Mathematical Modeling and Analysis Enzyme Kinetics in the sense of Caputo Fabrizio Fractional Derivative

A Thesis Submitted to the Department of Mathematics, Jimma University in Partial Fulfillment for the Requirements of the Degree of Masters of Science (M.Sc.) in Mathematics

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Jimma, Ethiopia

Declaration

Here, I submit a thesis entitled "**Mathematical Modeling and Analysis Enzyme Kinetics in the sense of Caputo Fabrizio Fractional Derivative"** for the award of degree of Master of Science in Mathematics. I, the undersigned declare that, this study is original and it has not been submitted to any institution elsewhere for the award of any academic degree or the like, where other sources of information have been used, they have been acknowledged.

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The work has been done under the supervision and approval of advisor and Co-Advisor

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Abstract

In this thesis, Mathematical model of enzyme kinetics in the sense of Caputo-Fabrizio fractional derivative was investigated. The thesis encompasses the following fruitful findings. Existence and uniqueness solution of the model was proved. Iterative numerical scheme (Adams Bash forth method) was proposed for the model. In order to verify the applicability of the result, MATLAB simulation was implemented and agreed with analytical result.

Key words: Mathematical model, Fractional derivative, Existence and uniqueness of solution, Iterative numerical scheme.

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CHAPTER ONE

1. INTRODUCTION

1.1 Background of the Study

Enzyme kinetics is the study of the rates of enzyme-catalyzed chemical reactions. In enzyme kinetics, the reaction rate is measured and the effects of varying the conditions of the reaction are investigated. Studying an enzyme's kinetics in this way can reveal the catalytic mechanism of this enzyme, its role in metabolism, how its activity is controlled, and how a drug or a modifier (inhibitor or activator) might affect the rate. An enzyme is typically a protein molecule that promotes a reaction of another molecule, its substrate. This binds to the active site of the enzyme to produce an enzyme-substrate complex, and is transformed into an enzyme-product complex and from there to product. The study of enzyme kinetics is important for two basic reasons. Firstly, it helps explain how enzymes work, and secondly, it helps predict how enzymes behave in living organisms. For prediction, there is important tool called mathematical modeling.

Mathematical model plays indispensable role in different field of disciplines such as physics, biology, and electrical engineering and also in the social sciences (such as economics, sociology and political science). Physicist, Engineers, Computer scientist and Economists use mathematical models most extensively. Mathematical modeling can play a significant role in the efficient and sustainable management of renewable resources. It is mainly used to describe the real phenomena leading to design better prediction, prevention, management and control techniques. Several well documented mathematical models regarding real life problems can be found by (Biswas *et al.,* 2017; Biswas *et al.*, 2016; Chaudhary, 1988; Clark, 1979; Dubey *et al.,* 2003 and Mondal *et al.*, 2017).

Mathematical models using ordinary differential equations with integer order have remarkable role in understanding the dynamics of enzyme kinetics. Several scholars applied mathematical model with integer order for enzyme kinetics and obtained interesting results. Mathematical models involving the known ordinary differentiation could be used to capture dynamical systems of infectious disease, when only initial conditions are used to predict future behaviors of the spread of the disease. However, when the situation is unpredictable, due to uncertainties associated with, ordinal derivatives and their associated integral operators show deficiency (Pinto *et al.*, 2018). In order to overcome such restriction, fractional order differential equation models seem more realistic than the integer order models. Mathematical models with integer order derivative do not determine the high degree of accuracy to model infectious diseases. As a result, fractional differential equations were introduced to handle such problems, which have many applications in applied fields like production problems, optimization problem, artificial intelligence, medical diagnoses, robotics, cosmology and many more.

In the last few decades, the fractional differential has been used in mathematical modeling of biological phenomena (Lia *et al.*, 2017 and Ahmed *et al.*, 2020). Recently, some authors have considered mathematical models of COVID-19 under fractional order derivatives and produced very good results (Abdo *et al.*, 2020 and Khan and Atangana, 2020). In spite of all the above investigations for corona virus disease prediction and control via mathematical model, there is still a room for improvement.

Accordingly, the subject of fractional calculus has gained popularity and importance, mainly due to its demonstrated applications in numerous diverse and widespread fields of science and engineering. For example, fractional calculus has been successfully applied to system biology (Cole, 1933), physics (Debnath, 2003), chemistry and biochemistry (Yuste *et al.*2004), hydrology (Lin, 2007), medicine (Assaleh and Ahmad, 2007) and finance (Chen, 2008). Nowadays, fractional order derivative is widely used in the mathematical modeling and have noticeable importance (Magin, 2010). Some researcher (Owolabi and Pindza, 2019; Owolabi and Atangana, 2019 and Owolabi and Atangana, 2018) used mathematical model in the sense of fractional order derivative and have received tremendous success.

Bearing in mind the useful applications of fractional derivative several scholars conducted a research on modeling using fractional derivative for different infectious disease. For example, Dokuyucu and Dutta (2020) modeled fractional order based mathematical model for Ebola Virus spreading in certain parts of Africa. They provided numerical solution for the generalized model by using Atangana and Owolabi numerical method. Mathematical model based on fractional order derivative for HIV infection was modeled by (Ding and Ye, 2009). They showed that model has non-negative solutions, as preferred in any population dynamics and also point out analysis on the stability of equilibrium in a detailed.

Arshad *et al.*(2016) also investigated a fractional order derivative model and obtained numerical simulation for immunogenic tumors. They studied the model based on fractional derivative growing tumor cell population and also observed that growth rate in death of immune cells has significant role in tumor dynamical and system consisting saddle-node and trans critical bifurcation analysis.

Recently, Khan and Atangana (2020) developed a fractional order model for the COVID-19 pandemic. Wu *et al.* (2020) developed susceptible exposed infected recovered (SEIR) model to study the transmission of the Covid-19 and reported the basic reproductive number for validated data recoded from December 31, 2019 to January 28, 2020.

Despite all the above studies, as per the authors knowledge there is still paucity of knowledge with regard to mathematical model of enzyme kinetics in the sense of fractional derivatives. Consequently, the main objective of this study is to develop a new mathematical model of enzyme kinetics in the sense of Caputo-Fabrizio fractional order derivatives followed by some mathematical analysis and MATLAB simulation.

1.2. Statement of the problem

Mathematical models with integer order derivative do not determine the high degree of accuracy to model infectious diseases. As a result, fractional differential equations were introduced to handle such problems, which have many applications in applied fields like production problems, optimization problem, artificial intelligence, medical diagnoses, robotics, cosmology and many more. In the last few decades, the fractional differential has been used in mathematical modeling of biological phenomena (Lia *et al.*, 2017 and Ahmed *et al.*, 2020). This is because fractional calculus can explain and process the retention and heritage properties of various materials more accurately than integer-order models. Researchers, therefore, expanded the classical calculus to the fractional-order via fractional-order modeling using different mathematical techniques (Baleanu *et al.*, 2020 and Yildiz *et al.*, 2018).

Several fractional differential operators like Riemann-Liouville, Hilfer, Caputo, etc. are mostly used in the modeling of physical problems. However, these fractional derivative possess a power law kernel and have own limitations, and reduce the field of application of fractional derivative.

To deal with such type of difficulty, Caputo and Fabrizio (2015) have developed an alternate fractional differential operator having a non-singular kernel with exponential decay. The Caputo-Fabrizio operator has attracted many research scholars due to the fact that it has a non-singular kernel and to be found most appropriate for modeling some class of real world problem.

As a result, motivated by the useful applications of fractional order derivative and the above studies, it sounds to attempt the following further investigation for enzyme kinetics.

- ❖ Developing a new mathematical model for enzyme kinetics in the sense of Caputo - Fabrizio fractional order derivative,
- ❖ Existence and uniqueness solution for the model,
- ❖ Proposing iterative numerical scheme for the approximate solution of the model.

1.3 Objectives of the Study

1.3.1 General Objective

The general objective of this study is to develop a new mathematical model for enzyme kinetics in the sense of Caputo-Fabrizio fractional derivative based on compartmental approach and to investigate some rigorous mathematical analysis for the model.

1.3.2 Specific objectives

The specific objectives of the study are to:

- develop a new mathematical model for enzyme kinetics in the sense of Caputo -Fabrizio fractional order derivative,
- prove existence and uniqueness solution for the model,
- Propose iterative numerical scheme for the approximate solution of the model.

1.4 Significance of the Study

The findings of this research is used for others scholars working on this area as foot step. It also used to give clear understanding on how enzyme substrate works in the sense of mathematics.

1.5 Delimitation of the Study

The study is delimited to mathematical modeling and analysis of enzyme kinetics for reversible process.

CHAPTER TWO

2. LITERATURE REVIEW

Recently, experimental evidence shows that dynamics problems in nature follow a fractional calculus analysis. The relevant field of research is a fast growing area, due to its numerous applications in diverse and widespread fields of engineering and science; such as chemical models, physics, signal and image processing, quantum mechanics, control theory, nonlinear dynamics, biological population models, optimization theory, and much more (Hilfer, 2000; Samko *et al.,* 1993; Yang & Huang, 2013). Instantly, it is evident that dealing with a dynamical system with memory effects is one of the biggest challenges for researchers. Fractional calculus has a direct link to dynamical systems (with memory effect). Therefore, fractional differential equations (FDEs) present a novel technique developed to model phenomena related to the dynamics of the aforesaid fields of science (Ali *et al.,* 2016).

Fractional derivatives are global in nature and offer a greater degree of freedom compared to the conventional derivatives. Numerous researchers have investigated various features of FDEs concerning the existence, stability analysis, and approximate solutions. They utilized different techniques of fixed-point theory and numerical analysis to investigate the existence theory, stability analysis, and approximate solutions of FDEs (Wu *et al.,* 2013; Nanware & Dhaigude, 2014).

The importance of biocatalytic processes and reactions for organic synthesis and the pharmaceutical food and cosmetics industry has been constantly growing during the last few years (Beloqui *et al.,* 2008; Nestl *et al.,* 2011) palette of reactions. Enzymes of one type, but from different origins, are specialized for substrates, positions in substrates, and products (Clouthier & Pelletier, 2012).

Enzyme reactions do not follow the law of mass action directly. The rate of the reaction only increases to a certain extent as the concentration of substrate increases. The maximum reaction rate is reached at high substrate concentration due to enzyme saturation. This is in contrast to the law of mass action that states that the reaction rate increases as the concentration of substrate increases (Bornscheuer *et al.,* 2012). Various simplified analytical models have been developed over the last 20 years. In brief, the analysis involves the construction and solution of reaction/diffusion differential equations, resulting in the development of approximate analytical expressions for nonlinear enzyme catalyzed reaction processes.

The simplest model that explains the kinetic behaviour of enzyme reactions is the classic 1913 model of Michaelis and Menten which is widely used in biochemistry for many types of enzymes (Michaelis & Menten, 1913). The Michaelis-Menten model is based on the assumption that the enzyme binds the substrate to form an intermediate complex which then dissociates to form the final product and release the enzyme in its original form.

CHAPTER THREE

METHODOLOGY

3.1. Study Area and Period

The study was conducted in Jimma University under the department of Mathematics from January, 2021 to January, 2022 G.C.

3.2. Study Design

This study employed mixed-design (documentary review design and MATLAB simulation).

3.3. Source of Information

The relevant sources of information for this study were books, published articles and related studies from internet.

3.4. Mathematical Procedures

This study was conducted based on the following procedures:

1. Developing a new mathematical model for enzyme kinetics in the sense of fractional order derivative,
2. Proving Existence and uniqueness solution for the model,
3. Proposing iterative numerical scheme for the approximate solution of the model,
4. Approximating terms in integral using Lagrange polynomial,
5. Presenting the result of the numerical solution via graph by implementing MATLAB.

CHAPTER FOUR

RESULT AND DISCUSSION

4.1 Mathematical Model Formulation

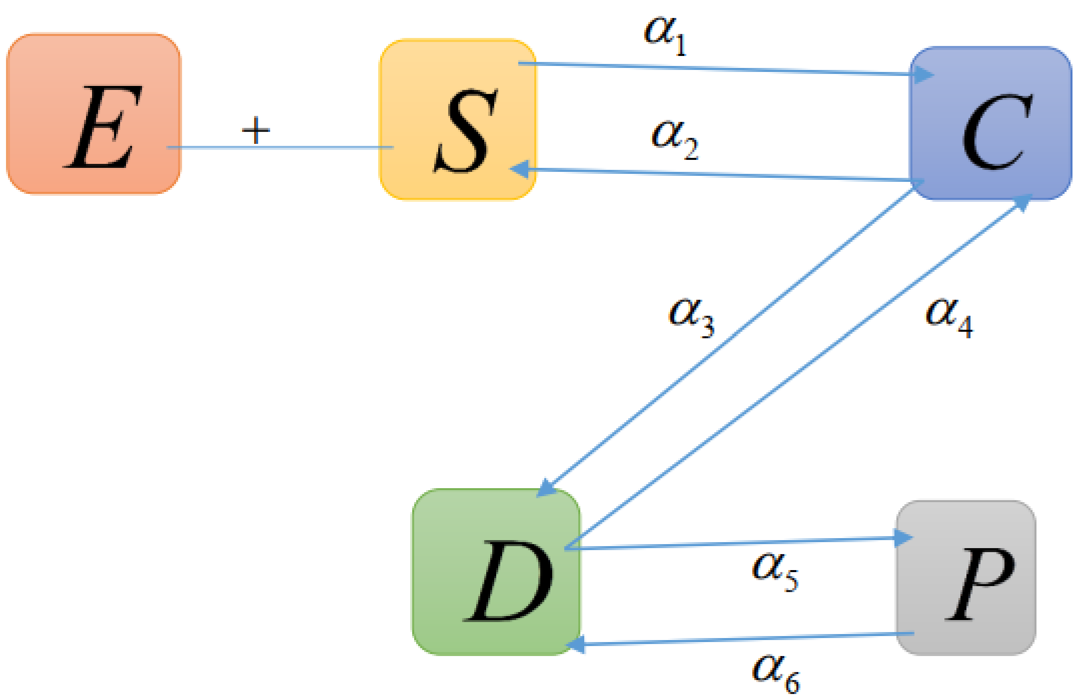

Figure 1: Schematic Flow diagram Enzyme kinetics

From the above schematic diagram, we have the following system of non-linear governing ordinary differential equation.

$$\begin{aligned}
\frac{dS}{dt} &= -\alpha_1 SE + \alpha_2 C \quad , \\
\frac{dE}{dt} &= -\alpha_1 SE + (\alpha_2 - \alpha_3)C + (\alpha_4 - \alpha_5)D + \alpha_6 PE \quad , \\
\frac{dC}{dt} &= \alpha_1 SE - (\alpha_2 + \alpha_3)C + \alpha_4 D \quad , \\
\frac{dD}{dt} &= \alpha_3 C - (\alpha_4 + \alpha_5)D + \alpha_6 PE \quad , \\
\frac{dP}{dt} &= \alpha_5 D - \alpha_6 PE \quad .
\end{aligned} \tag{4.1}$$

Subjected to initial conditions

$$S(0) = S_0 > 0\ , \ \ E(0) = E_0 > 0\ , \ C(0) = C_0 \geq 0\ , \ \ D(0) = D_0 \geq 0\ , \ P(0) = P_0 \geq 0 \tag{4.2}$$

Extending the mathematical model proposed in Eq.(4.1) to Caputo-Fabrizio fractional derivative yields:

$$\begin{aligned}
{}^{CF}D_t^{\eta} S(t) &= -\alpha_1 SE + \alpha_2 C \quad , \\
{}^{CF}D_t^{\eta} E(t) &= -\alpha_1 SE + (\alpha_2 - \alpha_3)C + (\alpha_4 - \alpha_5)D + \alpha_6 PE \, , \\
{}^{CF}D_t^{\eta} C(t) &= \alpha_1 SE - (\alpha_2 + \alpha_3)C + \alpha_4 D \, , \\
{}^{CF}D_t^{\eta} D(t) &= \alpha_3 C - (\alpha_4 + \alpha_5)D + \alpha_6 PE \quad , \\
{}^{CF}D_t^{\eta} P(t) &= \alpha_5 D - \alpha_6 PE \, .
\end{aligned} \tag{4.3}$$

with initial conditions given by Eq. (4.2).

Table 1: Description of parameters and variables of the model (4.1)

Parameters	Description of parameters
α_1	The rate at which enzyme substrate associate to form enzyme substrate complex.
α_2	The rate at which enzyme substrate complex dissociate to enzyme substrate
α_3	The rate at which enzyme substrate complex catalyzed to enzyme product complex
α_4	The rate at which enzyme product complex catalyzed to enzyme substrate complex
α_5	The rate at which enzyme product complex dissociate to enzyme product
α_6	The rate at which enzyme product associate to enzyme product complex
η	Order of Caputo-Fabrizio fractional derivative
Variables	Description of variables
S	Substrate
E	Enzyme
C	Enzyme substrate complex
D	Enzyme product complex
P	Product

4.2 Preliminaries

Definition 1: Norm on a (real or complex) vector space X is a real-valued function on X whose value at an $x \in X$ is denoted by $\|x\|$ and which has the properties (Kreyszig, 1991).

(N_1) $\|x\| \geq 0$
(N_2) $\|x\| = 0 \Leftrightarrow x = 0$
(N_3) $\|\alpha x\| = |\alpha| \|x\|$
(N_4) $\|x + y\| \leq \|x\| + \|y\|$

Here x & y are arbitrary vectors in X and α is any arbitrary scalar.

Definition 2: Let E be any open subset of $\Re^n$. A function $f : E \to \Re^n$ is said to satisfy a Lipschitz condition on E if there is a positive constant K such that for all $x, y \in E$ $|f(x) - f(y)| \leq K|x - y|$ (Perko, 2013).

Definition 3: *Let* $f \in H^1(a,b)$ *and* $\eta \in (0,1)$. *Then the Caputo–Fabrizio fractional derivative of order* η *is defined as* (Caputo & Fabrizio, 2015).

$$^{CF}D_t^{\eta}\left(f(t)\right) = \frac{M(\eta)}{1-\eta} \int_a^t f'(x) e^{\frac{-\eta(t-x)}{1-\eta}} dx,$$

where $M(\eta)$ is a normalization function such that $M(0) = M(1) = 1$. *If* $f \notin H^1(a,b)$, *then the derivative is defined as:*

$$^{CF}D_t^{\eta}\left(f(t)\right) = \frac{\eta M(\eta)}{1-\eta} \int_a^t \left(f(t) - f(x)\right) e^{\frac{-\eta(t-x)}{1-\eta}} dx.$$

Definition 4: *The Caputo–Fabrizio fractional derivative in definition 1 was later modified by (Losada and Nieto, 2015) as:*

$$^{CF}D_t^{\eta}\left(f(t)\right) = \frac{(2-\eta)M(\eta)}{2(1-\eta)} \int_a^t f'(x) e^{\frac{-\eta(t-x)}{1-\eta}} dx.$$

Definition 5: *Let* $0<\eta<1$. *The Caputo–Fabrizio fractional integral of order* η *in definition 2 is defined by (Losada and Nieto, 2015) as:*

$$^{CF}I_t^{\eta}\left(f(t)\right)=\frac{2(1-\eta)}{(2-\eta)M(\eta)}f(t)+\frac{2\eta}{(2-\eta)M(\eta)}\int_a^t f(x)dx \quad ,t\geq 0$$

Remark 1: From definition 3, the fractional integral of Caputo–Fabrizio type of a function f of order $\eta\in(0,1)$ is a mean between the function f and its integral of order one, i.e.,

$$\frac{2(1-\eta)}{(2-\eta)M(\eta)}+\frac{2\eta}{(2-\eta)M(\eta)}=1$$

Therefore, $M(\eta)=\dfrac{2}{2-\eta}$, $0<\eta<1$

4.3 Existence and Uniqueness of Solutions

Applying Caputo-Fabrizio fractional integral to both sides of Eq. (4.3) gives:

$$\begin{aligned}
S(t)-S_0 &= {}^{CF}I_t^{\eta}\left\{-\alpha_1 SE+\alpha_2 C\right\}\\
E(t)-E_0 &= {}^{CF}I_t^{\eta}\left\{-\alpha_1 SE+(\alpha_2-\alpha_3)C+(\alpha_4-\alpha_5)D+\alpha_6 PE\right\}\\
C(t)-C_0 &= {}^{CF}I_t^{\eta}\left\{\alpha_1 SE-(\alpha_2+\alpha_3)C+\alpha_4 D\right\}\\
D(t)-D_0 &= {}^{CF}I_t^{\eta}\left\{\alpha_3 C-(\alpha_4+\alpha_5)D+\alpha_6 PE\right\}\\
P(t)-P_0 &= {}^{CF}I_t^{\eta}\left\{\alpha_5 D-\alpha_6 PE\right\}
\end{aligned} \tag{4.4}$$

Using the definition of Caputo–Fabrizio fractional integral, we obtain

$$
\begin{aligned}
S(t)-S(0) &= \frac{2(1-\eta)}{(2-\eta)M(\eta)}\{-\alpha_1 SE+\alpha_2 C\}+\frac{2\eta}{(2-\eta)M(\eta)}\int_0^t[-\alpha_1 S(x)E(x)+\alpha_2 C(x)]dx \\
E(t)-E(0) &= \frac{2(1-\eta)}{(2-\eta)M(\eta)}\{-\alpha_1 SE+(\alpha_2-\alpha_3)C+(\alpha_4-\alpha_5)D+\alpha_6 PE\} \\
&\quad +\frac{2\eta}{(2-\eta)M(\eta)}\int_0^t\left[-\alpha_1 S(x)E(x)+(\alpha_2-\alpha_3)C(x)+(\alpha_4-\alpha_5)D(x)+\alpha_6 P(x)E(x)\right]dx \\
C(t)-C(0) &= \frac{2(1-\eta)}{(2-\eta)M(\eta)}\{\alpha_1 SE-(\alpha_2+\alpha_3)C+\alpha_4 D\} \\
&\quad +\frac{2\eta}{(2-\eta)M(\eta)}\int_0^t\left[\alpha_1 S(x)E(x)-(\alpha_2+\alpha_3)C(x)+\alpha_4 D(x)\right]dx \qquad (4.5) \\
D(t)-D(0) &= \frac{2(1-\eta)}{(2-\eta)M(\eta)}\{\alpha_3 C-(\alpha_4+\alpha_5)D+\alpha_6 PE\} \\
&\quad +\frac{2\eta}{(2-\eta)M(\eta)}\int_0^t\left[\alpha_3 C(x)-(\alpha_4+\alpha_5)D(x)+\alpha_6 P(x)E(x)\right]dx \\
P(t)-P(0) &= \frac{2(1-\eta)}{(2-\eta)M(\eta)}\{\alpha_5 D-\alpha_6 PE\}+\frac{2\eta}{(2-\eta)M(\eta)}\int_0^t\left[\alpha_5 D(x)-\alpha_6 P(x)E(x)\right]dx
\end{aligned}
$$

For the sake of convenience, consider the following:

$$
\begin{aligned}
K_1(t,S) &= -\alpha_1 SE+\alpha_2 C \\
K_2(t,E) &= -\alpha_1 SE+(\alpha_2-\alpha_3)C+(\alpha_4-\alpha_5)D+\alpha_6 PE \\
K_3(t,C) &= \alpha_1 SE-(\alpha_2+\alpha_3)C+\alpha_4 D \qquad (4.6) \\
K_4(t,D) &= \alpha_3 C-(\alpha_4+\alpha_5)D+\alpha_6 PE \\
K_5(t,P) &= \alpha_5 D-\alpha_6 PE
\end{aligned}
$$

Theorem 4.1: *The kernel* $K_1(t)$ *satisfies the Lipschitz condition and contraction if the following inequality holds*: $0<\alpha_1\ell_1\leq 1$

Proof: Consider functions $S(t)$ and $S_1(t)$,

$$
\begin{aligned}
&\left\|K_1(t,S(t))-K_1(t,S_1(t))\right\| \\
&\qquad =\left\|-\alpha_1 S(t)E(t)+\alpha_2 C(t)-(-\alpha_1 S_1(t)E(t)+\alpha_2 C(t))\right\| \\
&\qquad =\left\|-\alpha_1 E(t)(S(t)-S_1(t))\right\| \\
&\qquad =\left\|(S(t)-S_1(t))\right\| \\
&\qquad =\left\|-\alpha_1 E(t)\right\|\left\|(S(t)-S_1(t))\right\| \\
&\qquad =\alpha_1\left\|E\right\|\left\|S(t)-S_1(t)\right\| \\
&\qquad \le \alpha_1\ell_1\left\|S(t)-S_1(t)\right\| \\
&\qquad \le \lambda_1\left\|S(t)-S_1(t)\right\|
\end{aligned}
$$

Let $\lambda_1=\alpha_1\ell_1$, where $\ell_1=\left\|E(t)\right\|$ is bounded function, then we have

$$\left\|K_1(t,S(t))-K_1(t,S_1(t))\right\|\le\lambda_1\left\|S(t)-S_1(t)\right\|$$

Thus, the Lipschitz condition is fulfilled for P_1. In addition, if $0<\alpha_1\ell_1\le 1$, then K_1 is a contraction. Similarly, K_2, K_3, K_4 and K_5 satisfy the Lipschitz condition as follows:

$$\left\|K_2(t,E(t))-K_2(t,E_1(t))\right\|\le\lambda_2\left\|E(t)-E_1(t)\right\|$$

$$\left\|K_3(t,C(t))-K_3(t,C_1(t))\right\|\le\lambda_3\left\|C(t)-C_1(t)\right\|$$

$$\left\|K_4(t,D(t))-K_4(t,D_1(t))\right\|\le\lambda_4\left\|D(t)-D_1(t)\right\|$$

$$\left\|K_5(t,P(t))-K_5(t,P_1(t))\right\|\le\lambda_5\left\|P(t)-P_1(t)\right\|$$

Using Eq. (4.6) into Eq. (4.5),

$$S(t)=S(0)+\frac{2(1-\eta)}{(2-\eta)M(\eta)}K_1(t,S)+\frac{2\eta}{(2-\eta)M(\eta)}\int_0^t K_1(x,S(x))dx$$

$$E(t)=E(0)+\frac{2(1-\eta)}{(2-\eta)M(\eta)}K_2(t,E)+\frac{2\eta}{(2-\eta)M(\eta)}\int_0^t K_2(x,E(x))dx$$

$$C(t)=C(0)+\frac{2(1-\eta)}{(2-\eta)M(\eta)}K_3(t,C)+\frac{2\eta}{(2-\eta)M(\eta)}\int_0^t K_3(x,C(x))dx$$

$$D(t)=D(0)+\frac{2(1-\eta)}{(2-\eta)M(\eta)}K_4(t,D)+\frac{2\eta}{(2-\eta)M(\eta)}\int_0^t K_4(x,D(x))dx$$

$$P(t)=P(0)+\frac{2(1-\eta)}{(2-\eta)M(\eta)}K_5(t,P)+\frac{2\eta}{(2-\eta)M(\eta)}\int_0^t K_5(x,P(x))dx$$

Thus, consider the following recursive formula:

$$S_n(t)=\frac{2(1-\eta)}{(2-\eta)M(\eta)}K_1(t,S_{n-1})+\frac{2\eta}{(2-\eta)M(\eta)}\int_0^t K_1(x,S_{n-1})dx$$

$$E_n(t)=\frac{2(1-\eta)}{(2-\eta)M(\eta)}K_2(t,E_{n-1})+\frac{2\eta}{(2-\eta)M(\eta)}\int_0^t K_2(x,E_{n-1})dx$$

$$C_n(t)=\frac{2(1-\eta)}{(2-\eta)M(\eta)}K_3(t,C_{n-1})+\frac{2\eta}{(2-\eta)M(\eta)}\int_0^t K_3(x,C_{n-1})dx$$

$$D_n(t)=\frac{2(1-\eta)}{(2-\eta)M(\eta)}K_4(t,D_{n-1})+\frac{2\eta}{(2-\eta)M(\eta)}\int_0^t K_4(x,D_{n-1})dx,$$

$$P_n(t)=\frac{2(1-\eta)}{(2-\eta)M(\eta)}K_5(t,P_{n-1})+\frac{2\eta}{(2-\eta)M(\eta)}\int_0^t K_5(x,P_{n-1})dx$$

where $S_0(t)=S(0),\quad E_0(t)=E(0),\ C_0(t)=C(0),\ D_0(t)=D(0),\ P_0(t)=P(0)$

Now consider, the differences between successive terms as follows:

$$\begin{aligned}A_n&=S_n-S_{n-1}\\&=\frac{2(1-\eta)}{(2-\eta)M(\eta)}\left[K_1(t,S_{n-1})-K_1(t,S_{n-2})\right]+\frac{2\eta}{(2-\eta)M(\eta)}\int_0^t\left[K_1(x,S_{n-1})-K_1(x,S_{n-2})\right]dx\end{aligned}$$

$$\begin{aligned}B_n&=E_n-E_{n-1}\\&=\frac{2(1-\eta)}{(2-\eta)M(\eta)}\left[K_2(t,E_{n-1})-K_2(t,E_{n-2})\right]+\frac{2\eta}{(2-\eta)M(\eta)}\int_0^t\left[K_2(x,E_{n-1})-K_2(x,E_{n-2})\right]dx\end{aligned}$$

$$F_n = C_n - C_{n-1}$$
$$= \frac{2(1-\eta)}{(2-\eta)M(\eta)}\left[K_3(t,C_{n-1}) - K_3(t,C_{n-2})\right] + \frac{2\eta}{(2-\eta)M(\eta)}\int_0^t \left[K_3(x,C_{n-1}) - K_3(x,C_{n-2})\right]dx$$

$$H_n = D_n - D_{n-1}$$
$$= \frac{2(1-\eta)}{(2-\eta)M(\eta)}\left[K_4(t,D_{n-1}) - K_4(t,D_{n-2})\right] + \frac{2\eta}{(2-\eta)M(\eta)}\int_0^t \left[K_4(x,D_{n-1}) - K_4(x,D_{n-2})\right]dx$$

$$G_n = P_n - P_{n-1}$$
$$= \frac{2(1-\eta)}{(2-\eta)M(\eta)}\left[K_5(t,P_{n-1}) - K_5(t,P_{n-2})\right] + \frac{2\eta}{(2-\eta)M(\eta)}\int_0^t \left[K_5(x,P_{n-1}) - K_5(x,P_{n-2})\right]dx$$

We can write that,

$$\left.\begin{array}{lll} S_n = \sum_{j=1}^{n} A_j \;, & E_n = \sum_{j=1}^{n} B_j \;, & C_n = \sum_{j=1}^{n} F_j \;, \\ D_n = \sum_{j=1}^{n} H_j \;, & P_n = \sum_{j=1}^{n} G_j & \end{array}\right\} \tag{4.7}$$

Taking norm to the differences between successive recursive terms,

$$\|A_n\| = \|S_n - S_{n-1}\|$$
$$= \left\| \frac{2(1-\eta)}{(2-\eta)M(\eta)}\left[K_1(t,S_{n-1}) - K_1(t,S_{n-2})\right] + \frac{2\eta}{(2-\eta)M(\eta)}\int_0^t \left[K_1(x,S_{n-1}) - K_1(x,S_{n-2})\right]dx \right\|$$
$$\leq \frac{2(1-\eta)}{(2-\eta)M(\eta)}\left\|\left[K_1(t,S_{n-1}) - K_1(t,S_{n-2})\right]\right\| + \frac{2\eta}{(2-\eta)M(\eta)}\int_0^t \left\|K_1(x,S_{n-1}) - K_1(x,S_{n-2})\right\|dx$$

Since K_1 satisfy Lipschitz condition,

$$\|S_n - S_{n-1}\| \leq \frac{2(1-\eta)\lambda_1}{(2-\eta)M(\eta)}\|S_{n-1} - S_{n-2}\| + \frac{2\eta\lambda_1}{(2-\eta)M(\eta)}\int_0^t \|S_{n-1} - S_{n-2}\|dx$$

$$\|A_n\| \le \frac{2(1-\eta)\lambda_1}{(2-\eta)M(\eta)}\|A_{n-1}\| + \frac{2\eta\lambda_1}{(2-\eta)M(\eta)}\int_0^t \|A_{n-1}\| dx \tag{4.8}$$

Similar results are obtained as follows:

$$\left.\begin{aligned}
\|B_n\| &\le \frac{2(1-\eta)\lambda_2}{(2-\eta)M(\eta)}\|B_{n-1}\| + \frac{2\eta\lambda_2}{(2-\eta)M(\eta)}\int_0^t \|B_{n-1}\| dx \\
\|F_n\| &\le \frac{2(1-\eta)\lambda_3}{(2-\eta)M(\eta)}\|F_{n-1}\| + \frac{2\eta\lambda_3}{(2-\eta)M(\eta)}\int_0^t \|F_{n-1}\| dx \\
\|H_n\| &\le \frac{2(1-\eta)\lambda_4}{(2-\eta)M(\eta)}\|H_{n-1}\| + \frac{2\eta\lambda_4}{(2-\eta)M(\eta)}\int_0^t \|H_{n-1}\| dx \\
\|G_n\| &\le \frac{2(1-\eta)\lambda_5}{(2-\eta)M(\eta)}\|G_{n-1}\| + \frac{2\eta\lambda_5}{(2-\eta)M(\eta)}\int_0^t \|G_{n-1}\| dx
\end{aligned}\right\} \tag{4.9}$$

Theorem 4.2: *The Caputo-Fabrizio fractional derivative model in Eq. (4.3) has system of solutions if there exists* t *such that*

$$\frac{2(1-\eta)}{(2-\eta)M(\eta)}\lambda_i + \frac{2\eta}{(2-\eta)M(\eta)}\lambda_i t < 1 \quad, i = 1,2,3,4,5$$

Proof: By using recursive method and result from Eq. (4.8) and Eq.(4.9),

$$\left.\begin{aligned}
\|A_n\| &\le \|S(0)\|\left[\frac{2(1-\eta)}{(2-\eta)M(\eta)}\lambda_1 + \frac{2\eta}{(2-\eta)M(\eta)}\lambda_1 t\right]^n \\
\|B_n\| &\le \|E(0)\|\left[\frac{2(1-\eta)}{(2-\eta)M(\eta)}\lambda_2 + \frac{2\eta}{(2-\eta)M(\eta)}\lambda_2 t\right]^n \\
\|F_n\| &\le \|C(0)\|\left[\frac{2(1-\eta)}{(2-\eta)M(\eta)}\lambda_3 + \frac{2\eta}{(2-\eta)M(\eta)}\lambda_3 t\right]^n \\
\|H_n\| &\le \|D(0)\|\left[\frac{2(1-\eta)}{(2-\eta)M(\eta)}\lambda_4 + \frac{2\eta}{(2-\eta)M(\eta)}\lambda_4 t\right]^n \\
\|G_n\| &\le \|P(0)\|\left[\frac{2(1-\eta)}{(2-\eta)M(\eta)}\lambda_5 + \frac{2\eta}{(2-\eta)M(\eta)}\lambda_5 t\right]^n
\end{aligned}\right\} \tag{4.10}$$

This result proved the existence and smoothness of solution in Eq. (4.7).

To show that $S(t), E(t), C(t), D(t), P(t)$ are solutions of Eq.(4.3), consider the following.

$$\begin{aligned} S(t)-S(0) &= S_n(t)-R_{1n} \\ E(t)-E(0) &= E_n(t)-R_{2n} \\ C(t)-C(0) &= C_n(t)-R_{3n} \quad , \\ D(t)-D(0) &= D_n(t)-R_{4n} \\ P(t)-P(0) &= P_n(t)-R_{5n} \end{aligned}$$

where $R_{jn} \quad j=1,2,3,4,5$ defines the remainder term after n[th] iteration.

$$\begin{aligned} \|R_{1n}\| &= \|S(t)-S_n\| \\ &= \left\| \frac{2(1-\eta)}{(2-\eta)M(\eta)}\left[K_1(t,S)-K_1(t,S_{n-1})\right] + \frac{2\eta}{(2-\eta)M(\eta)}\int_0^t \left[K_1(x,S)-K_1(x,S_{n-1})\right] \right\| dx \\ &\le \frac{2(1-\eta)}{(2-\eta)M(\eta)}\left\|\left[K_1(t,S)-K_1(t,S_{n-1})\right]\right\| + \frac{2\eta}{(2-\eta)M(\eta)}\int_o^t \|K_1(x,S)-K_1(x,S_{n-1})\| dx \end{aligned}$$

$$\begin{aligned} \|R_{1n}\| &\le \frac{2(1-\eta)\lambda_1}{(2-\eta)M(\eta)}\|S-S_{n-1}\| + \frac{2\eta\lambda_1}{(2-\eta)M(\eta)}\int_0^t \|S-S_{n-1}\| dx \\ \|R_{1n}\| &\le \left[\frac{2(1-\eta)}{(2-\eta)M(\eta)}\lambda_1 + \frac{2\eta}{(2-\eta)M(\eta)}\lambda_1 t\right]\|S-S_{n-1}\| \end{aligned}$$

Applying the above process recursively,

$$\|R_{1n}\| \le \left[\frac{2(1-\eta)}{(2-\eta)M(\eta)} + \frac{2\eta}{(2-\eta)M(\eta)}t\right]^{n+1} \left(\lambda_1\right)^{n+1} q\,,$$

where q is positive constant.

$$n \to \infty \quad , \quad \|R_{1n}\| \to 0$$

Similarly, $n \to \infty \quad , \quad \|R_{2n}\| \to 0\ , \|R_{3n}\| \to 0 \ \ , \|R_{4n}\| \to 0 \ \ , \|R_{5n}\| \to 0$ for

$\frac{2(1-\eta)}{(2-\eta)M(\eta)}\lambda_i + \frac{2\eta}{(2-\eta)M(\eta)}\lambda_i t < 1$. Hence, the proof completed.

Theorem 4.3: *The Caputo-Fabrizio fractional derivative model in Eq. (4.3) has system of unique solutions provided that:*

$$1-\frac{2(1-\eta)}{(2-\eta)M(\eta)}\lambda_i - \frac{2\eta}{(2-\eta)M(\eta)}\lambda_i t \geq 0 \quad , i = 1,2,3,4,5 \tag{4.11}$$

Proof: Suppose Eq. (3) has another solutions say $S_1(t)$, $E_1(t)$, $C_1(t)$, $D_1(t)$, $P_1(t)$:

$$S(t)-S_1(t) = \frac{2(1-\eta)}{(2-\eta)M(\eta)}\left[K_1(t,S)-K_1(t,S_1)\right] + \frac{2\eta}{(2-\eta)M(\eta)}\int_0^t \left[K_1(x,S)-K_1(x,S_1)\right]dx$$

$$\begin{aligned}\left\|S(t)-S_1(t)\right\| &= \left\|\frac{2(1-\eta)}{(2-\eta)M(\eta)}\left[K_1(t,S)-K_1(t,S_1)\right] + \frac{2\eta}{(2-\eta)M(\eta)}\int_0^t \left[K_1(x,S)-K_1(x,S_1)\right]dx\right\| \\ &\leq \frac{2(1-\eta)}{(2-\eta)M(\eta)}\left\|\left[K_1(t,S)-K_1(t,S_1)\right]\right\| + \frac{2\eta}{(2-\eta)M(\eta)}\int_0^t \left\|K_1(x,S)-K_1(x,S_1)\right\|dx \\ &\leq \frac{2(1-\eta)}{(2-\eta)M(\eta)}\lambda_1\left\|S(t)-S_1(t)\right\| + \frac{2\eta}{(2-\eta)M(\eta)}\lambda_1 t\left\|S(t)-S_1(t)\right\|\end{aligned}$$

$$\left\|S(t)-S_1(t)\right\| \leq \left(\frac{2(1-\eta)}{(2-\eta)M(\eta)}\lambda_1 + \frac{2\eta}{(2-\eta)M(\eta)}\lambda_1 t\right)\left\|S(t)-S_1(t)\right\|$$

$$\left\|S(t)-S_1(t)\right\|\left(1-\frac{2(1-\eta)}{(2-\eta)M(\eta)}\lambda_1 - \frac{2\eta}{(2-\eta)M(\eta)}\lambda_1 t\right) \leq 0 \tag{4.12}$$

From Eq.(4.11) and Eq. (4.12),

$$\left\|S(t)-S_1(t)\right\|\left(1-\frac{2(1-\eta)}{(2-\eta)M(\eta)}\lambda_1 - \frac{2\eta}{(2-\eta)M(\eta)}\lambda_1 t\right) = 0$$

Therefore, $\left\|S(t)-S_1(t)\right\| = 0 \quad \Rightarrow S(t) = S_1(t)$

In the same manner,

$$\|E(t)-E_1(t)\|=0 \quad \Rightarrow E(t)=E_1(t) \;\;, \|C(t)-C_1(t)\|=0 \quad \Rightarrow C(t)=C_1(t)$$
$$\|D(t)-D_1(t)\|=0 \quad \Rightarrow D(t)=D_1(t) \;\;, \|P(t)-P_1(t)\|=0 \quad \Rightarrow P(t)=P_1(t)$$

Hence, the proof completed.

4.4 Iterative Numerical Scheme

For the desired numerical solution of the proposed model in Eq. (4.1), we apply the technique of fractional Adams-Bash-forth for Caputo-Fabrizio fractional derivative. To develop the desired iterative numerical scheme, consider the first equation of Eq. (4.3):

$$^{CF}D_t^{\eta}S(t) = -\alpha_1 SE + \alpha_2 C$$
$$^{CF}D_t^{\eta}S(t) = K_1(t, S(t))$$

Applying Caputo-Fabrizio fractional integral to both sides gives:

$$S(t)-S(0) = {}^{CF}I_t^{\eta}\left(K_1(t,S(t))\right)$$

$$S(t) = S(0) + \frac{(1-\eta)}{M(\eta)}K_1(t,S) + \frac{\eta}{M(\eta)}\int_0^t K_1(x,S(x))dx$$

At $t = t_{n+1}$,

$$S(t_{n+1}) = S(0) + \frac{(1-\eta)}{M(\eta)}P_1(t_n, S_n) + \frac{\eta}{M(\eta)}\int_0^{t_{n+1}} K_1(t,S(t))dt \tag{4.13}$$

At $t = t_n$,

$$S(t_n) = S(0) + \frac{(1-\eta)}{M(\eta)}K_1(t_{n-1}, S_{n-1}) + \frac{\eta}{M(\eta)}\int_0^{t_n} K_1(t,S(t))dt \tag{4.14}$$

Subtracting equation (4.14) from (4.13) leads to the following equation (4.15).

$$S(t_{n+1}) = S(t_n) + \frac{(1-\eta)}{M(\eta)}\{K_1(t_n, S_n) - K_1(t_{n-1}, S_{n-1})\} + \frac{\eta}{M(\eta)}\int_{t_n}^{t_{n+1}} K_1(t, S(t))dt \tag{4.15}$$

Taking $h = t_{n+1} - t_n$, approximating the integral $\int_{t_n}^{t_{n+1}} K_1(t, S(t))dt$ with the help of Lagrange interpolation polynomial of degree two passing through three points $\left(t_{n-2}, K_1(t_{n-2}, S_{k-2})\right), \left(t_{n-1}, K_1(t_{n-1}, S_{k-1})\right), \left(t_n, K_1(t_n, S_k)\right)$

$$\int_{t_n}^{t_{n+1}} K_1(t, S(t))dt = \int_0^1 \left[\frac{(s-2)(s-3)}{(1-2)(1-3)} K_1(t_n, S_n) + \frac{(s-1)(s-3)}{(2-1)(2-3)} K_1(t_{n-1}, S_{n-1}) + \frac{(s-2)(s-1)}{(3-2)(3-1)} K_1(t_{n-2}, S_{n-2})\right] ds$$

$$\int_{t_n}^{t_{n+1}} K_1(t, S(t))dt = h\left[\frac{23}{12} K_1(t_n, S_n) - \frac{4}{3} K_1(t_{n-1}, S_{n-1}) + \frac{5}{12} K_1(t_{n-2}, S_{n-2})\right] \tag{4.16}$$

Substituting this approximated value in Eq. (4.15),

$$S(t_{n+1}) = S(t_n) + \left[\frac{(1-\eta)}{M(\eta)} + \frac{23\eta h}{12M(\eta)}\right] K_1(t_n, S_n) - \left[\frac{(1-\eta)}{M(\eta)} + \frac{4\eta h}{3M(\eta)}\right] K_1(t_{n-1}, S_{n-1}) + \frac{5\eta h}{12M(\eta)} K_1(t_{n-2}, S_{n-2}) \tag{4.17}$$

Similarly,

$$\left.\begin{aligned}
E(t_{n+1}) &= E(t_n) + \left[\frac{(1-\eta)}{M(\eta)} + \frac{23\eta h}{12M(\eta)}\right] K_2(t_n, E_n) - \left[\frac{(1-\eta)}{M(\eta)} + \frac{4\eta h}{3M(\eta)}\right] K_2(t_{n-1}, E_{n-1}) + \frac{5\eta h}{12M(\eta)} K_2(t_{n-2}, E_{n-2}) \\
C(t_{n+1}) &= C(t_n) + \left[\frac{(1-\eta)}{M(\eta)} + \frac{23\eta h}{12M(\eta)}\right] K_3(t_n, C_n) - \left[\frac{(1-\eta)}{M(\eta)} + \frac{4\eta h}{3M(\eta)}\right] K_3(t_{n-1}, C_{n-1}) + \frac{5\eta h}{12M(\eta)} K_3(t_{n-2}, C_{n-2}) \\
D(t_{n+1}) &= D(t_n) + \left[\frac{(1-\eta)}{M(\eta)} + \frac{23\eta h}{12M(\eta)}\right] K_1(t_n, D_n) - \left[\frac{(1-\eta)}{M(\eta)} + \frac{4\eta h}{3M(\eta)}\right] K_4(t_{n-1}, D_{n-1}) + \frac{5\eta h}{12M(\eta)} K_4(t_{n-2}, D_{n-2}) \\
P(t_{n+1}) &= P(t_n) + \left[\frac{(1-\eta)}{M(\eta)} + \frac{23\eta h}{12M(\eta)}\right] K_5(t_n, P_n) - \left[\frac{(1-\eta)}{M(\eta)} + \frac{4\eta h}{3M(\eta)}\right] K_5(t_{n-1}, P_{n-1}) + \frac{5\eta h}{12M(\eta)} K_5(t_{n-2}, P_{n-2})
\end{aligned}\right\} \tag{4.18}$$

4.5 MATLAB Simulation

MATLAB simulation was implemented by using the following parameters value subjected to initial conditions. Some of the parameters values were taken from different literatures and others are assumed.

Parameters	Value	Variables	Value
α_1	0.065	Initial Conditions	
α_2	0.016	$S(0)$	0.8
α_3	0.01	$E(0)$	0.3
α_4	0.03	$C(0)$	0.3
α_5	0.055	$D(0)$	0.2
α_6	0.00056	$P(0)$	0.1

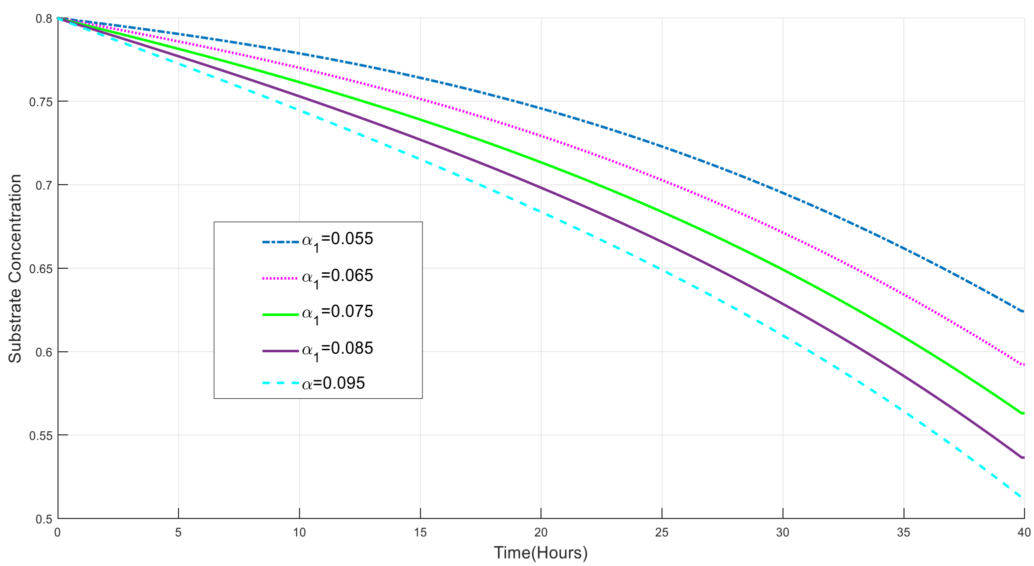

Figure 2: Graph of substrate verses time for different values of α_1 by keeping others parameters constant.

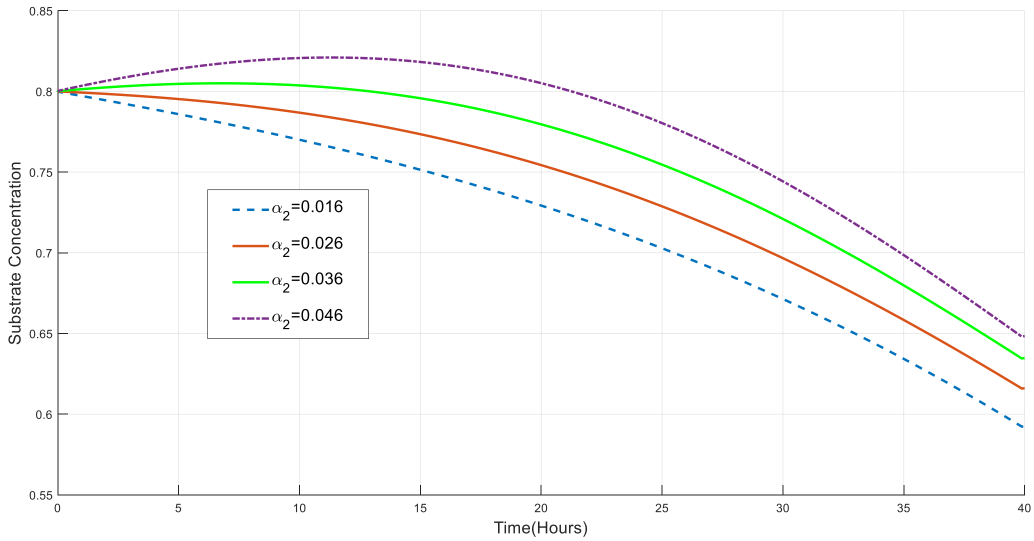

Figure 3: Graph of substrate verses time for different values of α_2 by keeping others parameters constant.

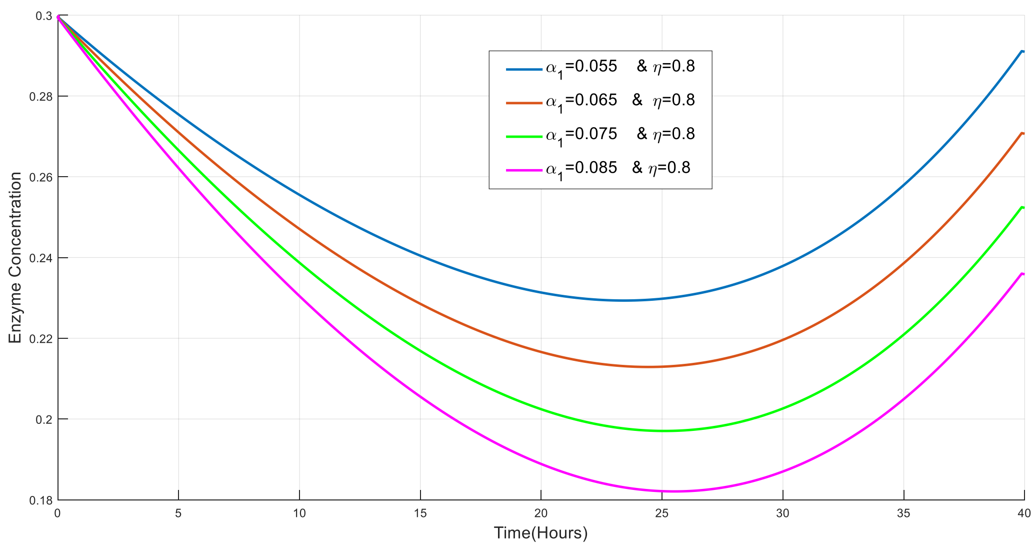

Figure 4: Graph of enzyme concentration verses time for different values of α_1 by keeping others parameters constant.

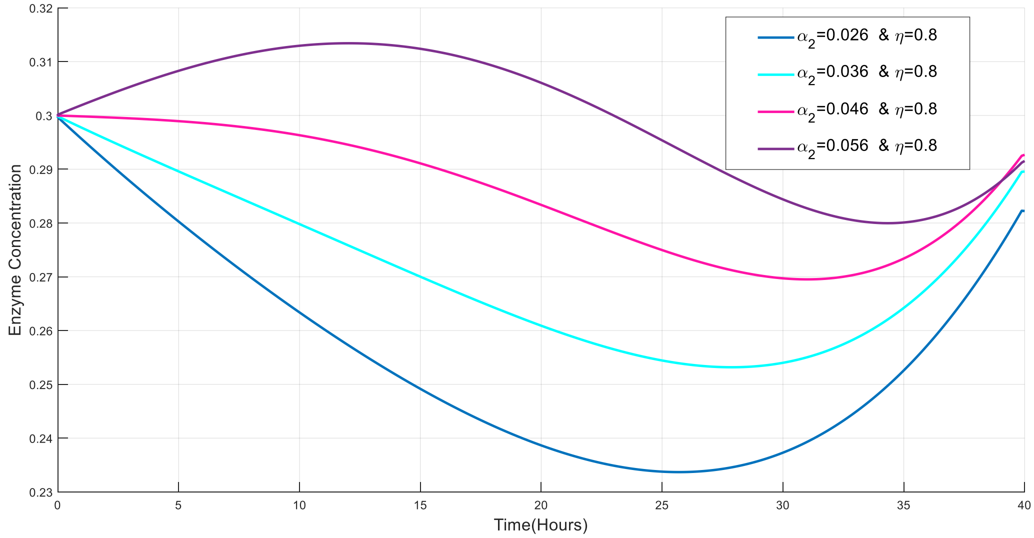

Figure 5: Graph of enzyme concentration verses time for different values of α_2 by keeping others parameters constant.

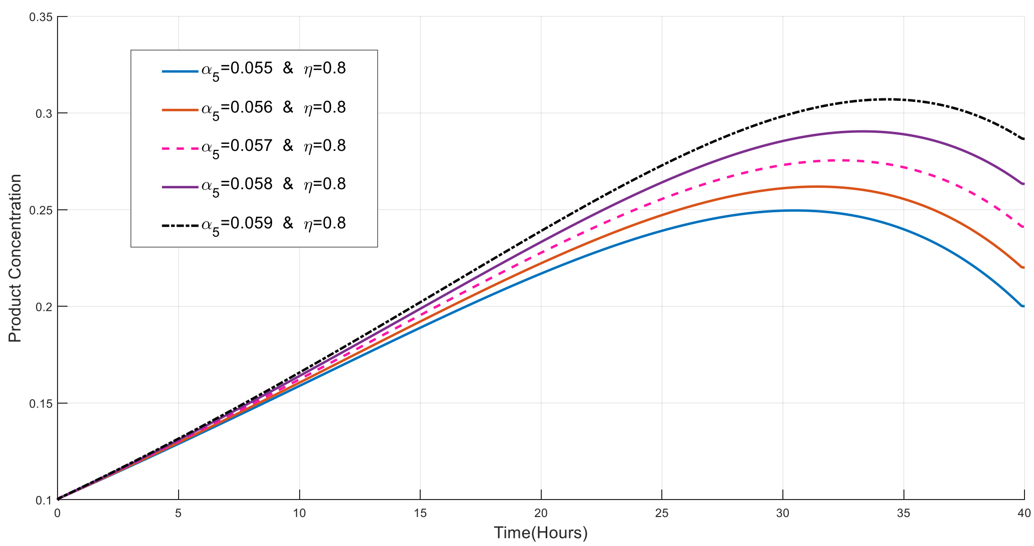

Figure 6: Graph of product verses time for different values of α_5 by keeping others parameters constant.

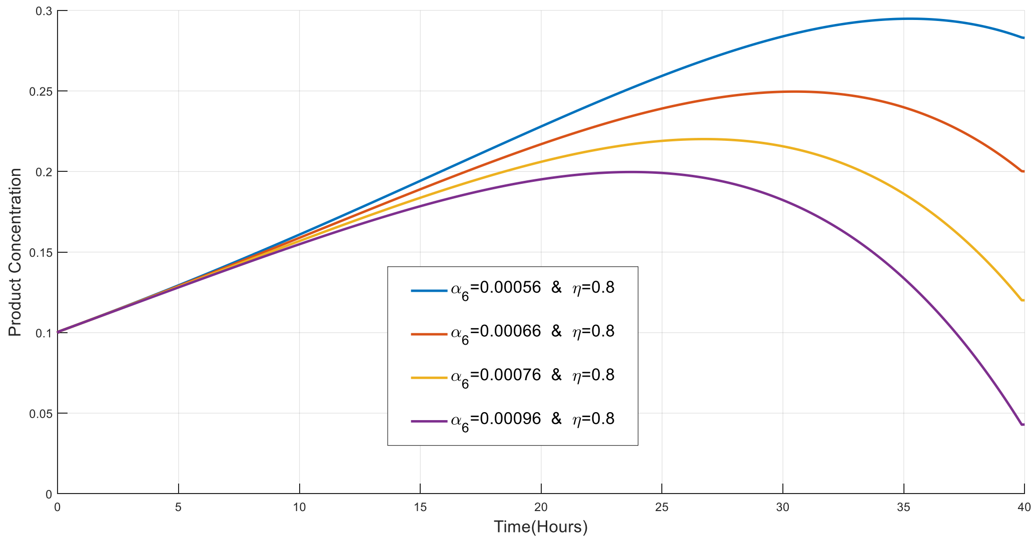

Figure 7: Graph of product verses time for different values of α_6 by keeping others parameters constant.

4.6 Discussion

Figure 2 & Figure 3 revealed that, substrate concentration increases and decreased as the rate at which enzyme substrate associate to form enzyme substrate complex increases and the rate at which enzyme substrate complex dissociate to enzyme substrate increase respectively. Figure 4 & Figure 5 indicates enzyme concentration decreased and increased as the rate at which enzyme substrate associate to form enzyme substrate complex increases and the rate at which enzyme substrate complex dissociate to enzyme substrate increase respectively.

CHAPTER FIVE

5. CONCLUSION AND FUTURE SCOPE

5.1Conclusions

In this study, mathematical model of enzyme kinetics in the sense of Caputo-Fabrizio fractional derivative was developed and investigated. Firstly, some basic definitions were discussed in the preliminary parts. The findings of this study were summarized as follows.

- Existence and uniqueness of the solution of the model was proved,
- Iterative numerical scheme (Adams Bash forth method) was proposed for the model,
- Finally, MATLAB simulation was implemented to verify the applicability of the result.

5.2 Future Scope

One can conduct further investigation on the following points.

- Making similar analysis for other types of fractional derivative comparing the result is one of the future scope.
- Stability analysis of the model with fractional order derivative is also another future investigation,
- Refining the mathematical model supported by new anlysis and new result,
- Introducing time delay in the model in the sense of fractional derivative is also another future investigation.

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