharmaceutical researchers understand in the process of predicting, and manipulating immune responses in various disease contexts. In fact, the applications of T-cell modeling are as

immunotherapy optimization, autoimmune disease modeling, vaccine response prediction, drug targeting for kinase inhibitors. These modeling help us to optimize dosing and timing of immune checkpoint inhibitors. Used to simulate T-cell responses to tumor antigens and predict patient specific outcomes. For instance, predict how inhibitors of enzymes like *ZAP*-70 affect CD8+ T-cell expansion and cytotoxicity in solid tumors. Predicts T-cell dynamics during viral infections (such as HIV, *COVID*-19), supports design of antiviral therapies that enhance T-cell responses. It seems wise that some of the proposed reactions may not occur in reality. Finally, we should note that the results align well with expectations from biochemical kinetics may serve as a foundation for simulation tools in chemical biology and systems immunology. One may extend the current model to include soluble mediators. And so one may incorporate IL 2 dynamics through an additional variable L(t) representing free IL 2, with production proportional to T cell density and consumption via receptor binding. This extension provides a more realistic representation of T cell activation while maintaining the core APC mediated mechanism. In some related future researches, one may consider this topic in which having practical applications.

Acknowledgments

Authors would like to express their gratitude to Dr. B. Haghighi, Professor of University of Neyshabur for carefully reading this article and giving his valuable idea.

References

[1] Bisswanger, H. 2008. *Enzyme Kinetics Principles and Methods*, Wiley-VCH.

[2] Borghans, J.A.M., DeBore, R.J. and Segal, L.A., 1996. Extending The Quasi-Steady State Approximiation by Changing Variables, *Bull. Math. Biol.*, *58* pp.43-63.

[3] Castellano, F., Frenkel, V.M., 2020. Control of T-cell Activation and Signaling by Aminoacid Catabolizing Enzymes, *Frontiers in Cell and Developmental Biology*, *8*, 613416. 10.3389/fcell.2020.613416. hal-03192105.

[4] Espenson, J.H., 1995. *Chemical Kinetics and Reaction Mecanisms*, Mc-Graw-Hill.

[5] Gardiner, W.C., 1969. *Rates and Mechanisms of Chemical Reactions*, Benjamin.

[6] Ghasem Abadi, A. , Rahmani Doust, M.H., 2021. A Study on The Ecological Initial Value Problems: The Exponential and Logistic Growth Rates for Harvested Single Species Models, Part of Book: *Advances in Intelligent Systems and Computing*, *1356*, pp.155-166.

[7] Ghasem Abadi, A., Rahmani Doust, M.H. 2021. Investigating the dynamics of Lotka Volterra model with disease in the prey and predator species', International Journal of Nonlinear Analysis and Applications, *12*(1), pp.633-648. doi: 10.22075/ijnaa.2021.4867.

[8] Jarrett, A.M., Lima, E.A.B.F., Hormuth,D.A., McKenna, M.T., Feng, X., Ekrut, D.A., Resende, A.C.M., Brock, A., and Yankeelov, T.E., 2018. Mathematical Models of Tumor Cell Proliferation: A Review of the Literature, *Expert Rev Anticancer Ther. 18* (12), pp.1271-1286. doi:10.1080/14737140.2018.1527689.

[9] Ho, C.P., Lin, C.H., 2016. A New Approach to The Logistic Modeling Population Having Harvesting Factor, *Yugoslav Journal of Operations Research*, *26* (3) pp.381-392.

[10] Kerneves, J.P. , 1980. *Enzyme Mathematics*, North Holland Publishing.

[11] Laidler, K.J., 1987. *Chemical Kinetics*, Harper and Row Clarendon Press.

[12] Laidler, K.J., Bunting, P.S., 1977. *The Chemical Kinetics of Enzyme Action*, Oxford, Clarendon Press.

[13] Levine, IRA.N., 2009. *Physical Chemistry*, The McGraw-Hill.

[14] Li, J., Ma, S., Pei, H., Jiang, J., Zou, Q., Lv, Z., 2023. Review of T-cell Proliferation Regulatory Factors in Treatment and Prognostic Prediction for Solid Tumors, *Heliyon*, *9*, pp.321-329.

[15] Lotka, A.J., 1956. *Elements of Mathematical Biology*, Dover.

[16] Mak, D.A. , Dunn, S., Coombes, D., Carere,C.R., Allison, J.R. , Nock, V. , Hudson, A.O. , Dobson, R.C.J., , 2024. Enzyme Kinetics Analysis: An Online Tool for Analyzing Enzyme Initial Rate Data and Teaching Enzyme Kinetics, *Biochem Mol. Biol. Educ.*, *52*(3), pp.348-358.

[17] Michaelis, L., Menten, M.I., 1913. Die Kinetics Der Invertinwirkung, *Biochem*, *49*, pp.333-369.

[18] Moore, , Pearson,R.G., 1981. *Kinetics and Mechanism*, Wiley-Interscience.

[19] Morel, P.A., 1998. *Mathematical Modeling of Immunological Reactions*, *3*, pp.338-347.

[20] Murray, J.D. , 2003. *Mathematical Biology*, *Vol.1*, New York, Springer.

[21] Murray, J.D. , 1977. *Nonlinear Differential Equations Models in Biology*, Oxford, Clarendon Press.

[22] Penny, E., 2005. *Differential Equations and Boundary Value Problems Computing and Modeling*, New Delhi, Pearson Education.

[23] Rahmani Doust, M.H. 2015. An Analysis on The Lotka-Volterra Food Chain Model: Stability, *Caspian Journal of Mathematical Sciences*, *4*(1), pp. 87-94.

[24] Rahmani Doust, M.H., 2015. The Efficiency of Harvested Factor; Lotka-Volterra Predator-Prey Model, *Caspian Journal of Mathematical Sciences*, *4*(1), pp. 51-59.

[25] Rahmani Doust, M.H., Ghsem Abadi, A. 2016. Permanency and Asymptotic Behavior of The Generalized Lotka-Volterra Food Chain System, *Caspian Journal of Mathematical Sciences*, *5*(1), pp. 1-5.

[26] Rahmani Doust, M.H., Gholizade, S., 2014. An Analysis of The Modified Lotka-Volterra Predator-Prey Equations, *General Mathematical Notes*, *25*(2), pp.1-5.

[27] Rahmani Doust, M.H., GHolizade, S., 2014. The Lotka-Volterra Predator-Prey Equations, *Caspian Journal of Mathematical Sciences*, *3*(2), pp. 221-225.

[28] Rahmani Doust, M.H., Haghighifar, F., 2021. *Differential Equations and Ecology*, University of Neyshabur.

[29] Rahmani Doust, M.H., Haghighifar, F., 2011. The Lotka-Volterra Predator-Prey System; Having Interspecific Interactions or Harvested Factor, *Journal of Intelligent System Research*, *5*(2), pp. 105-111.

[30] Rahmani Doust, M. H., Haghighifar, F., 2014. The Stability of Some Systems of Harvested Lotka-Volterra Predator-Prey Equations, *Caspian Journal of Mathematical Sciences*, *3*(1), pp. 131-139.

[31] Rahmani Doust, M. H., Haghighifar, F., 2011. Two Species Lotka-Volterra Harvested Model Having Competition Interaspecific Factor, *Journal of Analysis and computation*, *7*(2), pp. 105-112.

[32] Rahmani Doust, M. H., Haghighifar, F., Modoodi, M.N., 2012. he Lotka-Volterra Competition Model, *Proc. Jangjeon Math. Soc.*, *15*(3), pp. 259-265.

[33] Rahmani Doust, M.H., Rangarajan, R., 2008. Global Analysis of a Lotka- Volterra Predator-Prey Model with Intraspecies Competition, *Journal of Analysis and comptation*, *4*(1), pp. 43-50.

[34] Rahmani Doust, M.H., Rangarajan, R., M.N. Modoodi, 2008. Analysis of Predator-Prey Equations with Intraspecies Coexistence, *Ultra Sciences*, *20*(3), pp.819-824.

[35] Rahmani Doust, M.H. , Lokesha, V. , Ghsem Abadi, A., 2020. Analysis of The Picards Iteration Method and Stability for Ecological Initial Value Problems of Single Species Models with Harvesting Factor, *European J. Appl. Math.*, *13*(5), pp. 1176-1198.

[36] Rahmani Doust, M.H. , Saraj, M., 2015., The Logistic Modeling Population; Having Harvesting Factor, *Yugoslav Journal of Operations Research*, *25*(1), pp. 107-115.

[37] Reberts, D.V. ,1977. *Enzyme Kinetics*, Cambridge University Press.

[38] Rubinow, S.L., 1975. *Introduction to Mathematical Biology*, John Wiley.

[39] Schulz, A.R. 1994. *Enzyme Kinetics*, Cambridge University Press.

[40] Segal, A.L. 1988. On The Validity of The Steady State Assumption of Enzyme Kinetics, *Bull. Math. Biol.*, *50*, pp. 579-593.

[41] Sun, L., Su,Y., Jiao, A., Wang, X., and Zhang, B., 2023. T-cells in Health and Disease, *Signal Transduction and Targeted Therapy* 8:235 ; https://doi.org/10.1038/s41392-023-01471-y.

[42] Volterra, V., 1931. *Variations and Fluctuations of The Number of Individuals in Animal Species Living Together*, Translated from 1928 edition by R. N. Chapman, Animal Ecology.

M.H. Rahmani Doust
Department of Mathematics,
Faculty of Sciences,
University of Neyshabur,
Neyshabur, Iran
Email: mh.rahmanidoust@neyshabur.ac.ir

M. Saraj
Department of Mathematics,
Faculty of Mathematical Sciences and Computer,
Shahid Chamran University of Ahvaz,
Ahvaz, Iran
Email: msaraj@scu.ac.ir

S. Samarghandian
Department of Medical Physiology,
Faculty of Medicine,
Neyshabur University of Medidical Sciences,
Neyshabur, Iran
Email:samarghandians1@nums.ac.ir

©2024 Shahid Chamran University of Ahvaz, Ahvaz, Iran. This article is an open-access article distributed under the terms and conditions of the Creative Commons Attribution-NonComertial 4.0 International (CC BY-NC 4.0 license) (http://creativecommons.org/licenses/by-nc/4.0/).