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A Fractional-Order Mathematical Model of the Human Liver Using the Caputo Derivative and Mathematical Analysis

Zafer ÖZTÜRK[a]

[a]*Department of Mathematics, Nevşehir Hacı Bektaş Veli University, 50300, Nevşehir, Türkiye*

Abstract. In this study, fractional order mathematical modelling of the human liver using the Caputo fraction derivative is considered. This model was divided into two compartments, Bromsulphthalein (BDP) content in blood (Z) and Bromsulphthalein (BDP) content in liver (W). The Caputo derivative was used as the fractional derivative. A stability analysis was performed on the fractional-order mathematical model of the human liver. The system's existence, uniqueness and non-negativity were analysed mathematically. Numerical solutions were obtained using the Generalized Euler method and interpreted graphically.

1. Introduction

The liver is a roughly triangular organ that extends across the entire abdominal cavity just below the diaphragm [1]. The liver is one of the most active and complex organs with the most functions in the human body. It is a very important organ in terms of fulfilling vital functions such as purifying the blood from many foreign and toxic substances such as drugs and alcohol, digesting fats in the body, removing wastes from the body and producing bile [2]. Bromsulphalein (BSP) is a dye injected into the bloodstream. The liver is the only organ thatabsorbs BSP and secretes it directly into bile. Measuring the BSP level in the blood at differenttimes provides a finite sequence of values showing the rapid or slow decline of BSP in the blood,and this sequence is used to investigate liver function. Bromsulphalein is a dye used in liver function tests. Bromsulphalein allows the calculation of the volume of blood flowing from the liver based on differences in dye levels. Determining the rate at which the dye is removed from the bloodstream provides a measure of liver function [3].

Mathematical modelling is to describe a process, a real-world problem, with a mathematical formulation. For this, first, all possible details of the process should be evaluated and accordingly a model as simple as possible should be established. The mathematical formulation should be suitable for general real world problems [4]. In order to create a model of any problem to be solved, the model must be established systematically and go through certain stages. First of all, it should be determined what the problem is and a process should be started for the solution by making all necessary analyses about the problem. In modelling, each step in this process is a logical continuation of the previous step. The mathematical modelling process is generally seen as perception and processing. The reliability and accuracy of these two

Corresponding author: ZÖ mail address: zaferozturk@aksaray.edu.tr ORCID: 0000-0001-5662-4670
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stages lead the modeller to the real solution. All this is to convert the model into a mathematical form. Thus, general equations are formed and the factors affecting the problem are revealed [5, 6].

Since fractional order differential equations are generalised versions of full order differential equations, modelling studies using fractional order differential equations help us to minimise the errors arising from the parameters that we have to neglect when modelling real life events. Thus, models using fractional order differential equations give more realistic and applicable results. For this reason, models created with fractional order differential equations are emerging as interesting and special studies [7-12]. It has been proven that employing a fractional method to represent the mechanism is significantly superior to adopting an integer order optimisation, as it facilitates analysis to understand the actual evidence and possesses several substantial advantages. Furthermore, the device's capacity for recollection and inheritance features renders it a highly valuable asset in the domains of simulating and interpreting real phenomena. It is evident that a multitude of notions and expressions inherent to fractional calculus are advantageous for the modelling of infection transmission. This includes the Atangana-Baleanu, Caputo-Fabrizio, and Caputo derivatives [13-22].

This paper consists of four parts. In the first part, the importance of fractional mathematical modelling and information about human liver is given. In the second part, the formation of a fractional order mathematical model of the human liver, the mathematical analysis of the existence, uniqueness and non-negativity of the system, the Generalized Euler Method and the stability analysis of the model are presented. In the third section, the fractional model is applied and numerical results are obtained and graphs are drawn. In the fourth section, conclusions are given.

2. Fractional Derivation and Fractional Order Mathematical Model of Human Liver

The most commonly used definitions of the fractional derivative are Riemann-Liouville, Caputo, Atangana-Baleanu and the Conformable derivative. In this study, because the classical initial conditions are easily applicable and provide ease of calculation, the Caputo derivative operator was preferred and modeling was created. The definition of the Caputo fractional derivative is given below.

Definition 2.1. *[4] Let $f(t)$ be a function that can be continuously differentiable n times. The value of the function $f(t)$ for the value of α that satisfies the condition $n-1 < \alpha < n$. The Caputo fractional derivative of α-th order $f(t)$ is defined by*

$$D_t^{\alpha} f(t) = \frac{1}{\Gamma(n-\alpha)} \int_a^t (t-x)^{(n-\alpha-1)} f^n(x)\, dx.$$

Definition 2.2. *[4] The Riemann-Liouville (RL) fractional-order integral of a function $A(t) \in C_n$ $(n \geq -1)$ is given by*

$$J^{\gamma} A(t) = \frac{1}{\Gamma(\alpha)} \int_0^t (t-s)^{(\gamma-1)} A(s)\, ds, \quad J^0 A(t) = A(t). \tag{2.1}$$

Definition 2.3. *[4] The series expansion of two-parametrized form of Mittag-Leffler function for $a, b > 0$ is given by*

$$E_{a,b}(t) = \sum_{i=0}^{\infty} \frac{t^i}{\Gamma(ai+b)}. \tag{2.2}$$

2.1. The Fractional Order Mathematical Model of Human Liver

The fractional order human liver mathematical model was divided into two compartments, the amount of Bromsulphthalein (BDP) in the blood (Z) and the amount of Bromsulphthalein (BDP) in the liver (W). The expression of the fractional order human liver mathematical model as a system of fractional differential equations is as follows.

$$\begin{aligned} \frac{d^\alpha Z}{dt^\alpha} &= -aZ + bW \\ \frac{d^\alpha W}{dt^\alpha} &= aZ - (b+d)W. \end{aligned} \tag{2.3}$$

Here $\frac{d^\alpha}{dt^\alpha}$ is the Caputo fractional derivative of α-th order with respect to time t. The constants a,b,d are transfer rates and are unknown. The compartments are shown in Table 1. The initial values are defined as,

$$Z(0) = Z_0, \quad W(0) = W_0$$

$0 < \alpha \leq 1$.

Table 1: Variables used in the model and their meanings

Variables used in the systems	Meaning
$Z(t)$	amount of Bromsulphthalein in the blood at time t
$W(t)$	amount of Bromsulphthalein in the liver at time t

Because fractional-order models have a memory feature in events related to a time variable, they show more realistic and accurate results than integer-order models [5–14]. Therefore, the established model was created as a fractional order. In the system of (2.3), the fractional-order differential equation for $\alpha = 1$ is reduces to a full order differential equation.

2.2. Existence, Uniqueness and Non-Negativity of the System

We investigate the exintence and uniqueness of the solutions of the fractional-order system (2.3) in the region $B \times [t_0, T]$ where

$$B = \{(Z, W) \in R_+^2 : max\{|\ Z\ |, |\ W\ |\} \leq \Psi, min\{|\ Z\ |, |\ W\ |\} \geq \Psi_0\} \tag{2.4}$$

and $T < +\infty$.

Theorem 2.4. *For each $X_0 = (Z_0, W_0) \in B$ there exists a unique solution $X(t) \in B$ of the fractional-order system (2.3) with intial condition X_0, which is defined for all $t \geq 0$.*

Proof: We denote $X = (Z, W)$ and $\bar{X} = (\bar{Z}, \bar{W})$. Consider a mapping $M(X) = (M_1(X), M_2(X))$ and

$$\begin{aligned} M_1(X) &= -aZ + bW \\ M_2(X) &= aZ - (b+d)W \end{aligned} \tag{2.5}$$

For any $X, \bar{X} \in B$ it follows from equation (2.5) that

$$||\ M(X) - M(\bar{X})\ || = |M_1(X) - M_1(\bar{X})| + |M_2(X) - M_2(\bar{X})| \tag{2.6}$$

$$\begin{aligned} |M_1(X) - M_1(\bar{X})| &= |-aZ + bW + a\bar{Z} - b\bar{W}| \\ &= |-a(Z - \bar{Z}) + b(W - \bar{W})| \\ &\leq a|Z - \bar{Z}| + b|W - \bar{W}| \\ |M_2(X) - M_2(\bar{X})| &= |aZ - (b+d)W - a\bar{Z} + (b+d)\bar{W}| \\ &= |a(Z - \bar{Z}) - (b+d)(W - \bar{W})| \\ &\leq a|Z - \bar{Z}| + (b+d)|W - \bar{W}| \end{aligned}$$

Then equation (2.6) becomes,

$$||\ M(X) - M(\bar{X})\ || \leq a|Z - \bar{Z}| + b|W - \bar{W}| + a|Z - \bar{Z}| + (b+d)|W - \bar{W}| \leq 2a|Z - \bar{Z}| + (2b+d)|W - \bar{W}|$$

$\| M(X) - M(\bar{X}) \| \leq L \| X - \bar{X} \|$ where $L = max(2a, 2b + d)$.

Therefore $M(X)$ obeys Lipschitz condition which implies the existence and uniqueness of solution of the fractional-order system (2.3).

Theorem 2.5. *$\forall\ t \geq 0$, $Z(0) = Z_0 \geq 0$, $W(0) = W_0 \geq 0$, the solutions of the system in (2.3) with initial conditions $(Z(t), W(t)) \in R_+^2$ are not negative [16–18].*

Proof: (Generalized Mean Value Theorem) Let $f(x) \in C[a, b]$ and $D^\alpha f(x) \in C[a, b]$ for $0 < \alpha \leq 1$. Then we have

$$f(x) = f(\alpha) + \frac{1}{\Gamma(\alpha)} D^\alpha f(\epsilon)(x - a)^\alpha \tag{2.7}$$

with $0 \leq \epsilon \leq x$, $\forall x \in (a, b]$.

The existence and uniqueness of the solution (2.3) in $(0, \infty)$ can be obtained via Generalized Mean Value Theorem. We need to show that the domain R_+^2 is positively invariant. Since

$$D^\alpha Z = -aZ + bW \geq 0$$
$$D^\alpha W = aZ - (b + d)W \geq 0$$

on each hyperplane bounding the nonnegative orthant, the vector field points into R_+^2.

2.3. Fractional Order Mathematical Model of Human Liver Equilibrium Point and Stability Analysis

Definition 2.6. *That the equilibrium point of the first-order difference equation system given as*

$$X_{t+1} = F(X_t) \tag{2.8}$$

is the point $\bar{X}$ that satisfies the equations $\bar{X} = F(\bar{X})$. Also, let us consider $J(\bar{X})$ to be the Jacobian matrix calculated at this equilibrium point. If the eigenvalues obtained from the equation $det(J(\bar{X}) - \lambda I) = 0$ satisfy the conditions $\lambda_i \neq 1$ for $i = 1, 2, ..., n$ then this point is called hyperbolic equilibrium, otherwise it is called non-hyperbolic equilibrium [9].

In order to find the equilibrium point (2.3) in the system , $D^\alpha Z = 0$, $D^\alpha W = 0$, it is considered to be.

$$\frac{d^\alpha Z}{dt^\alpha} = -aZ + bW$$
$$\frac{d^\alpha W}{dt^\alpha} = aZ - (b + d)W.$$

$E_0 = (z_0, w_0)$ including,

$$E_0 = (0, 0) \tag{2.9}$$

equilibrium point is obtained. Jacobian matrix of the system at the equilibrium point

$$J(E_0) = \begin{bmatrix} -a & b \\ a & -b - d \end{bmatrix} \tag{2.10}$$

it is obtained. The eigenvalues obtained from the Jacobian matrix (2.10) are given below.

$$\lambda_1 = \frac{-(a + b + d) + \sqrt{(a + b + d)^2 - 4ad}}{2}$$
$$\lambda_2 = \frac{-(a + b + d) - \sqrt{(a + b + d)^2 - 4ad}}{2}$$

where a, b, d are the parameters of positively defined real numbers. It is clear that $\lambda_2 < 0$. If $\lambda_1 < 0$, the equilibrium point of the system is locally asymptotically stable. If $\lambda_1 > 0$, the equilibrium point of the system is unstable.

2.4. Generalized Euler Method

In this paper, we used the Generalized Euler method to solve the initial value problem with the Caputo fractional derivative. Many of the mathematical models consist of nonlinear systems and finding solutions to these systems can be quite difficult. In most cases, analytical solutions cannot be found and a numerical approach should be considered for this. One of these approaches is the Generalized Euler method [15]. $D^{\alpha}y(t) = f(t, y(t)), y(0) = y_0, 0 < \alpha \leq 1, 0 < t < \alpha$ for the initial value problem, $h = \frac{a}{n}$ impending $[t_j, t_{j+1}]$ is divided into n sub with $j = 0, 1, .., n-1$. Suppose that $y(t), D^{\alpha}y(t)$ and $D^{2\alpha}y(t)$ are continuous in the range $[0, a]$ and using the generalized Taylor's formula, the following equation is obtained [15].

$$y(t_1) = y(t_0) + \frac{h^{\alpha}}{\Gamma(\alpha+1)} f(t_0, y(t_0)).$$

This process will be repeated to create an array. Let $t_j = t_{j+1} + h$ such that

$$y(t_{j+1}) = y(t_j) + \frac{h^{\alpha}}{\Gamma(\alpha+1)} f(t_j, y(t_j))$$

$j = 0, 1, .., n-1$ the generalized formula in the form is obtained. For each $k = 0, 1, ..., n-1$ with step size h,

$$\begin{aligned} D^{\alpha}Z(t) &= -aZ(k) + bW(k) \\ D^{\alpha}W(t) &= aZ(k) - (b+d)W(k) \end{aligned} \tag{2.11}$$

For $t \in [0, h)$, $\frac{t}{h} \in [0, 1)$ we have

$$\begin{aligned} D^{\alpha}Z(t) &= -aZ(0) + bW(0) \\ D^{\alpha}W(t) &= aZ(0) - (b+d)W(0) \end{aligned} \tag{2.12}$$

The solution of (2.12) reduces to

$$\begin{aligned} Z(1) &= Z(0) + \frac{h^{\alpha}}{\Gamma(\alpha+1)}(-aZ(0) + bW(0)) \\ W(1) &= W(0) + \frac{h^{\alpha}}{\Gamma(\alpha+1)}(aZ(0) - (b+d)W(0)) \end{aligned} \tag{2.13}$$

For $t \in [h, 2h)$, $\frac{t}{h} \in [1, 2)$, we get

$$\begin{aligned} Z(2) &= Z(1) + \frac{h^{\alpha}}{\Gamma(\alpha+1)}(-aZ(1) + bW(1)) \\ W(2) &= W(1) + \frac{h^{\alpha}}{\Gamma(\alpha+1)}(aZ(1) - (b+d)W(1)) \end{aligned} \tag{2.14}$$

Repeating the process n times, we obtain

$$\begin{aligned} Z(n+1) &= Z(n) + \frac{h^{\alpha}}{\Gamma(\alpha+1)}(-aZ(n) + bW(n)) \\ W(n+1) &= W(n) + \frac{h^{\alpha}}{\Gamma(\alpha+1)}(aZ(n) - (b+d)W(n)) \end{aligned} \tag{2.15}$$

is obtained.

3. Numerical Simulation of Fractional Order Mathematical Model of Human Liver

In this section, numerical simulation and graphs of the fractional order human liver mathematical model will be presented. Now let us obtain the numerical simulation of the fractional order human liver mathematical model using the Generalized Euler method. Let us consider the following parameters. Let $Z = 250, W = 0, a = 0.054736, b = 0.0152704, d = 0.0093906$ and let the step size be $h = 0.1$. Using the Euler method, the following tables are obtained.

Table 2: The values of Z and W at the moment t for $\alpha = 1$.

t	$Z(t)$	$W(t)$
0	250,00	0,00
1	248,63	1,36
2	247,27	2,72
3	245,92	4,07
4	244,58	5,40
5	243,25	6,73
6	241,93	8,04
7	240,61	9,35
8	239,31	10,64
9	238,02	11,93
10	236,73	13,20
11	235,46	14,46
12	234,19	15,72
13	232,93	16,96
14	231,68	18,19

Table 3: The values of Z and W at the moment t for $\alpha = 0.9$.

t	$Z(t)$	$W(t)$
0	250,00	0,00
1	248,20	1,79
2	246,43	3,56
3	244,67	5,31
4	242,93	7,05
5	241,20	8,77
6	239,49	10,47
7	237,80	12,15
8	236,12	13,81
9	234,45	15,46
10	232,80	17,09
11	231,17	18,70
12	229,55	20,30
13	227,95	21,88
14	226,36	23,44

Table 4: The values of Z and W at the moment t for $\alpha = 0.8$.

t	$Z(t)$	$W(t)$
0	250,00	0,00
1	247,67	2,32
2	245,37	4,62
3	243,09	6,89
4	240,85	9,12
5	238,63	11,33
6	236,43	13,50
7	234,27	15,65
8	232,12	17,76
9	230,01	19,85
10	227,92	21,91
11	225,85	23,94
12	223,81	25,94
13	221,79	27,92
14	219,80	29,87

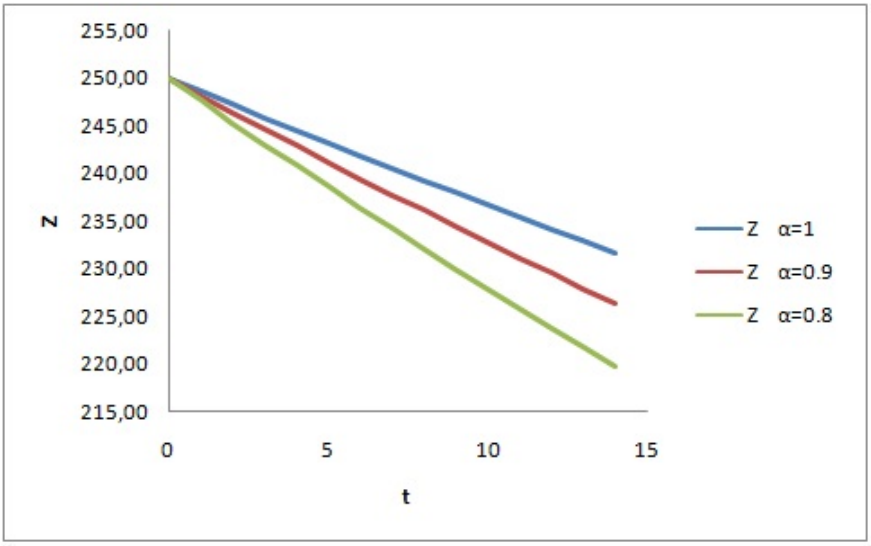

Figure 1: The graph of change of the Z compartment model.

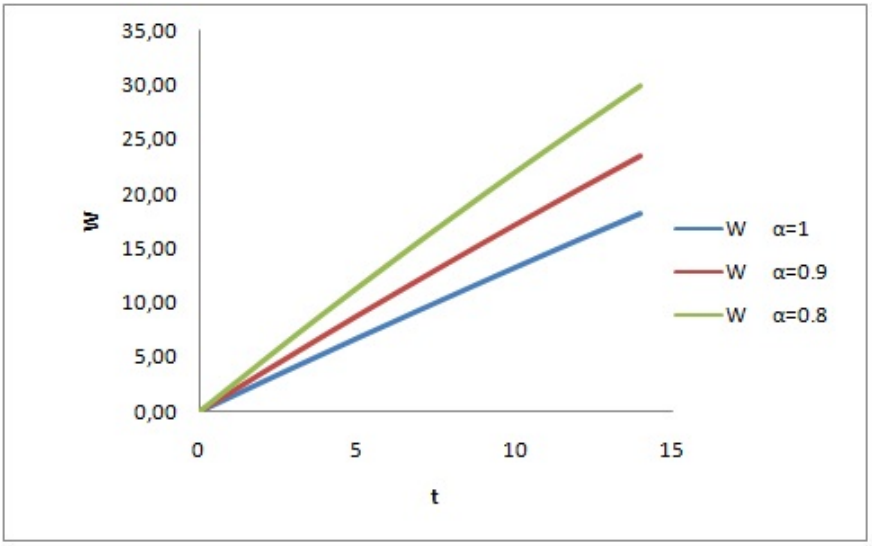

Figure 2: The graph of change of the W compartment model.

In Table 3, Table 4 and Table 5, the changes of Z and W are observed for different states of α. By the above figures, we observe the following highlights:

1. It has been observed that the level of bromsulphthalein (BSP) in the bloodstream decreases over time (Fig.1).
2. Over time, an increase in the amount of bromsulphthalein (BSP) in the liver has been observed (Fig.2).

4. Conclusions and Comments

In this study, a new implementation of the system, which is analysed as a realistic fractional order human liver mathematical model, is performed and graphs are drawn with the help of the numerical results obtained. In this study, mathematical analysis and stability analysis of the existence, uniqueness and non-negativity of the fractional orderhuman liver mathematical model system were performed. The equilibrium point of the fractional order human liver mathematical model was obtained and stability analysis was performed. In the obtained graphs, it is observed that the amount of Bromsulphthalein (BSP) in the blood decreases with time and the amount of Bromsulphthalein (BSP) in the liver increases with time. In addition, the high fractional order value α, which is considered for the related systems, represents the high load of the system. This shows that the fractional derivative gives effective results in real life problems that depend on past and future, such as the human liver model system, due to its memory and inheritance properties.

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