Chapter 3

Fractional modelling of Breast Cancer Dynamics

3.1 Introduction

Breast cancer is a kind of malignant tumor that develops from cells in the breast. **Cancer Cells**: These are cells that proliferate and divide at an uncontrolled and accelerated rate. They are illustrated in red inside the breast ducts and lobules. **Lymph Nodes**: These are little bean-shaped structures that create and store immune-fighting cells. They are highlighted in green in the illustration. **Lobules**: These are the glands in the breast that create milk. **Ducts** are tubes that transport milk from the lobules to the nipple. Figure 3.1 displays all the terms [136]. The initiation of Breast cancer often occurs inside the epithelial lining of the milk ducts or the lobules responsible for milk production. A malignant tumor has the ability to metastasize to other regions of the body [49]. An individual diagnosed with Breast cancer may have localized cancerous cells in a specific area of the breast, often detectable as a palpable mass. Cancer has the ability to metastasize to either one or both breasts. Occasionally, Breast cancer metastasizes to other regions of the body, such as the skeletal system, the liver, or other locations. Following Lung cancer, Breast cancer has been identified as the most prevalent kind of cancer worldwide, affecting women around the globe [147]. According to the World Health Organization (WHO), the global prevalence of Breast cancer among women is estimated to be around 8 to 9 percent.

The classification of cancer stages serves to ascertain the extent of malignancy. The TNM system, often known as Tumor, Node, Metastasis, is the approach used by medical professionals to characterize the stage of cancer. The classification of cancer stages in this method is based on three primary factors: tumor size, lymph node involvement, and metastasis to other parts. The successful management of Breast cancer is facilitated by early detection of the disease. As the stage increases, the likelihood of recovery decreases. There are many distinct modalities for the treatment of cancer, including chemotherapy, hormone therapy, radiation, surgery, and targeted therapy. This cancer therapy is used to induce apoptosis in cancer tissues, eliminate malignant tissues, or impede the transmission of cell division signals to cancerous cells.

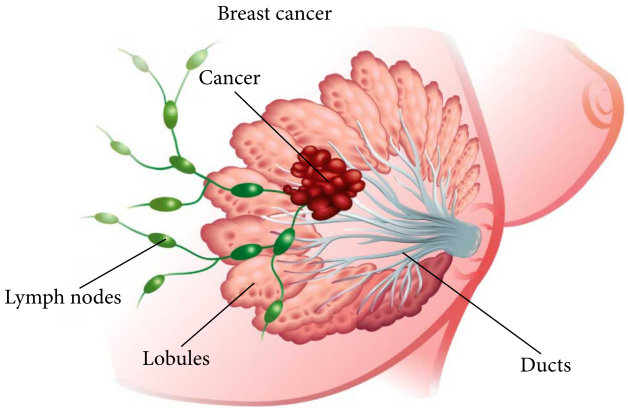

Figure 3.1: Overview of Breast cancer

Many mathematical models constructed to understand the dynamics of Breast cancer. In [30], the author's shows the rivalry between dead cells and normal cells in currently used chemotherapy treatment combined with monoclonal antibody medicines and the kito diet is demonstrated via system of non-linear ordinary differential equations with and without using z-control. Yousef et al. [160] investigated the role of mathematical simulations in breast carcinoma immuno-chemotherapeutic treatment with controlled conditions (Immune-booster, Keto diet, Tamoxifen anti cancer drug) without including the z-control. Solis et al. [133] developed a fractional mathematical model of Breast cancer competition model. Fathoni et al. [44] presented a mathematical model study of the different phases of Breast cancer in patients undergoing chemotherapy, focusing specifically on the cardiac adverse effects. Alzahrani et al. [10] investigated the mathematical model to get a deeper comprehension of the dynamics of Breast cancer, as well as its prevention, detection, and treatment. The author validates the traditional model by using reported fourth-stage Breast cancer cases in the Saudi female population from 2004 to 2016. Through the CF fractional derivative operator, the author [136] envisioned and analyzed Breast cancer with unfavorable responses to chemotherapy treatment.

We have structured this chapter into three parts:

In the first section 3.2 of this chapter, a novel approach is introduced to model Breast cancer dynamics using the Caputo fractional derivative operator. The study includes an analysis of Breast cancer growth and control through chemotherapy treatment with three control parameters. Sadovskii's fixed-point theorem establishes the existence and uniqueness of solutions, and stability is examined using the Routh-Hurwitz criteria and Ulam-Hyers criteria. Numerical simulations are presented to illustrate the results via predictor-corrector scheme.

The second section 3.3 focuses on modelling and analyzing various phases of Breast cancer in a fractional framework, utilizing a CF derivative. Simulations with real data from Breast cancer incidences in Saudi Arabia from 2004 to 2016 demonstrate the efficacy of the CF model compared to classical model. The Picard-Lindelof method is employed for existence and uniqueness, and the two-steps Adams-Bashforth technique is used for simulation. Graphical representations highlight the impact of fractional order on Breast cancer behavior and chemotherapy rates.

The third section 3.4 explores the development, analysis, and simulation of fractional mathematical model investigating the transmission dynamics of different phases of Breast cancer. Incorporating Caputo, Caputo-Fabrizio-Caputo, and Atangana-Baleanu-Caputo operators, the study establishes solutions' existence and uniqueness using Krasnoselskii's fixed-point theory. Equilibrium points and stability are analyzed with the Routh-Hurwitz criterion. Model verification is done using reported occurrences of stage-IV Breast cancer in Saudi Arabia, and parameters are estimated using least squares methodology. Numerical simulations offer insights into each suggested fractional order model.

3.2 Fractional order mathematical modelling and analysis of Breast cancer epidemiology under control parameters

3.2.1 Introduction

In this part of chapter 3, we improved a mathematical system of breast tumor dynamics [30] in the context of a Caputo fractional derivative operator with a power kernel. The approximate solution is achieved using the numerical approach described as well as qualitative analysis is also done for the system. The remaining part of this endeavor is as follows: Section 3.2.2 covers the prerequisites for fractional calculus. Section 3.2.3 provides a mathematical modelling of Breast cancer dynamics with a variable-order fractional Caputo derivative. Sections 3.2.4 and 3.2.5 investigate the equilibrium points and the analysis of fractional - order derivative model for the Caputo version. Section 3.2.6 includes numerical scheme to solve system of FDEs. Section 3.2.7 discuss the numerical findings with the help of simulation. Section 3.2.8 gives the conclusion.

3.2.2 Preliminaries

Here, we provide some essential definitions which are further used in this paper.

Definition 3.2.1. *For $\eta > 0$ and $\varphi : \mathbb{R}^+ \to \mathbb{R}$, Liouvillie [106] established a fractional integral operator as*

$$ {}_0I^{\eta}(\varphi(t)) = \frac{1}{\Gamma(\eta)} \int_0^t (t - \mathfrak{K})^{\eta-1} \varphi(\mathfrak{K}) d\mathfrak{K}, t > 0. \tag{3.1} $$

Definition 3.2.2. *Caputo ([106]) contributed in the field of fractional calculus by defining the derivative of fractional order $\eta > 0$ for the function $\varphi(t)$ as*

$$ {}_0^C D^{\eta}(\varphi(t)) = \frac{1}{\Gamma(\mathfrak{m}-\eta)} \int_0^t (t-\mathfrak{K})^{\mathfrak{m}-\eta-1} \varphi^{\mathfrak{m}}(\mathfrak{K}) d\mathfrak{K}, t > 0, \tag{3.2} $$

where, $\mathfrak{m}-1 < \eta \leq \mathfrak{m}, \mathfrak{m} \in \mathbb{N}$.

3.2.3 Model formulation in Caputo sense

In this section, we consider modified Breast cancer epidemiology with control parameters [30]. We replace conventional derivatives by the caputo derivative as (3.2) to obtain the fractional order system.

A system of FDEs are formulated in the following manner:

$$ \begin{aligned} {}_0^C D_t^{\eta} H(t) &= J_1(t, H, D, A); \quad H(0) = H_0 \\ {}_0^C D_t^{\eta} D(t) &= J_2(t, H, D, A); \quad D(0) = D_0 \\ {}_0^C D_t^{\eta} A(t) &= J_3(t, H, D, A); \quad A(0) = A_0 \end{aligned} \tag{3.3} $$

where

$$ \begin{aligned} J_1(t, H, D, A) &= l_H - d_1 HD - \Delta_H \\ J_2(t, H, D, A) &= l_D - d_2 HD - \Delta_D - uD \\ J_3(t, H, D, A) &= i_g - h_w A - \omega_1 - \omega_2 + u_1(t)A \end{aligned} $$

In addition, all parameters inside the model are considered to be positive constants with the following definitions. The state variables are: H(t) represents healthy(Normal) cells population, D(t) represents dead(cancer) cells and A(t) represents monoclonal anti-body drugs.

The description of parameters are:

- $l_H = a_1 H \left(1 - \frac{H}{b_1}\right)$: Logarithmic expansion of healthy cells. It demonstrates a natural growth in healthy cells with a rate of division and carrying capacity.

- d_1HD : Cancer cells and healthy cells are in competition with rate d_1.
- $\Delta_H = \frac{e_1HA}{f_1+H}$: Holling class-II phrase, which indicates the absorption of normal cells at rate e_1 as a result of a combination of chemotherapy and monoclonal antibody medicines.
- $l_D = a_2D\left(d - \frac{D}{b_2}\right)$: Cancer cell proliferation is facilitated by logistics. It demonstrates natural growth of cancer cells with division rate a_2 and carrying capacity b_2. Kitodiet has an effect on cancer cell development at a steady rate d.
- d_2HD : At rate d_2, there is battle between healthy and cancerous cells.
- $\Delta_D = \frac{e_2DA}{f_2+D}$: Holling type-II terms that demonstrate absorption of malignant cells as a consequence of the combination of chemotherapy and monoclonal antibody pharmaceuticals at a rate of e_2.
- uD : The toxicity of the ketogenic diet causes the death of cancer cells.
- i_g : The rate at which chemotherapy drugs and monoclonal antibody medicines are infused.
- h_wM : With an expulsion rate of h, monoclonal antibody pharmaceuticals and chemotherapy agents are eliminated.
- $\omega_1 = \frac{j_1HA}{f_1+H}$: This word reflects normal cell absorption of monoclonal antibody drugs and chemotherapeutic agents at rate j_1, which is also represented by the holling type-II term, and f_1 is the rate without competition and healthy cell absorption achieves carrying capacity.
- $\omega_2 = \frac{j_2DA}{f_2+D}$: Absorption of monoclonal antibody medicines and chemotherapeutic agents by cancer cells at rate j_2, which is also a holling type-II word, and f_2 be the rate of absorption Cancer cells acquire carrying capacity in the absence of competition and absorption.

- $u_1(t)$: It is the variable of interest in this study pertains to the indirect regulation of chemotherapeutic treatment and monoclonal antibody medicines.

The given table provides parameter values and descriptions.

Table 3.1: Parameters, its values and description

Parameter	Symbol	Value and Unit
Division rate of Normal cells	a_1	1.5/day
Division rate of Cancer cells	a_2	10.0/day
Transport ability of healthy cells	b_1	1460/day
Transport ability of Cancer cells	b_2	2100/day
Competition rate of malignant cells kills healthy cells	d_1	0.0075 /day
Competition rate of Normal cells kills Cancer cells	d_2	0.005/day
Absorption rate of Normal cells due to combine effect of chemotherapy and monoclonal antibody drugs	e_1	0.000384/day
Absorption rate of Cancer cells due to combine effect of chemotherapy and monoclonal antibody drugs	e_2	0.1216/day
Without competition and absorption normal cells reaches at carrying capacity	f_1	1/day
Without competition and absorption cancer cells reaches at carrying capacity	f_2	1/day
Absorption rate of chemotherapy and monoclonal antibody due to drugs normal cells	j_1	0.001152/day
Absorption rate of chemotherapy and monoclonal antibody due to drugs cancer cells	j_2	0.1152/day
Death rate of cancer cells due to keto diet	u	2.0/day
Infusion rate of chemotherapy and monoclonal antibody drugs	i_g	2450/day
Washout rate of chemotherapy and monoclonal antibody drugs	h_w	9.6/day
Keto diet at a constant pace	d	0.5/day

3.2.4 Equilibria

There are four equilibrium points of system (3.3). The first is a tumor-free equilibrium phase(B_{CEEP}), cancerous endemic equilibrium phase(B_{TFEP}) and two of them are dead

equilibrium points (B_{DEP_1} and B_{DEP_2}) which are listed below :

1. $B_{TFEP}(H^*, 0, A^*)$: This point denotes the absence of cells that are cancerous and the presence simply of H^* healthy cells and A^* therapy agent.

2. $B_{DEP_1}(0, D^*, A^*)$: This sort of point states that there are no healthy cells, but just D^* dead cells and A^* quantity of therapeutic agent.

3. $B_{DEP_2}(0, i_g h_w^{-1})$: Reflects the presence of no dead cells or healthy cells in the body, but only $i_g h_w^{-1}$ quantity of monoclonal antibody medicine and chemotherapeutic drug agent.

4. $B_{CEEP}(H^*, D^*, A^*)$: Represents the situation in which each of the three elements is present.

Theorem 3.2.1. *([30]) Let B_{TFEP} be the system's*(3.3) *tumor-free equilibrium position and if $a_1^{-1} i_g e_1 < h_w f_1$ then B_{TFEP} exists uniquely and if $h_w f_1 < \frac{i_g e_1}{a_1} < \frac{(h_w f_1 + b_1(h_w + j_1))^2}{4(h_w + j_1) b_1}$ admit, then two separate equilibria exist of type B_{TFEP}.*

Theorem 3.2.2. *([30]) Suppose that $H^* > \frac{b_1}{2}$ and $a_2 d > d_2 H^* + u + \frac{e_2 A^*}{f_2}$ then B_{TFEP} is unstable and if $H^* > \frac{b_1}{2}$ and $a_2 d < d_2 H^* + u + \frac{e_2 A^*}{f_2}$ then it is asymptotically stable.*

Theorem 3.2.3. *([30]) B_{DEP_1} be the dead equilibrium point of the system* (3.3) *exists uniquely if $i_g e_2 < h_w f_2 (a_2 d - u)$. Also if*

$$h_w f_2 (a_2 d - u) < i_g e_2 < \frac{(h_w f_2 a_2 - b_2 (a_2 d - u)(h_w + j_2))^2}{4 a_2 (h_w + j_2) b_2}$$

admit. Consequently, two distinct equilibria exists of type B_{DEP_1}.

Theorem 3.2.4. *([30]) If $D^* > \frac{d b_2}{2}$ and $a_1 > d_1 D^* + \frac{e_1 A^*}{f_1}$ then B_{DEP_1} is unstable and asymptotically stable if $D^* > \frac{d b_2}{2}$ and $a_1 < d_1 D^* + \frac{e_1 A^*}{f_1}$.*

Theorem 3.2.5. *([30]) Let B_{DEP_2} be the system's* (3.3) *dead point of equilibrium is asymptotically stable if $a_1 < (f_1 h_w)^{-1} e_1 i_g$ and $a_2 d < (f_2 h_w)^{-1} e_2 i_g$ and unstable if $a_1 > (f_1 h_w)^{-1} e_1 i_g$ and $a_2 d > (f_2 h_w)^{-1} e_2 i_g$.*

3.2.5 Qualitative analysis

Consider the Initial Value Problem (IVP) which will be used in the following subsections.

$$ {}_0^C D_t^{\eta} \Lambda(t) = \varphi(t, \Lambda(t)), \text{ where, } \Lambda(0) = \Lambda_0; \Lambda \in \mathbb{R}, t \in (0, +\infty). \tag{3.4} $$

Solution for the System: Existence and Uniqueness

Using Sadovskii's fixed point theorem, we discuss the existence and uniqueness of solutions of (3.3) by considering banach space Y with $t \in [0, \mathsf{T}], H, D, A \in \mathsf{C}(\mathfrak{G}, Y) \cap L^1{}_{loc}(\mathfrak{G}, Y)$ and for $\mathsf{T}, \mathfrak{r} > 0$, $\mathfrak{G} = \{(t, K) : t \in [0, \mathsf{T}], K \in \mathbb{B}(0, \mathfrak{r})\}$.

Theorem 3.2.6. *Consider $\mathbb{B} \subset Y$ and let $\Phi : \mathbb{B} \to \mathbb{B}$ be a mapping with condensation property. Then, there exists a definite point of the mapping Φ within the set $\mathbb{B}$.*

Examine IVP (3.4) *on $\mathfrak{G} = \{(t, K) \in \mathbb{R} \times Y : t \in [0, \mathsf{T}], K \in \mathbb{B}(0, \mathfrak{r})\}$ for some $\mathsf{T}, \mathfrak{r} > 0$. Then, $\exists\ \lambda \in (0, \eta)$, $\mathfrak{M}_1{}^*, \mathfrak{M}_2{}^*, L, L_1 \in L_{1/\lambda}([0, \mathsf{T}], \mathbb{R}^+)$ and H_1, H_2, D_1, D_2,*
$A_1, A_2 \in \mathbb{C}(\mathbb{R}, Y) \cap L^1{}_{loc}(\mathbb{R}, Y) \ni H = H_1 + H_2$, $D = D_1 + D_2$, $A = A_1 + A_2$ and the subsequent premises are legitimate

Assumption 1– *H_1, D_1 and A_1 are bounded and Lipschitz.*

Assumption 2– *H_2, D_2 and A_2 are compact.*

Assumption 3– *$|\mathbb{R}(t, K) - \mathbb{R}(t, Q)| \leq L_1(t)\|K - Q\|\ \forall\ (t, K), (t, Q) \in \mathbb{R}$.*

Applying Definition (3.2.1) on system of FDEs (3.3), the Lemma can be formulated as follows:

Lemma 3.2.1. *As the model under discussion was derived with a single condition for each equation, the IVP* (3.4) *is identical to the subsequent system of integral equations:*

$$H(t) = H(0) + \frac{1}{\Gamma(\eta)}\left(\int_0^t (t-\mathfrak{K})^{\eta-1} H_1(\mathfrak{K}, H(\mathfrak{K}))\, d\mathfrak{K} + \int_0^t (t-\mathfrak{K})^{\eta-1} H_2(\mathfrak{K}, H(\mathfrak{K}))\, d\mathfrak{K}\right),$$

$$D(t) = D(0) + \frac{1}{\Gamma(\eta)}\left(\int_0^t (t-\mathfrak{K})^{\eta-1} D_1(\mathfrak{K}, D(\mathfrak{K}))\, d\mathfrak{K} + \int_0^t (t-\mathfrak{K})^{\eta-1} D_2(\mathfrak{K}, D(\mathfrak{K}))\, d\mathfrak{K}\right),$$

$$A(t) = A(0) + \frac{1}{\Gamma(\eta)}\left(\int_0^t (t-\mathfrak{K})^{\eta-1} A_1(\mathfrak{K}, A(\mathfrak{K}))\, d\mathfrak{K} + \int_0^t (t-\mathfrak{K})^{\eta-1} A_2(\mathfrak{K}, A(\mathfrak{K}))\, d\mathfrak{K}\right).$$

After structuring the above claims it is now simple to explain the existence and uniqueness of solution (3.3), as shown in the following two theorems.

Theorem 3.2.7. *The IVP* (3.4) *has an optimum solution in* $[0, \mathsf{T}]$ *if*

$$\gamma = \frac{q\|L\|_{1/\lambda}(\mathsf{T})^{\theta}}{\Gamma(\eta)} < 1, \qquad where\, \theta = (\eta - \lambda), q = \left(\frac{1-\lambda}{\eta-\lambda}\right)^{1-\lambda}$$

Proof. Choose $\mathfrak{r} \ni |H_0| + \Gamma(\eta)^{-1} q\left(\|\mathfrak{M}_1{}^*\|_{1/\lambda} + \|\mathfrak{M}_2{}^*\|_{1/\lambda}\right)\mathsf{T}^{\theta} \leq \mathfrak{r}$ and let $B_{\mathfrak{r}} = \{K : \|K\| \leq \mathfrak{r}\}$ be the closed ball in $\mathbb{BC}([0, \mathsf{T}], Y)$ with sup norm $\|.\|$. Using Lemma 3.2.1, one can obtain that point of $H : B_{\mathfrak{r}} \to \mathbb{BC}([0, \mathsf{T}], Y), K \mapsto H_1 K + H_2 K$ with the following:

$$H_1 K(t) = H(0) + \frac{1}{\Gamma(\eta)} \int_0^t (t-\mathfrak{K})^{\eta-1} H_1(\mathfrak{K}, K(\mathfrak{K}))\, d\mathfrak{K},$$

$$H_2 K(t) = \frac{1}{\Gamma(\eta)} \int_0^t (t-\mathfrak{K})^{\eta-1} H_2(\mathfrak{K}, K(\mathfrak{K}))\, d\mathfrak{K},$$

as a solution of (3.3). We show in three steps that $H(t)$ is condensing and thus the existence of a definite point for $H(t)$ then from Theorem 3.2.6.

Step 1: We must demonstrate $H\left(B_{\mathfrak{r}}\right) \subset B_{\mathfrak{r}}$. For $K \in B_{\mathfrak{r}}$, we have

$$
\begin{aligned}
|H(t)| &\leq |H_0| + \frac{1}{\Gamma(\eta)} \int_0^t (t-\mathfrak{K})^{\eta-1} |H(\mathfrak{K}, K(\mathfrak{K}))| \, d\mathfrak{K} \\
&\leq |H_0| + \frac{1}{\Gamma(\eta)} \left(\int_0^t (t-\mathfrak{K})^{\eta-1} |H_1(\mathfrak{K}, K(\mathfrak{K}))| \, d\mathfrak{K} + \int_0^t (t-\mathfrak{K})^{\eta-1} |H_2(\mathfrak{K}, K(\mathfrak{K}))| \, d\mathfrak{K} \right) \\
&\leq |H_0| + \frac{1}{\Gamma(\eta)} \int_0^t (t-\mathfrak{K})^{\eta-1} \mathfrak{M}_1{}^*(\mathfrak{K}) \, d\mathfrak{K} + \frac{1}{\Gamma(\eta)} \int_0^t (t-\mathfrak{K})^{\eta-1} \mathfrak{M}_2{}^*(\mathfrak{K}) \, d\mathfrak{K} \\
&\leq |H_0| + \frac{1}{\Gamma(\eta)} \left(\int_0^t (t-\mathfrak{K})^{\frac{\eta-1}{1-\lambda}} d\mathfrak{K} \right)^{1-\lambda} \left(\int_0^t \left(\mathfrak{M}_1{}^*(\mathfrak{K})\right)^{\frac{1}{\lambda}} d\mathfrak{K} \right)^{\lambda} \\
&\quad + \frac{1}{\Gamma(\eta)} \left(\int_0^t (t-\mathfrak{K})^{\frac{\eta-1}{1-\lambda}} d\mathfrak{K} \right)^{1-\lambda} \left(\int_0^t \left(\mathfrak{M}_2{}^*(\mathfrak{K})\right)^{\frac{1}{\lambda}} d\mathfrak{K} \right)^{\lambda} \\
&\leq |H_0| + \frac{q\left(\|\mathfrak{M}_1{}^*\|_{\frac{1}{\lambda}} + \|\mathfrak{M}_2{}^*\|_{\frac{1}{\lambda}} \right)}{\Gamma(\eta)} \mathsf{T}^{\theta} \leq \mathfrak{r}
\end{aligned}
$$

and thus $H\left(B_{\mathfrak{r}}\right) \subset B_{\mathfrak{r}}$.

Step 2: We illustrate that H_1 is a contraction. Let $K, Q \in B_{\mathfrak{r}}$ then

$$
\begin{aligned}
&|H_1(K(t)) - H_1(Q(t))| \\
&\leq \frac{1}{\Gamma(\eta)} \int_0^t (t-\mathfrak{K})^{\eta-1} L(\mathfrak{K}) \, |K(\mathfrak{K}) - Q(\mathfrak{K})| \, d\mathfrak{K} \\
&\leq \frac{1}{\Gamma(\eta)} \left(\int_0^t (t-\mathfrak{K})^{\frac{\eta-1}{1-\lambda}} d\mathfrak{K} \right)^{1-\lambda} \left(\int_0^t L^{\frac{1}{\lambda}}(\mathfrak{K}) \, d\mathfrak{K} \right)^{\lambda} \|K - Q\| \\
&\leq \frac{q\|L\|_{\frac{1}{\lambda}} \mathsf{T}^{\theta}}{\Gamma(\eta)} \|K - Q\|,
\end{aligned}
$$

and hence $H_1(t)$ is a contraction with $\|H_1(K) - H_1(Q)\| \leq \gamma \|K - Q\|$.

Step 3: H_2 is compact. For $0 \leq \tau_1 \leq \tau_2 \leq \mathsf{T}$, we have

$$
\begin{aligned}
&|H_2(K(\tau_2)) - H_2(K(\tau_1))| \\
&\leq \frac{1}{\Gamma(\eta)} \left| \int_0^{\tau_2} (\tau_2 - \mathfrak{K})^{\eta-1} H_2(\mathfrak{K}, K(\mathfrak{K}))\, d\mathfrak{K} \right| - \frac{1}{\Gamma(\eta)} \left| \int_0^{\tau_1} (\tau_1 - \mathfrak{K})^{\eta-1} H_2(\mathfrak{K}, K(\mathfrak{K}))\, d\mathfrak{K} \right| \\
&\leq \frac{1}{\Gamma(\eta)} \left| \int_0^{\tau_1} (\tau_2 - \mathfrak{K})^{\eta-1} H_2(\mathfrak{K}, K(\mathfrak{K}))\, d\mathfrak{K} \right| + \frac{1}{\Gamma(\eta)} \left| \int_{\tau_1}^{\tau_2} (\tau_2 - \mathfrak{K})^{\eta-1} H_2(\mathfrak{K}, K(\mathfrak{K}))\, d\mathfrak{K} \right| \\
&\quad - \frac{1}{\Gamma(\eta)} \left| \int_0^{\tau_1} (\tau_1 - \mathfrak{K})^{\eta-1} H_2(\mathfrak{K}, K(\mathfrak{K}))\, d\mathfrak{K} \right| \\
&\leq \frac{1}{\Gamma(\eta)} \int_0^{\tau_1} ((\tau_1 - \mathfrak{K})^{\eta-1} - (\tau_2 - \mathfrak{K})^{\eta-1}) \left| H_2(\mathfrak{K}, K(\mathfrak{K})) \right| d\mathfrak{K} \\
&\quad + \frac{1}{\Gamma(\eta)} \int_{\tau_1}^{\tau_2} (\tau_2 - \mathfrak{K})^{\eta-1} \left| H_2(\mathfrak{K}, K(\mathfrak{K})) \right| d\mathfrak{K} \\
&\leq \frac{1}{\Gamma(\eta)} \int_0^{\tau_1} ((\tau_1 - \mathfrak{K})^{\eta-1} - (\tau_2 - \mathfrak{K})^{\eta-1}) \mathfrak{M}_2{}^*(\mathfrak{K}) d\mathfrak{K} + \frac{1}{\Gamma(\eta)} \int_{\tau_1}^{\tau_2} (\tau_2 - \mathfrak{K})^{\eta-1} \mathfrak{M}_2{}^*(\mathfrak{K}) d\mathfrak{K} \\
&\leq \frac{1}{\Gamma(\eta)} \left(\int_0^{\tau_1} \left((\tau_1 - \mathfrak{K})^{\frac{\eta-1}{1-\lambda}} - (\tau_2 - \mathfrak{K})^{\frac{\eta-1}{1-\lambda}} \right) d\mathfrak{K} \right)^{1-\lambda} \left(\int_0^{\tau_1} (\mathfrak{M}_2{}^*(\mathfrak{K}))^{\frac{1}{\lambda}} d\mathfrak{K} \right)^{\lambda} \\
&\quad + \frac{1}{\Gamma(\eta)} \left(\int_{\tau_1}^{\tau_2} (\tau_2 - \mathfrak{K})^{\frac{\eta-1}{1-\lambda}} d\mathfrak{K} \right)^{1-\lambda} \left(\int_0^{\tau_1} (\mathfrak{M}_2{}^*(\mathfrak{K}))^{\frac{1}{\lambda}} d\mathfrak{K} \right)^{\lambda} \\
&\leq \frac{q}{\Gamma(\eta)} \|\mathfrak{M}_2{}^*\|_{\frac{1}{\lambda}} \left[\left((\tau_2 - \tau_1)^{\frac{\eta-1}{1-\lambda}} \right)^{1-\lambda} + (\tau_2 - \tau_1)^{\eta-\lambda} \right] \\
&\leq \frac{2q \|\mathfrak{M}_2{}^*\|_{\frac{1}{\lambda}}}{\Gamma(\eta)} (\tau_2 - \tau_1)^{\eta-\lambda}.
\end{aligned}
$$

The right side of the inequality is unaffected by K. We establish the compactness of H_2 by its relative compactness in $H_2(B_\mathfrak{r})$ using the Arzela-Ascoli theorem. Due to the fact that H_1

and H_2 have distinct features (contraction and compactness respectively), their composite, represented as H, forms a condensing map on $B_{\mathfrak{r}}$. This, along with Lemma 3.2.1, ensures a definite point for H, which is relevant to remaining variables such as $D(t)$ and $A(t)$. □

Theorem 3.2.8. *Under the Assumption 3 and* $\gamma = \dfrac{q\|L_1\|_{1/\lambda}(\mathsf{T})^{\theta}}{\Gamma(\eta)} < 1$*, then unique solution exists for the IVP* (3.4) *in* $[0, \mathsf{T}]$.

Proof. Define the relation $\digamma$ by

$$\digamma H(t) = H(0) + \frac{1}{\Gamma(\eta)} \int_0^t (t-\mathfrak{K})^{\eta-1} H(\mathfrak{K}, H(\mathfrak{K}))\, d\mathfrak{K}.$$

For $H(t), H_1(t) \in B_{\mathfrak{r}}$, we have

$$\begin{aligned}
|\digamma H(t) - \digamma H_1(t)| &\leq \frac{1}{\Gamma(\eta)} \int_0^t (t-\mathfrak{K})^{\eta-1} L_1(\mathfrak{K}) |H(\mathfrak{K}) - H_1(\mathfrak{K})|\, d\mathfrak{K} \\
&\leq \frac{1}{\Gamma(\eta)} \left(\int_0^t (t-\mathfrak{K})^{\frac{\eta-1}{1-\lambda}} d\mathfrak{K} \right)^{1-\lambda} \left(\int_0^t {L_1}^{\frac{1}{\lambda}}(\mathfrak{K})\, d\mathfrak{K} \right)^{\lambda} \|H - H_1\| \\
&\leq \frac{q\|L_1\|_{1/\lambda}(\mathsf{T})^{\theta}}{\Gamma(\eta)} \|H - H_1\| \\
&= \gamma \|H - H_1\|.
\end{aligned}$$

Thus, the condition $\gamma = \dfrac{q\|L_1\|_{1/\lambda}(\mathsf{T})^{\theta}}{\Gamma(\eta)} < 1$ ensure the existence of a unique solution. Similarly unique solution exists for other model equations. □

Stability analysis

We now examine global stability for IVP (3.4). Take $\epsilon > 0$ and a continuous $\varphi : [0, +\infty) \to \mathbb{R}^+$.

Consider

$$\left|{}_0^C D_t^\eta \Lambda(t) - \varphi\left(t, \Lambda\left(t\right)\right)\right| \leq \epsilon, \tag{3.5}$$

$$\left|{}_0^C D_t^\eta \Lambda(t) - \varphi\left(t, \Lambda\left(t\right)\right)\right| \leq \phi(t), \tag{3.6}$$

$$\left|{}_0^C D_t^\eta \Lambda(t) - \varphi\left(t, \Lambda\left(t\right)\right)\right| \leq \epsilon\phi. \tag{3.7}$$

Definition 3.2.3. *The IVP* (3.4) *reveals Ulam–Hyers(U-H) stability if* $\exists\ k_j > 0$ *such that* $\forall\ \epsilon > 0$ *and each* $\Lambda \in \mathbb{C}[0, +\infty)$ *satisfying* (3.5)*, a solution* $\mathfrak{K} \in \mathbb{C}[0, +\infty)$ *of* (3.4) *is present, satisfying* $|\Lambda\left(t\right) - \mathfrak{K}\left(t\right)| \leq \epsilon k_j$.

Definition 3.2.4. *The IVP* (3.4) *exhibits Generalized Ulam–Hyers(G-U-H) stability if* $\exists$ $k_j \in \mathfrak{R}^+$ *exists such that* $k_j(0) = 0$, $\forall\ \epsilon > 0$ *and* $\Lambda \in \mathbb{C}$ *of equation* (3.6)*, there exists a solution* $\mathfrak{K} \in \mathbb{C}$ *of* (3.4) *fullfilling* $|\Lambda\left(t\right) - \mathfrak{K}\left(t\right)| \leq k_j(\epsilon)$.

Definition 3.2.5. *The IVP* (3.4) *demonstrates Ulam–Hyers-Rassias(U-H-R) stability if* $\exists$ $k_{j,l} \in \mathfrak{R}$, $\forall\ \epsilon > 0$ *and every* $\Lambda \in \mathbb{C}$ *of* (3.7)*, there exists a solution* $\mathfrak{K} \in \mathbb{C}$ *of* (3.4) *addressing* $|\Lambda\left(t\right) - \mathfrak{K}\left(t\right)| \leq \epsilon k_{j,l}\phi(t)$.

Definition 3.2.6. *The IVP* (3.4) *is Generalized Ulam–Hyers–Rassias(G-U-H-R) stability if* $\exists\ k_{j,l} \in \mathfrak{R}$*, for every* $\Lambda \in \mathbb{C}$ *of* (3.6)*, there exists a solution* $\mathfrak{K} \in \mathbb{C}$ *of* (3.4) *with* $|\Lambda\left(t\right) - \mathfrak{K}\left(t\right)| \leq k_{j,l}\phi(t)$*, with respect to* ϕ.

Hypothesis 1. *Let* $\phi \in \mathbb{C}[0, \infty)$ *is an accumulating function, then* $\exists\ \varepsilon_\varphi > 0$*, implying that*

$$\frac{1}{\Gamma\left(\eta\right)} \int_0^t \left(t - \mathfrak{K}\right)^{\eta-1} \phi\left(\mathfrak{K}\right) d\mathfrak{K} \leq \varepsilon_\varphi \phi\left(t\right), \qquad (t \geq 0).$$

Lemma 3.2.2. *Consider* $\digamma_1$ *and* $\digamma_2$ *as continuous functions defined over* $[0,\infty)\times[0,\infty)$. *If* $\digamma_2$ *is increasing and* $\exists\ \mu,\zeta>0$, *implying that*

$$\digamma_1(t)\leq \digamma_2(t)+\mu\int_0^t (t-\mathfrak{K})^{\zeta-1}\digamma_1(\mathfrak{K})\,d\mathfrak{K},\qquad (t\geq 0),$$

then

$$\digamma_1(t)\leq \digamma_2(t)+\int_0^t\left[\sum_{j=0}^{\infty}\frac{(\mu\Gamma(\zeta))^j}{\Gamma(j\zeta)}(t-\mathfrak{K})^{\zeta-1}\digamma_2(\mathfrak{K})\right]d\mathfrak{K}.$$

If $\digamma_2(t)=a$ *(constant), then* $\digamma_1(t)\leq \mathrm{a}\mathrm{E}_\zeta\left(\mu\Gamma(\zeta)t^{\zeta}\right)$, *where* $\mathrm{E}_\zeta(\bullet)$ *is the Mittag–Leffler function.*

Theorem 3.2.9. *If the criteria of Hypothesis 1 is fulfilled, then the IVP* (3.4) *is the G-U-H-R stable.*

Proof. Assuming Λ is a solution of (3.6) over the interval $\mathbb{C}[0,\mathsf{T}^*)$, we consider $\mathfrak{K}$ as a solution of (3.4). Thus,

$$\left|\Lambda(t)-\Lambda_0(t)-\frac{1}{\Gamma(\eta)}\int_0^t(t-\mathfrak{K})^{\eta-1}\varphi(\mathfrak{K},\Lambda(\mathfrak{K}))d\mathfrak{K}\right|\leq\frac{1}{\Gamma(\eta)}\int_0^t(t-\mathfrak{K})^{\eta-1}\varphi(\mathfrak{K})\,d\mathfrak{K}$$
$$\leq\chi_\varphi\varphi(t).$$

It follows from these connections:

$$|\Lambda(t)-\varrho(t)|\leq\chi_\varphi\varphi(t)+\frac{N}{\Gamma(\eta)}\int_0^t(t-\mathfrak{K})^{\eta-1}|\Lambda(\mathfrak{K})-\varrho(\mathfrak{K})|\,d\mathfrak{K}.$$

As per *Lemma* 3.2.2, there exists a constant $N^*>0$ that is independent of $\chi_\varphi\varphi(t)$. This constant satisfies $|\Lambda(t)-\mathfrak{K}(t)|\leq N^*\chi_\varphi\varphi(t)$, denoted as $a_{f,\varphi}\varphi(t)$. As a result, the IVP (3.4) can be classified as having G-U-H-R stability. □

Corollary 3.2.1. *Using the same logic as in Theorem 3.2.9, one can demonstrate that IVP* (3.4)*, coupled by* (3.5)*, achieves U-H-R stability.*

Corollary 3.2.2. *By employing the same techniques of Theorem 3.2.9 with inequality* (3.7)*, one can demonstrate IVP* (3.4) *is U–H stable.*

3.2.6 Numerical algorithm

We provide a numerical approach for our suggested model (3.3) in this section. First, we provide the predictor - corrector technique [34] for solving FDE with starting conditions:

$$ {}_0^C D_t^{\eta} \Lambda(t) = \varphi(t, \Lambda(t)), \qquad \eta > 0, \tag{3.8} $$

with initial conditions:

$$ \Lambda^k(0) = \Lambda_0^k, \tag{3.9} $$

where, $k = 0, 1, 2, 3, ..., \lceil \eta \rceil - 1$.

If we take the integral of (3.8) according to definition (3.2.1), it gives us a second order Volterra integral equation

$$ \Lambda(t) = \sum_{q=0}^{\lceil \eta \rceil - 1} \Lambda^q(0) \frac{t^q}{q!} + \frac{1}{\Gamma(\eta)} \int_0^t (t-s)^{\eta-1} f(s, \Lambda(s)) ds. \tag{3.10} $$

Now, set $h = \frac{\mathsf{T}}{N}$ and $t_m = mh, (m = 0, 1, 2, ..., N)$.

As a result, (3.10) may be discretized in the following way:

$$ \Lambda_{i+1} = \sum_{q=0}^{\lceil \eta \rceil - 1} \Lambda^q(0) \frac{t_{i+1}^q}{q!} + \frac{h^{\eta}}{\Gamma(\eta+2)} \left\{ f\left(t_{i+1}, \Lambda_{i+1}^p\right) + \sum_{q=0}^{i} a_{q,i+1} f\left(t_q, \Lambda_q\right) \right\}, \tag{3.11} $$

where,

$$a_{q,m+1} = \begin{cases} m^{\eta+1} - (m-\eta)(m+1)^{\eta}, & if \quad q = 0, \\ (m-q+2)^{\eta+1} + (m-q)^{\eta+1} - 2(m-q+1)^{\eta+1}, & if \quad 1 \leq q \leq m, \\ 1, & if \quad q = m+1. \end{cases} \tag{3.12}$$

and, Λ_{i+1}^{p} is given by :

$$\Lambda_{i+1}^{p} = \sum_{q=0}^{\lceil \eta \rceil - 1} \Lambda^{q}(0) \frac{t_{i+1}^{q}}{q!} + \frac{1}{\Gamma(\eta)} \left\{ \sum_{q=0}^{i} b_{q,i+1} f\left(t_q, \Lambda_q\right) \right\}, \tag{3.13}$$

where,

$$b_{q,m+1} = \frac{h^{\eta}}{\eta} \left((m+1-q)^{\eta} - (m-q)^{\eta} \right), \qquad 0 \leq q \leq m. \tag{3.14}$$

We utilize the above proposed numerical scheme on model (3.3) as:

$$\begin{aligned} H_{n+1} &= H(0) + \frac{h^{\eta}}{\Gamma(\eta+2)} \left\{ J_1(t_{n+1}, H_{n+1}^{p}, D_{n+1}^{p}, A_{n+1}^{p}) + \sum_{q=0}^{n} a_{q,n+1} J_1(t_q, H_q, D_q, A_q) \right\}, \\ D_{n+1} &= D(0) + \frac{h^{\eta}}{\Gamma(\eta+2)} \left\{ J_2(t_{n+1}, H_{n+1}^{p}, D_{n+1}^{p}, A_{n+1}^{p}) + \sum_{q=0}^{n} a_{q,n+1} J_2(t_q, H_q, D_q, A_q) \right\}, \\ A_{n+1} &= A(0) + \frac{h^{\eta}}{\Gamma(\eta+2)} \left\{ J_3(t_{n+1}, H_{n+1}^{p}, D_{n+1}^{p}, A_{n+1}^{p}) + \sum_{q=0}^{n} a_{q,n+1} J_3(t_q, H_q, D_q, A_q) \right\}, \end{aligned} \tag{3.15}$$

where,

$$\begin{aligned} H_{n+1}^{p} &= S(0) + \frac{1}{\Gamma(\eta)} \sum_{q=0}^{n} b_{q,n+1} J_1(t_q, H_q, D_q, A_q), \\ D_{n+1}^{p} &= T(0) + \frac{1}{\Gamma(\eta)} \sum_{q=0}^{n} b_{q,n+1} J_2(t_q, H_q, D_q, A_q), \\ A_{n+1}^{p} &= V(0) + \frac{1}{\Gamma(\eta)} \sum_{q=0}^{n} b_{q,n+1} J_3(t_q, H_q, D_q, A_q). \end{aligned} \tag{3.16}$$

3.2.7 Numerical simulation and Discussion

In this section, several numerical simulation were carried out in order to give empirical evidence to corroborate the theoretical results gained in this work. The numerical simulation which are generated using scheme (3.15) and (3.16) are designed to show the behaviours for $\eta = 0.7, 0.8, 0.9, 1$. Table 3.1 lists all parameter values utilized in the numerical simulation. The starting conditions for the model components were set at H(0)=1460, D(0)=0.01.

In figure 3.2, which illustrates a rise in the number of dead (cancer) cells and a decrease in the number of healthy cells for various orders of η. It has been shown that after a certain period of time, the tumor population grows so powerful that the immunological system need some more details assistance from the regulatory factors. In figure 3.3, we see that inserting control factors such as a kito diet, chemotherapy treatment, and monoclonal antibody medications which diminish the cancer cell population and enhance the healthy cell population for that model parameters were set at $H(0) = 500, D(0) = 100$, and $M(0) = 90$. Figure 3.4 shows that the impact of control situations persists for up to D(0)=179. As shown in figure 3.5, the influence of the control parameters is not visible beyond $D(0) = 179$. To address this, we included z - control in the model (3.3). Figure 3.6 depicts the behavior of z-control on the populations of healthy and dead cells. It is evident that when we add the z-control into the system, the count of healthy tissues increases while the dead cells decreases. It has been shown that in the classical model [30], the influence of control parameters remains significant until D(0)=131, after which the impact of drugs becomes insignificant. The fractional order model (3.3) demonstrates its relevance by exhibiting a prolonged impact, as shown by the value of D(0) reaching 179. Additionally, when we employ the parameter value $\eta = 1$, our results makes classical sense.

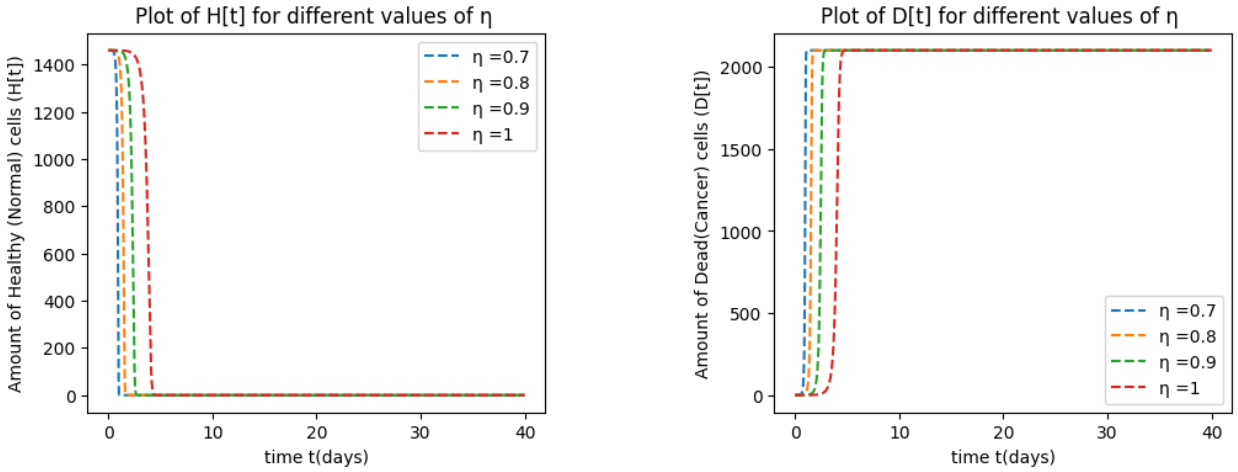

Figure 3.2: Decay of Healthy cells and growth of Dead cells for different value of η without treatment

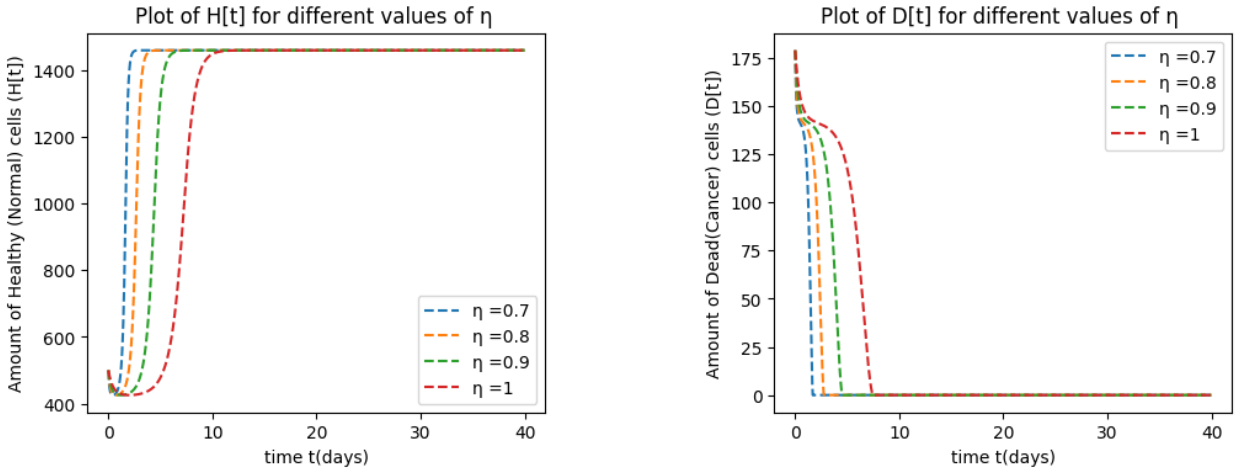

Figure 3.3: Growth of Healthy cells and Decay of Dead cells for different value of η with treatment at $D(0) = 100$

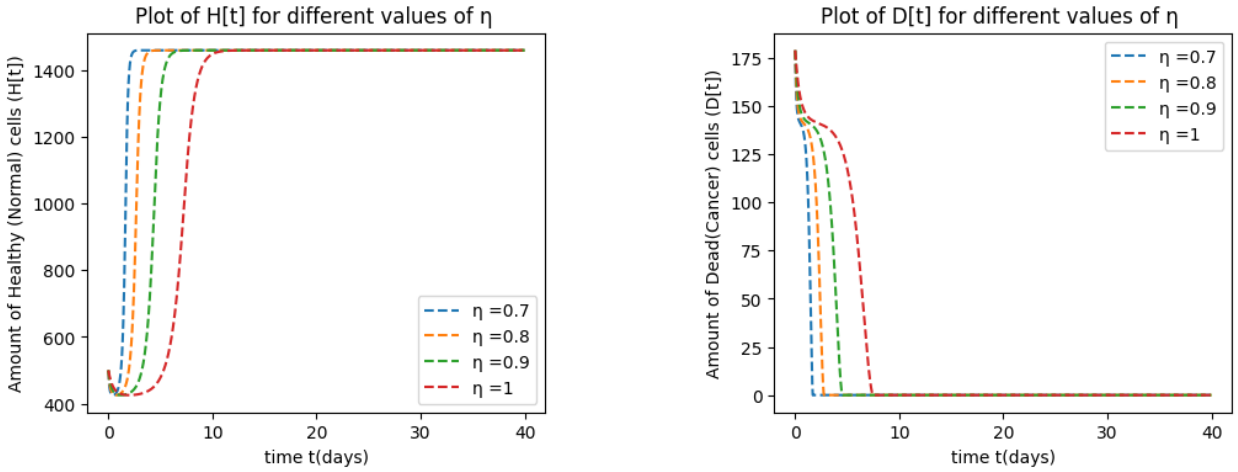

Figure 3.4: Growth of Healthy cells and Decay of Dead cells for different value of η with treatment at D(0) = 179

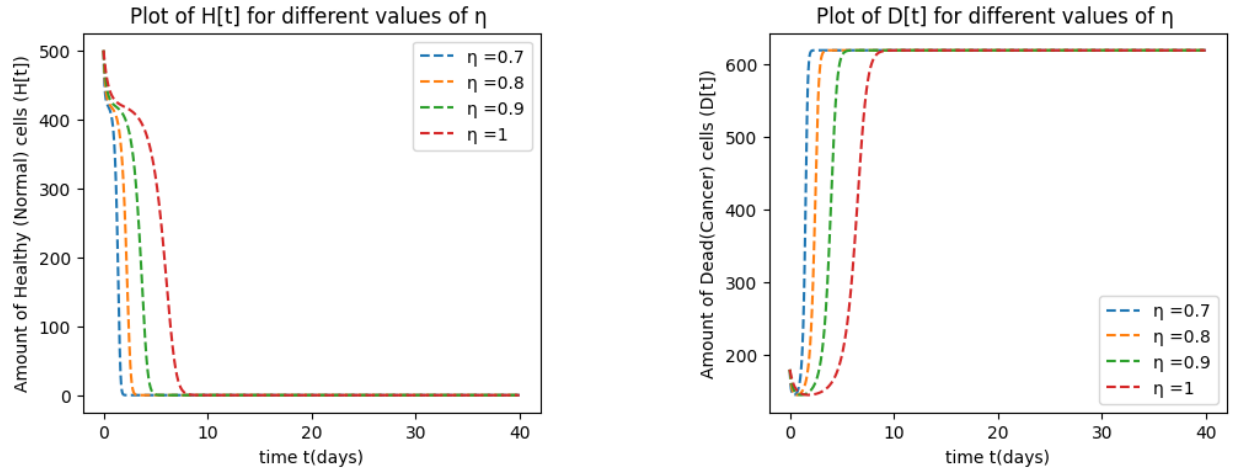

Figure 3.5: Decay of Healthy cells and growth of Dead cells for different value of η with treatment and without z – control

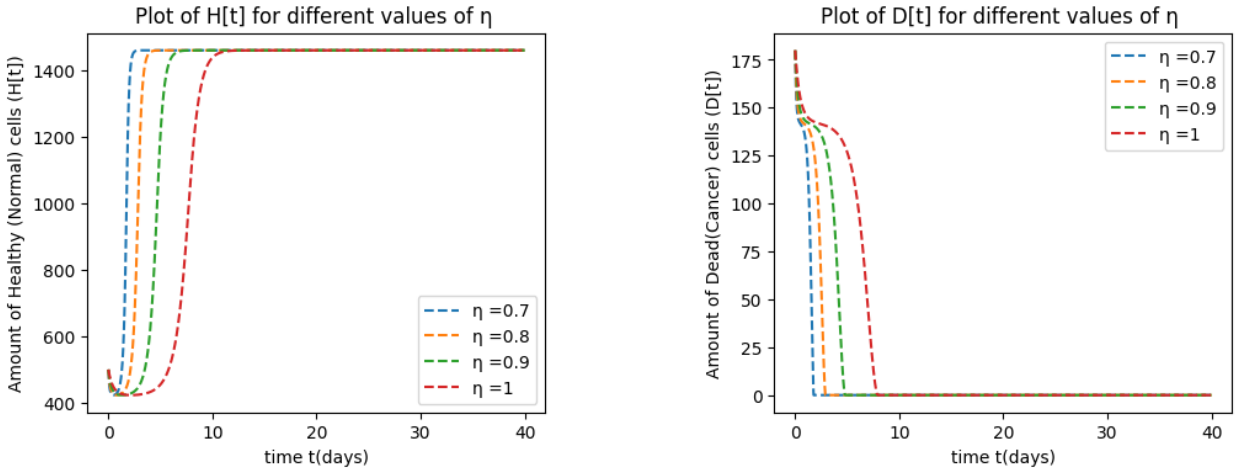

Figure 3.6: Growth of Healthy cells and Decay of Dead cells for different value of η with treatment and z – control

3.2.8 Conclusion

The study focuses on analyzing Breast cancer growth and control through chemotherapy treatment using a system of FDEs with three control parameters: monoclonal antibody drug, keto diet, and z-control. The existence and uniqueness of the system's solutions as shown by Sadovskii's fixed point theorem, ensuring the robustness of the proposed model. The stability analysis of equilibria was performed using the Routh-Hurwitz criteria, providing insights into the dynamic behavior of the system under different control scenarios. The global stability of the model was investigated using the Ulam-Hyers criteria, validating the effectiveness of the proposed approach in capturing the long-term behavior of Breast cancer dynamics under the influence of the control parameters. Numerical simulations were carried out using a predictor-corrector scheme. The graphical illustrations clearly demonstrate the superiority of the Breast cancer model with fractional derivatives over the traditional integer-order model.

3.3 Transmission dynamics of Breast cancer through Caputo Fabrizio frational derivative operator with real data

3.3.1 Introduction

The Breast cancer classical mathematical model was categorized into five epidemiological groups by authors in [10]. However, it fails to optimally capture non-local behavior for the dynamics of the cancer and the deviation between the real data and the data obtained through the simulation of classical model is found to be large. Moreover, the freedom of having access to the real data is the chief motivation behind detailed analysis of the Breast cancer model under CF fractional-order derivative operator. These precise fractional calculus findings and consequences drive us to examine and analyze the dynamics of Breast cancer using actual data, which are reported cases in Saudi Arabia from 2004 to 2016 [5]. It is noteworthy to mention that, unlike several previous studies, we have diligently ensured dimensional uniformity throughout the process of fractionalization.

The outline of the section 3.3 is as follows: Section 3.3.2 explains the fractional calculus requirements for system analysis. Section 3.3.3 use a CF framework to develop a fractional order model for Breast cancer. Section 3.3.4 and 3.3.5 investigate the existence, uniqueness and stability of a proposed system respectively. Numerical algorithm is given in section 3.3.6. In section 3.3.7, we numerically investigate the dynamics of the proposed model with variation in input parameters. Finally, final observations are offered in the concluding 3.3.8 portion.

3.3.2 Preliminaries

Definition 3.3.1. *Let $f \in \mathbb{H}^1(\iota_1, \iota_2)$ and $0 < r < 1$, then the CF fractional derivative [15] defined as follows:*

$$({}_0^{CF}D_t^r N)(t) = \frac{P(r)}{1-r}\int_{\iota_1}^{t} N'(\delta)\exp\left[-\frac{r(t-\delta)}{1-r}\right]d\delta, \tag{3.17}$$

where, $P(r)$ is a normalizing function with the property that $P(0) = P(1) = 1$.

Definition 3.3.2. *[87] If $0 < r < 1$, then the CF fractional integral of order r of a function N is:*

$$({}_0^{CF}I_t^r N)(t) = \frac{2(1-r)}{(2-r)P(r)}N(t) + \frac{2r}{(2-r)P(r)}\int_0^t N(\delta)d\delta. \tag{3.18}$$

3.3.3 Model formulation

Authors in [10] classified the Breast cancer model into five epidemiological categories. During the initial medical report, the overall population of Breast cancer patients was divided into phases 1 and 2 ($\mathbb{S}_{12}$), phase 3 ($\mathbb{S}_3$), phase 4($\mathbb{S}_4$), disease-free state ($\mathbb{S}_R$), and cardiotoxic ($\mathbb{S}_E$) sub populations. The traditional system is described as :

$$\begin{aligned}
\frac{d\mathbb{S}_{12}}{dt} &= \Delta - (\rho+\nu)\mathbb{S}_{12},\\
\frac{d\mathbb{S}_3}{dt} &= \Gamma + \nu\mathbb{S}_{12} + \psi\mathbb{S}_R - (\sigma+\mu+\kappa+\chi)\mathbb{S}_3,\\
\frac{d\mathbb{S}_4}{dt} &= \Omega + \mu\mathbb{S}_3 + \phi\mathbb{S}_R - (\tau+\omega+\delta)\mathbb{S}_4,\\
\frac{d\mathbb{S}_R}{dt} &= \rho\mathbb{S}_{12} + \sigma\mathbb{S}_3 + \tau\mathbb{S}_4 - (\psi+\phi+\zeta)\mathbb{S}_R,\\
\frac{d\mathbb{S}_E}{dt} &= \zeta\mathbb{S}_R + \omega\mathbb{S}_4 + \kappa\mathbb{S}_3 - \eta\mathbb{S}_E,
\end{aligned} \tag{3.19}$$

where, the following are the parameters of the system (3.19): Δ : People who have been diagnosed with cancer at stages 1 and 2, Γ : People suffering with stage 3 cancer, Ω : Cancer patients in the fourth stage, ρ : Chemotherapy recovery in phases 1 and 2, σ : Chemotherapy

recovery at stage 3, τ : Chemotherapy recovery at stage 4, μ : People in worse health enter the stage 4 population, ν : People in worse health enroll in class $\mathbb{S}_3$, κ : Patients undergoing severe treatment that induces cardiotoxicity, ω : People undergoing treatment for stage 4 cancer who suffer cardiotoxicity, ζ : At the disease-free stage, patients who have had extensive chemotherapy which leads to cardiotoxicity, χ : Cancer-related death at stage 3, δ : Cancer-related death at stage 4, η : Cardiotoxic patients' mortality rate, ψ :People regress to stage 3, ϕ : People regress to stage 4.

Now, to better approximate the spread of Breast cancer with varying treatment rates into various compartments and to quantitatively demonstrate the influence of the above-mentioned parameters, the integer order model must be replaced by a fractional order model. The goal of this research is to extend the traditional system (3.19) by adding a fractional time derivative operator that allows for the analysis of memory effects in an arbitrary-order system. During the process of fractionalization, the dimensional consistency for each of the equations in the model has been maintained. We place the fractional order power r on each time-dimensional parameter to make the equal time dimension ($time^{-r}$) on both sides of the model. The proposed Breast cancer transmission model, which includes the CF derivative, is offered as:

$$\begin{aligned}
{}_0^{CF}D_t^r\mathbb{S}_{12} &= \Delta^r - (\rho^r + \nu^r)\mathbb{S}_{12},\\
{}_0^{CF}D_t^r\mathbb{S}_3 &= \Gamma^r + \nu^r\mathbb{S}_{12} + \psi^r\mathbb{S}_R - (\sigma^r + \mu^r + \kappa^r + \chi^r)\mathbb{S}_3,\\
{}_0^{CF}D_t^r\mathbb{S}_4 &= \Omega^r + \mu^r\mathbb{S}_3 + \phi^r\mathbb{S}_R - (\tau^r + \omega^r + \delta^r)\mathbb{S}_4,\\
{}_0^{CF}D_t^r\mathbb{S}_R &= \rho^r\mathbb{S}_{12} + \sigma^r\mathbb{S}_3 + \tau^r\mathbb{S}_4 - (\psi^r + \phi^r + \zeta^r)\mathbb{S}_R,\\
{}_0^{CF}D_t^r\mathbb{S}_E &= \zeta^r\mathbb{S}_R + \omega^r\mathbb{S}_4 + \kappa^r\mathbb{S}_3 - \eta^r\mathbb{S}_E,
\end{aligned} \tag{3.20}$$

with initial conditions: $\mathbb{S}_{12}(0) = \mathbb{S}_{12_0}, \mathbb{S}_3(0) = \mathbb{S}_{3_0}, \mathbb{S}_4(0) = \mathbb{S}_{4_0}, \mathbb{S}_R(0) = \mathbb{S}_{R_0}, \mathbb{S}_E(0) = \mathbb{S}_{E_0}$.

3.3.4 Qualitative analysis

The present study aims to thoroughly examine the fractional system. The PL technique was used to investigate the presence and singularity of the offered solutions for the system (3.20). To begin the process, the system (3.20) is transformed into an integral equation with arbitrary order by applying (3.18) to both sides, resulting in

$$\begin{aligned}
\mathbb{S}_{12}(t) - \mathbb{S}_{12}(0) &= {}^{CF}I_t^r \left\{N_1(t, \mathbb{S}_{12})\right\}, \\
\mathbb{S}_3(t) - \mathbb{S}_3(0) &= {}^{CF}I_t^r \left\{N_2(t, \mathbb{S}_3)\right\}, \\
\mathbb{S}_4(t) - \mathbb{S}_4(0) &= {}^{CF}I_t^r \left\{N_3(t, \mathbb{S}_4)\right\}, \\
\mathbb{S}_R(t) - \mathbb{S}_R(0) &= {}^{CF}I_t^r \left\{N_4(t, \mathbb{S}_R)\right\}, \\
\mathbb{S}_E(t) - \mathbb{S}_E(0) &= {}^{CF}I_t^r \left\{N_5(t, \mathbb{S}_E)\right\},
\end{aligned} \tag{3.21}$$

where

$$\begin{aligned}
N_1(t, \mathbb{S}_{12}) &= \Delta^r - (\rho^r + \nu^r)\mathbb{S}_{12}, \\
N_2(t, \mathbb{S}_3) &= \Gamma^r + \nu^r \mathbb{S}_{12} + \psi^r \mathbb{S}_R - (\sigma^r + \mu^r + \kappa^r + \chi^r)\mathbb{S}_3, \\
N_3(t, \mathbb{S}_4) &= \Omega^r + \mu^r \mathbb{S}_3 + \phi^r \mathbb{S}_R - (\tau^r + \omega^r + \delta^r)\mathbb{S}_4, \\
N_4(t, \mathbb{S}_R) &= \rho^r \mathbb{S}_{12} + \sigma^r \mathbb{S}_3 + \tau^r \mathbb{S}_4 - (\psi^r + \phi^r + \zeta^r)\mathbb{S}_R, \\
N_5(t, \mathbb{S}_E) &= \zeta^r \mathbb{S}_R + \omega^r \mathbb{S}_4 + \kappa^r \mathbb{S}_3 - \eta^r \mathbb{S}_E,
\end{aligned}$$

are contractions with respect to the functions $\mathbb{S}_{12}, \mathbb{S}_3, \mathbb{S}_4, \mathbb{S}_R$ and $\mathbb{S}_E$ respectively. Applying (3.18) on (3.21),we obtain

$$\begin{aligned}
\mathbb{S}_{12}(t) - \mathbb{S}_{12}(0) &= \Omega(r) N_1(t, \mathbb{S}_{12}) + \omega(r) \int_0^t N_1(y, \mathbb{S}_{12}) dy, \\
\mathbb{S}_3(t) - \mathbb{S}_3(0) &= \Omega(r) N_2(t, \mathbb{S}_3) + \omega(r) \int_0^t N_2(y, \mathbb{S}_3) dy, \\
\mathbb{S}_4(t) - \mathbb{S}_4(0) &= \Omega(r) N_3(t, \mathbb{S}_4) + \omega(r) \int_0^t N_3(y, \mathbb{S}_4) dy,
\end{aligned} \tag{3.22}$$

$$\mathbb{S}_R(t) - \mathbb{S}_R(0) = \Omega(r)N_4(t, \mathbb{S}_R) + \omega(r)\int_0^t N_4(y, \mathbb{S}_R)dy,$$
$$\mathbb{S}_E(t) - \mathbb{S}_E(0) = \Omega(r)N_5(t, \mathbb{S}_E) + \omega(r)\int_0^t N_5(y, \mathbb{S}_E)dy,$$

where, $\Omega(r) = \dfrac{2(1-r)}{(2-r)P(r)}, \omega(r) = \dfrac{2r}{(2-r)P(r)}$.

By Picard's iterative algorithm

$$\begin{aligned}
\mathbb{S}_{12_{n+1}}(t) &= \Omega(r)N_1(t, \mathbb{S}_{12_n}) + \omega(r)\int_0^t N_1(y, \mathbb{S}_{12_n})dy,\\
\mathbb{S}_{3_{n+1}}(t) &= \Omega(r)N_2(t, \mathbb{S}_{3_n}) + \omega(r)\int_0^t N_2(y, \mathbb{S}_{3_n})dy,\\
\mathbb{S}_{4_{n+1}}(t) &= \Omega(r)N_3(t, \mathbb{S}_{4_n}) + \omega(r)\int_0^t N_3(y, \mathbb{S}_{4_n})dy,\\
\mathbb{S}_{R_{n+1}}(t) &= \Omega(r)N_4(t, \mathbb{S}_{R_n}) + \omega(r)\int_0^t N_4(y, \mathbb{S}_{R_n})dy,\\
\mathbb{S}_{E_{n+1}}(t) &= \Omega(r)N_5(t, \mathbb{S}_{E_n}) + \omega(r)\int_0^t N_5(y, \mathbb{S}_{E_n})dy.
\end{aligned} \tag{3.23}$$

The solutions are achieved as follows:

$$\lim_{n\to\infty} \mathbb{S}_{12_n}(t) = \mathbb{S}_{12}(t), \lim_{n\to\infty} \mathbb{S}_{3_n}(t) = \mathbb{S}_3(t), \lim_{n\to\infty} \mathbb{S}_{4_n}(t) = \mathbb{S}_4(t),$$
$$\lim_{n\to\infty} \mathbb{S}_{R_n}(t) = \mathbb{S}_R(t), \lim_{n\to\infty} \mathbb{S}_{E_n}(t) = \mathbb{S}_E(t).$$

To demonstrate the existence of the solution, we use the PL approach and the Banach fixed point theorem.

Let $N_1^* = \sup_{\mathbb{C}[a,b_1]} \|N_1(t, \mathbb{S}_{12})\|$, $N_2^* = \sup_{\mathbb{C}[a,b_2]} \|N_2(t, \mathbb{S}_3)\|$, $N_3^* = \sup_{\mathbb{C}[a,b_3]} \|N_1(t, \mathbb{S}_4)\|$,

$N_4^* = \sup_{\mathbb{C}[a,b_4]} \|N_1(t, \mathbb{S}_R)\|$, $N_5^* = \sup_{\mathbb{C}[a,b_5]} \|N_1(t, \mathbb{S}_E)\|$,

where,

$$\mathbb{C}[a, b_1] = [t-a, t+a] \times [\mathbb{S}_{12} - b_1, \mathbb{S}_{12} + b_1] = \mathbb{A} \times \mathbb{B}_1,$$
$$\mathbb{C}[a, b_2] = [t-a, t+a] \times [\mathbb{S}_3 - b_2, \mathbb{S}_3 + b_2] = \mathbb{A} \times \mathbb{B}_2,$$
$$\mathbb{C}[a, b_3] = [t-a, t+a] \times [\mathbb{S}_4 - b_3, \mathbb{S}_4 + b_3] = \mathbb{A} \times \mathbb{B}_3,$$
$$\mathbb{C}[a, b_4] = [t-a, t+a] \times [\mathbb{S}_R - b_4, \mathbb{S}_R + b_4] = \mathbb{A} \times \mathbb{B}_4,$$
$$\mathbb{C}[a, b_5] = [t-a, t+a] \times [\mathbb{S}_E - b_5, \mathbb{S}_E + b_5] = \mathbb{A} \times \mathbb{B}_5.$$

Consider an uniform norm on $\mathbb{C}[a, b_\iota]; (\iota = 1, 2, 3, 4, 5)$ as given by:

$$\|U(t)\|_\infty = \sup_{t \in [t-a, t+a]} |U(t)| .$$

We define Picard operator as: $\triangle : \mathbb{C}(\mathbb{A}, \mathbb{B}_1, \mathbb{B}_2, \mathbb{B}_3, \mathbb{B}_4, \mathbb{B}_5) \to \mathbb{C}(\mathbb{A}, \mathbb{B}_1, \mathbb{B}_2, \mathbb{B}_3, \mathbb{B}_4, \mathbb{B}_5)$ described by $\triangle(U(t)) = U_0(t) + \Omega(r)N(t, U(t)) + \omega(r) \int_0^t N(y, U(y))dy$,
where,
$U(t) = \{\mathbb{S}_{12}(t), \mathbb{S}_3(t), \mathbb{S}_4(t), \mathbb{S}_R(t), \mathbb{S}_E(t)\}$,
$U_0(t) = \{\mathbb{S}_{12}(0), \mathbb{S}_3(0), \mathbb{S}_4(0), \mathbb{S}_R(0), \mathbb{S}_E(0)\}$,
$N(t, U(t)) = \{N_1(t, \mathbb{S}_{12}), N_2(t, \mathbb{S}_3), N_3(t, \mathbb{S}_4), N_4(t, \mathbb{S}_R), N_5(t, \mathbb{S}_E)\}$.

We consider the solutions to the problem under examination are bounded within a time interval, i.e., $\|U(t)\|_\infty \leqslant max\{b_1, b_2, b_3, b_4, b_5\} = b$.

Let $N^* = max\{N_1^*, N_2^*, N_3^*, N_4^*, N_5^*\}$, and $\exists\ t_0$ so that $t \leqslant t_0$, then

$$\|\triangle U(t) - U_0(t)\| = \left\| \Omega(r)N(t, U(t)) + \omega(r) \int_0^t N(y, U(y))dy \right\|,$$
$$\leqslant \Omega(r) \|N(t, U(t))\| + \omega(r) \int_0^t \|N(y, U(y))\| dy,$$

$$\begin{aligned}
&\leqslant (\Omega(r) + \omega(r)t)\, N^*, \\
&\leqslant (\Omega(r) + \omega(r)t_0)\, N^*, \\
&\leqslant \mu^* N^* \leqslant b,
\end{aligned}$$

where, $\mu^* = (\Omega(r) + \omega(r)t_0) \leqslant \dfrac{b}{N^*}$.

Further, we prove the following equality:

$$\|\triangle U_1 - \triangle U_2\| = \sup_{t\in\mathbb{A}} |U_1(t) - U_2(t)|\,.$$

Using Picard operator, we get

$$\begin{aligned}
\|\triangle U_1 - \triangle U_2\| &= \left\| \Omega(r)\left\{N(t, U_1(t)) - N(t, U_2(t))\right\} + \omega(r)\int_0^t \left\{N(y, U_1(y)) - N(y, U_2(y))\right\} dy \right\|, \\
&\leqslant \Omega(r)\left\|N(t, U_1(t)) - N(t, U_2(t))\right\| + \omega(r)\int_0^t \left\|N(y, U_1(y)) - N(y, U_2(y))\right\| dy, \\
&\leqslant \Omega(r)\gamma^*\left\|U_1(t) - U_2(t)\right\| + \omega(r)\gamma^*\int_0^t \left\|U_1(y) - U_2(y)\right\| dy, \\
&\leqslant (\Omega(r) + \omega(r)t_0)\,\gamma^*\left\|U_1(y) - U_2(y)\right\|, \\
&\leqslant \mu^*\gamma^*\left\|U_1(y) - U_2(y)\right\|, \text{with} \quad \gamma^* < 1.
\end{aligned}$$

Since N is a contraction, then $\mu^*\gamma^* < 1$, so discussed operator Δ is a contraction. Hence, system (3.20) has a unique solution.

3.3.5 Stability analysis

In this section, we discuss the Ulam-Hyers (U-H) stabiity [143, 144] of the proposed fractional model (3.20) using the notion of nonlinear functional analysis. For the sake of simplicity we consider the proposed model (3.20) as:

$$ {}_0^{CF}D_t^{\tau}\mathbb{B}(t) = \Theta\left(t, \mathbb{B}(t)\right), \tag{3.24}$$

$$\mathbb{B}(0) = \mathbb{B}_0 \geq 0,$$

where, $\mathbb{B}(t) = (\mathbb{S}_{12}(t), \mathbb{S}_3(t), \mathbb{S}_4(t), \mathbb{S}_R(t), \mathbb{S}_E(t))^T$,
$\mathbb{B}_0 = (\mathbb{S}_{12_0}, \mathbb{S}_{3_0}, \mathbb{S}_{4_0}, \mathbb{S}_{R_0}, \mathbb{S}_{E_0})^T$,
$\Theta(t, \mathbb{B}(t)) = (N_1, N_2, N_3, N_4, N_5)^T$.

Applying fractional integral (3.18) on (3.24), we get

$$\mathbb{B}(t) = \mathbb{B}_0 + \Omega(r)\Theta(t, \mathbb{B}(t)) + \omega(r) \int_0^t \Theta(\delta, \mathbb{B}(\delta))d\delta. \tag{3.25}$$

Definition 3.3.3. *The proposed system* (3.20) *is U-H stable, if* $\exists\ \overline{\mu} > 0$ *with the following property. For any* $\epsilon > 0$ *and* $\overline{\mathbb{B}} \in \mathsf{B}$ *(Banach space). If*

$$\left|{}_0^{CF}D_t^r \overline{\mathbb{B}}(t) - \Theta\left(t, \overline{\mathbb{B}}(t)\right)\right| \leq \epsilon, \tag{3.26}$$

then $\exists\ \mathbb{B} \in \mathsf{B}$ *satisfying system* (3.20) *with initial condition* $\mathbb{B}(0) = \overline{\mathbb{B}}(0) = \overline{\mathbb{B}}_0$*, such that* $\left\|\overline{\mathbb{B}} - \mathbb{B}\right\| \leq \overline{\mu}\epsilon$*. Where,*

$$\begin{aligned}
\overline{\mathbb{B}}(t) &= \left(\overline{\mathbb{S}}_{12}(t), \overline{\mathbb{S}}_3(t), \overline{\mathbb{S}}_4(t), \overline{\mathbb{S}}_R(t), \overline{\mathbb{S}}_E(t)\right)^T, \\
\mathbb{B}_0 &= \left(\overline{\mathbb{S}}_{12_0}, \overline{\mathbb{S}}_{3_0}, \overline{\mathbb{S}}_{4_0}, \overline{\mathbb{S}}_{R_0}, \overline{\mathbb{S}}_{E_0}\right)^T, \\
\Theta(t, \overline{\mathbb{B}}(t)) &= \left(\overline{N}_1, \overline{N}_2, \overline{N}_3, \overline{N}_4, \overline{N}_5\right)^T, \\
\epsilon &= max(\epsilon_j)^T; j = 1, 2, 3, 4, 5, \\
\overline{\mu} &= max(\overline{\mu}_j)^T; j = 1, 2, 3, 4, 5.
\end{aligned}$$

Remark 3.3.1. *Consider a small perturbation* $k \in \mathsf{C}[0, \mathsf{T}]$ *such that* $k(0) = 0$ *along with the following property :* $|k(t)| \leq \overline{\epsilon}$*, for* $t \in [0, \mathsf{T}]$ *and* $\overline{\epsilon} > 0$*,*

Lemma 3.3.1. *[82] The solution $\overline{\mathbb{B}}_k(t)$ of the perturbed system*

$$ {}_0^{CF}D_t^r\overline{\mathbb{B}}(t) = \Theta\left(t, \overline{\mathbb{B}}(t)\right) + k(t), \quad \overline{\mathbb{B}}(0) = \overline{\mathbb{B}}_0, \tag{3.27} $$

saisfies the relation: $\left\|\overline{\mathbb{B}}_k(t) - \overline{\mathbb{B}}(t)\right\| \leq \Phi\overline{\epsilon}$,
where, $\Phi = \Omega(r) + \omega(r)T$, $k(t) = (k_1(t), k_2(t), k_3(t), k_4(t), k_5(t))^T$.

Proof. Applying fractional integral (3.18) on (3.27), we get

$$ \overline{\mathbb{B}}_k(t) = \overline{\mathbb{B}}_0 + \Omega(r)\Theta\left(t, \overline{\mathbb{B}}(t)\right) + \omega(r)\int_0^t \Theta\left(\delta, \overline{\mathbb{B}}(\delta)\right) d\delta + \Omega(r)k(t) + \omega(r)\int_0^t k(\delta)d\delta, \tag{3.28} $$

Also,

$$ \overline{\mathbb{B}}(t) = \overline{\mathbb{B}}_0 + \Omega(r)\Theta\left(t, \overline{\mathbb{B}}(t)\right) + \omega(r)\int_0^t \Theta\left(\delta, \overline{\mathbb{B}}(\delta)\right) d\delta. \tag{3.29} $$

Using Remark 3.3.1,

$$ \left\|\overline{\mathbb{B}}_k(t) - \overline{\mathbb{B}}(t)\right\| \leq \Omega(r)\left|k(t)\right| + \omega(r)\int_0^t \left|k(\delta)\right| d\delta \leq \left(\Omega(r) + \omega(r)T\right)\overline{\epsilon} = \Phi\overline{\epsilon}. $$

This complete the proof. □

Theorem 3.3.1. *[82] The proposed fractional system* (3.20) *is U-H stable if* $\left\|\overline{\mathbb{B}}(t) - \mathbb{B}(t)\right\| \leq \overline{\mu}\ \overline{\epsilon}$.

Proof. Let $\overline{\mathbb{B}}$ be the solution of (3.26) and due to uniqueness $\mathbb{B}$ be a unique solution of the system (3.24), then

$$ \begin{aligned} \left\|\overline{\mathbb{B}}(t) - \mathbb{B}(t)\right\| &\leq \left\|\overline{\mathbb{B}}_h(t) - \overline{\mathbb{B}}(t)\right\| + \left\|\overline{\mathbb{B}}_h(t) - \mathbb{B}(t)\right\|, \\ &\leq \Phi\overline{\epsilon} + \Omega(r)\left\|\Theta(t, \overline{\mathbb{B}}(t)) - \Theta(t, \mathbb{B}(t))\right\| \\ &\quad + \omega(r)\int_0^t \left\|\Theta(\delta, \overline{\mathbb{B}}(\delta)) - \Theta(\delta, \mathbb{B}(\delta))\right\| d\delta + \Phi\overline{\epsilon}, \\ &\leq 2\Phi\overline{\epsilon} + \Phi\overline{\delta}\left\|\overline{\mathbb{B}}(t)) - \mathbb{B}(t))\right\|. \end{aligned} $$

which implies that
$\left\|\overline{\mathbb{B}}(t) - \mathbb{B}(t)\right\| \leq \dfrac{2\Phi\overline{\epsilon}}{1-\Phi\overline{\delta}} = \overline{\mu}\ \overline{\epsilon}$, where $\overline{\mu} = \dfrac{2\Phi}{1-\Phi\overline{\delta}}$.

Hence, considered fractional system (3.20) is U-H stable. □

3.3.6 Numerical algorithm

The present part of the section provides an approximate solution for the fractional order model (3.20) using two-step fractional Adams-Bashforth technique [15]. We discretized model (3.20) as follows:

$$\begin{aligned}
\mathbb{S}_{12_{\iota+1}} &= \mathbb{S}_{12_\iota} + M_1(r)N_1(t_\iota, \mathbb{S}_{12_\iota}, \mathbb{S}_{3_\iota}, \mathbb{S}_{4_\iota}, \mathbb{S}_{R_\iota}, \mathbb{S}_{E_\iota}) \\
&\quad - M_2(r)N_1(t_{\iota-1}, \mathbb{S}_{12_{\iota-1}}, \mathbb{S}_{3_{\iota-1}}, \mathbb{S}_{4_{\iota-1}}, \mathbb{S}_{R_{\iota-1}}, \mathbb{S}_{E_{\iota-1}}), \\
\mathbb{S}_{3_{\iota+1}} &= \mathbb{S}_{3_\iota} + M_1(r)N_2(t_\iota, \mathbb{S}_{12_\iota}, \mathbb{S}_{3_\iota}, \mathbb{S}_{4_\iota}, \mathbb{S}_{R_\iota}, \mathbb{S}_{E_\iota}) \\
&\quad - M_2(r)N_2(t_{\iota-1}, \mathbb{S}_{12_{\iota-1}}, \mathbb{S}_{3_{\iota-1}}, \mathbb{S}_{4_{\iota-1}}, \mathbb{S}_{R_{\iota-1}}, \mathbb{S}_{E_{\iota-1}}), \\
\mathbb{S}_{4_{\iota+1}} &= \mathbb{S}_{4_\iota} + M_1(r)N_3(t_\iota, \mathbb{S}_{12_\iota}, \mathbb{S}_{3_\iota}, \mathbb{S}_{4_\iota}, \mathbb{S}_{R_\iota}, \mathbb{S}_{E_\iota}) \\
&\quad - M_2(r)N_3(t_{\iota-1}, \mathbb{S}_{12_{\iota-1}}, \mathbb{S}_{3_{\iota-1}}, \mathbb{S}_{4_{\iota-1}}, \mathbb{S}_{R_{\iota-1}}, \mathbb{S}_{E_{\iota-1}}), \\
\mathbb{S}_{R_{\iota+1}} &= \mathbb{S}_{R_\iota} + M_1(r)N_4(t_\iota, \mathbb{S}_{12_\iota}, \mathbb{S}_{3_\iota}, \mathbb{S}_{4_\iota}, \mathbb{S}_{R_\iota}, \mathbb{S}_{E_\iota}) \\
&\quad - M_2(r)N_4(t_{\iota-1}, \mathbb{S}_{12_{\iota-1}}, \mathbb{S}_{3_{\iota-1}}, \mathbb{S}_{4_{\iota-1}}, \mathbb{S}_{R_{\iota-1}}, \mathbb{S}_{E_{\iota-1}}), \\
\mathbb{S}_{E_{\iota+1}} &= \mathbb{S}_{E_\iota} + M_1(r)N_5(t_\iota, \mathbb{S}_{12_\iota}, \mathbb{S}_{3_\iota}, \mathbb{S}_{4_\iota}, \mathbb{S}_{R_\iota}, \mathbb{S}_{E_\iota}) \\
&\quad - M_2(r)N_5(t_{\iota-1}, \mathbb{S}_{12_{\iota-1}}, \mathbb{S}_{3_{\iota-1}}, \mathbb{S}_{4_{\iota-1}}, \mathbb{S}_{R_{\iota-1}}, \mathbb{S}_{E_{\iota-1}}),
\end{aligned} \tag{3.30}$$

where,

$$M_1(r) = \left(\frac{1-r}{P(r)} + \frac{3rh}{2P(r)}\right),$$

and,

$$M_2(r) = \left(\frac{1-r}{P(r)} + \frac{rh}{2P(r)}\right).$$

3.3.7 Numerical simulation and Discussion

The dynamical behaviour of the proposed fractional system (3.20) is investigated numerically using (3.30) for approximate solution of the state variables $\mathbb{S}_{12}(t), \mathbb{S}_3(t), \mathbb{S}_4(t), \mathbb{S}_R(t)$ and $\mathbb{S}_E(t)$ in (3.20). We take the initial values as $\mathbb{S}_{12}(0) = 30000, \mathbb{S}_3(0) = 12300, \mathbb{S}_4(0) = 783, \mathbb{S}_R(0) = 334, \mathbb{S}_E(0) = 10$ and parameters values: $\Delta = 14000, \Gamma = 80, \Omega = 90, \mu = 0.01, \nu = 0.034, \psi = 0.03, \phi = 0.3, \omega = 0.1, \zeta = 0.2, \chi = \delta = \eta = 0.0256$ [10], $\rho = 0.149(fitted), \kappa = 0.09(fitted), \sigma = 0.47(fitted)$ and $\tau = 0.01(fitted)$ as fitted with real data. In figure 3.7, we used real data [5] from KSA from 2004 to 2016 to fit the classical model (3.19) and the suggested fractional order model (3.20). This demonstrates that the fractional model better matches the actual data and may be used to forecast future instances than the classical model.

Figure 3.8 shows a long-term estimate of the cases based on a fractional model. Here, we can see from figure 3.8 that the data fits the model curve well, and we can also see that the number of long-term behavior cases grow in an exponential way over time. This case could be scary because the number of cases could go up even more in the next few years if the health department does not use the right treatment methods to get rid of Breast cancer.

Figures 3.9–3.13 show how the model compartments change alter over time ($t = 50$ years) as the fractional-order r varies for each compartment. We discovered that the memory index r has a significant impact on the Breast cancer model's solution route, and that controlling r gives us a lot of control over the way Breast cancer behaves in all subgroups.

Figures 3.14-3.17 show the solution of the proposed CF model while adjusting the input parameter κ. We found that raising this quantity makes fewer people get cancer in stage 3, stage 4, and disease free states, implying that the cancer mortality rate would be reduced. However, increasing κ increases the number of people who are cardiotoxic, increasing the risk of cardiac mortality.

The diagram shown in figure 3.18-3.20 illustrates the effects of rigorous chemotherapy on patients diagnosed with stage 4. This treatment approach has been found to potentially contribute to higher rates of morbidity and death within the population, particularly among

those who experience cardiotoxicity. By intensifying the administration of chemotherapy to individuals in phase 4, populations with disease-free status, and those experiencing cardiotoxicity, it becomes evident that stage 4 and disease-free individuals exhibit significant improvements in disease reduction. However, the same level of improvement is not observed in individuals with cardiotoxicity. The adverse effects of chemotherapy have been shown to significantly increase the risk of developing cardiovascular complications in individuals.

The simulations provide a visual representation of the parameters' functions, facilitating comprehension of strategies to reduce cancer and cardiac mortality rates in cancer patient healthcare facilities. Figure 3.21-3.24 depicts the simulation of the model compartment in the disease-free condition with intense treatment. The findings show a little rise in the cardiotoxicity population, whereas there are minor reductions in the population of phases 3, 4, and disease-free state. Figure 3.21 shows that there is minimal improvement in the decline of instances in phase 3 sufferers. Figure 3.22 shows a significant decrease in cases among phase 4 patients. Figure 3.23 shows a significant drop in the number of patients in the disease-free state but, figure 3.24 shows a modest rise in the number of instances of cardiotoxicity.

The CF operator demonstrates a 66.64% improvement in the accuracy of estimating actual data compared to the classical order model as determined by

$$\frac{\text{classcial model norm - fractional model norm}}{\text{classical model norm}}$$

$$= \frac{11045.11902 - 3685}{11045.11902}$$

$$= 0.6664$$

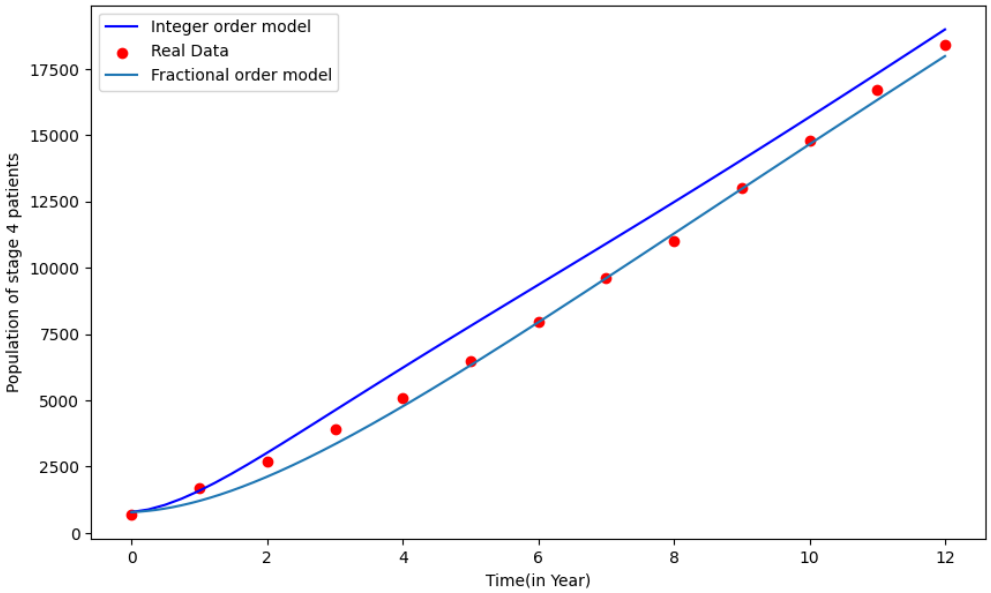

Figure 3.7: Fitting real data of Breast cancer with integer and fractional order($r = 1$) models.

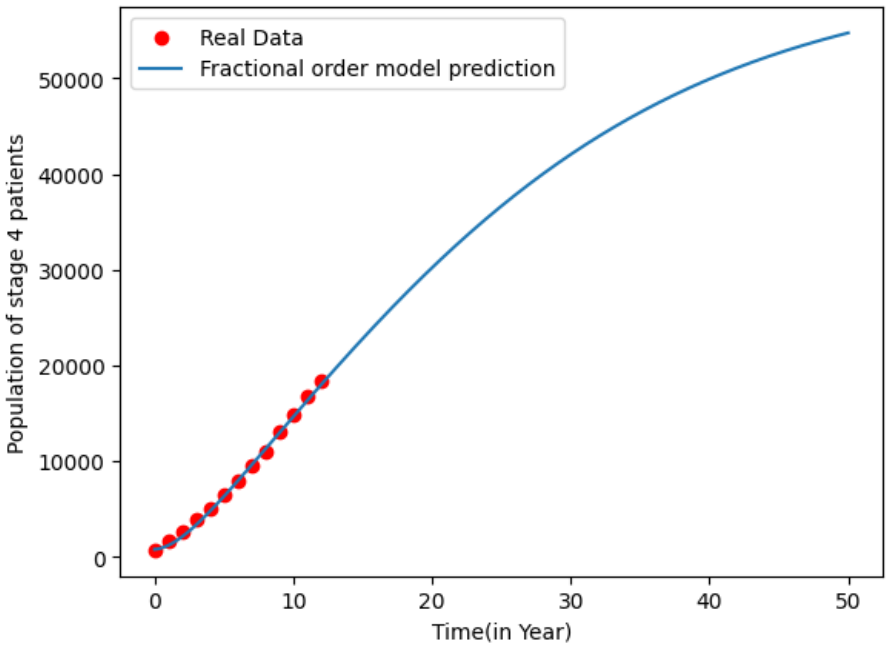

Figure 3.8: Fractional order ($r = 1$) model prediction with real data.

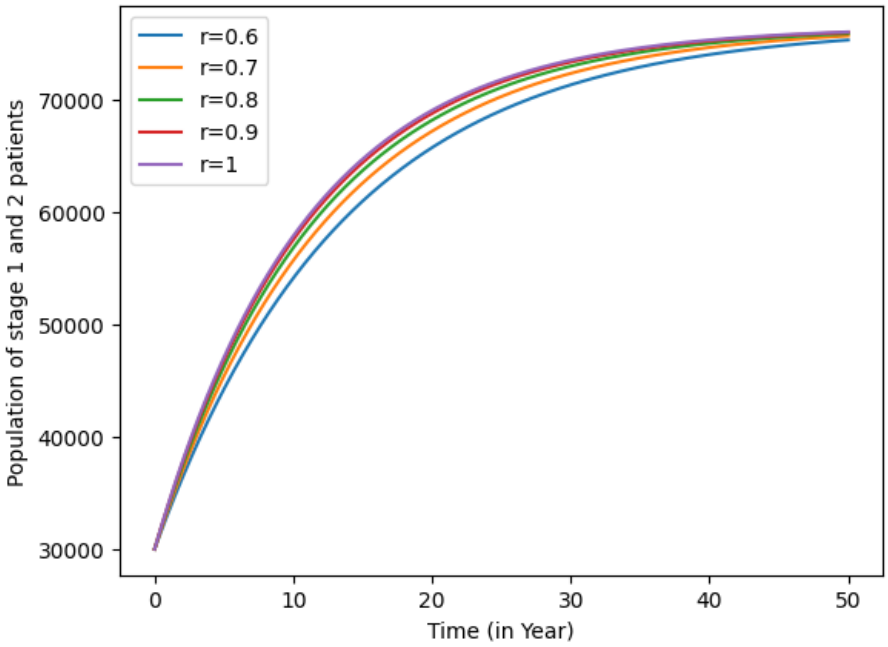

Figure 3.9: Simulation of stage 1 and 2 patients with variation of fractional order.

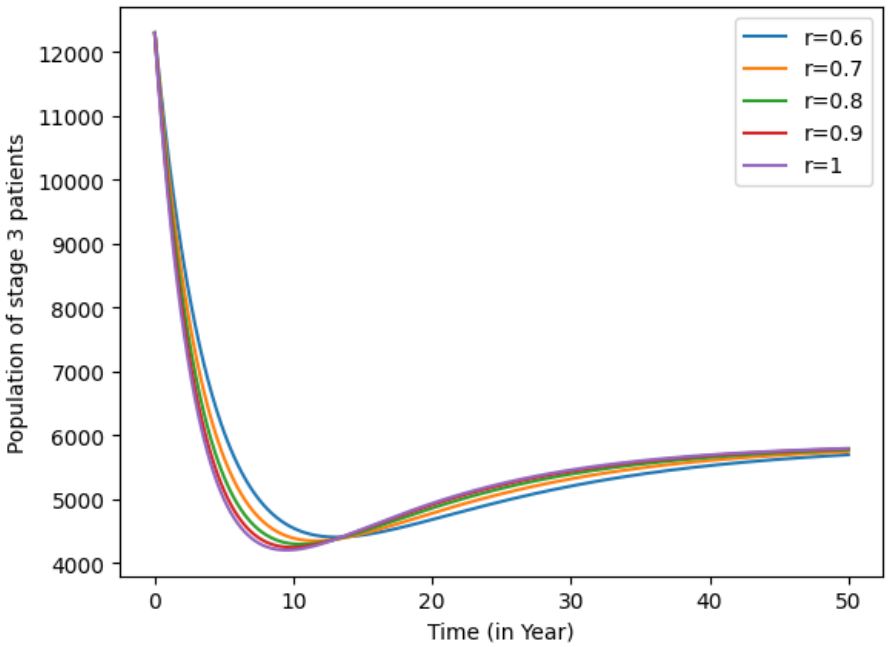

Figure 3.10: Simulation of stage 3 patients with variation of fractional order.

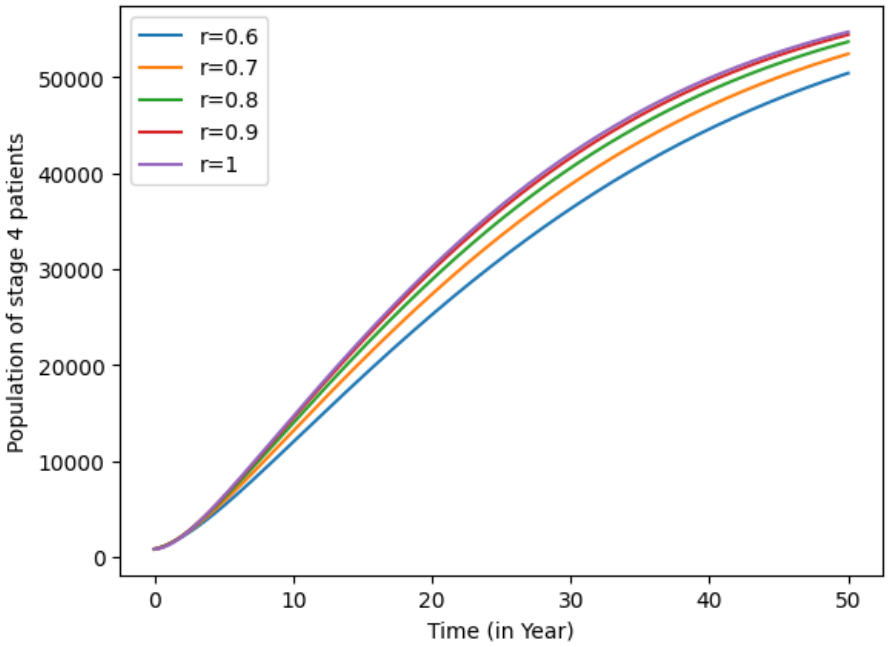

Figure 3.11: Simulation of stage 4 patients with variation of fractional order.

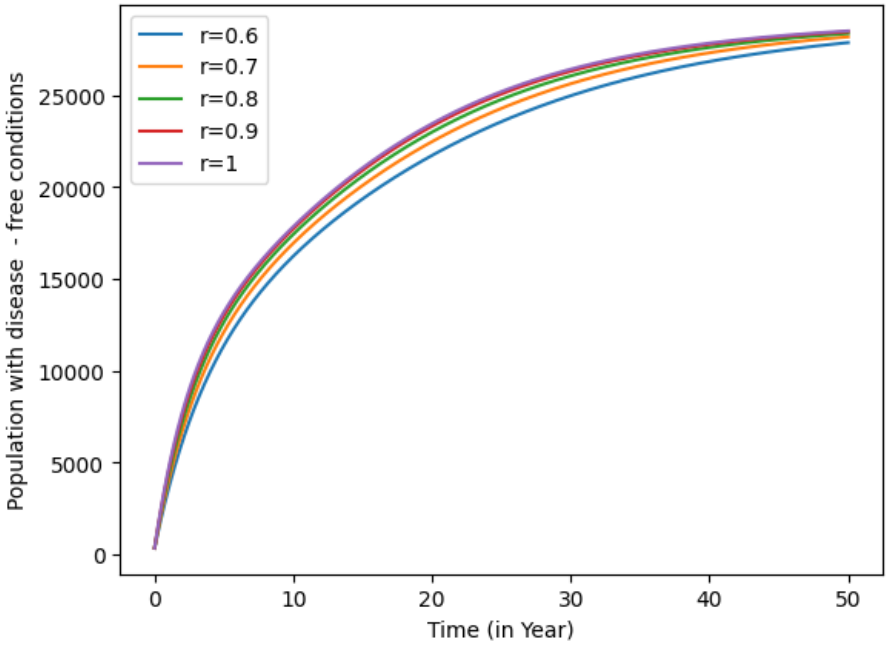

Figure 3.12: Simulation of patients at disease free state with variation of fractional order.

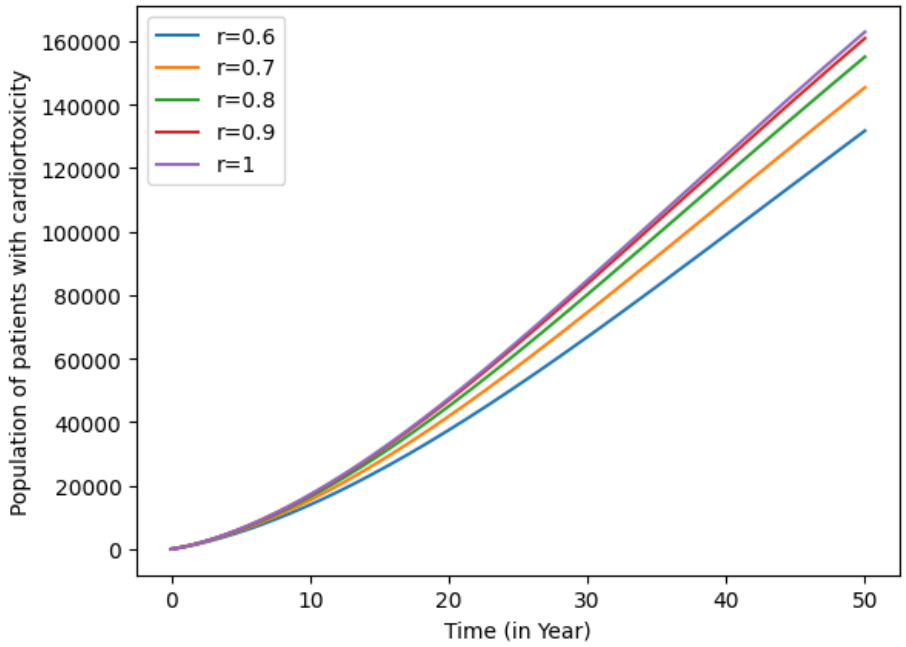

Figure 3.13: Simulation of cardiortoxicity patients with variation of fractional order.

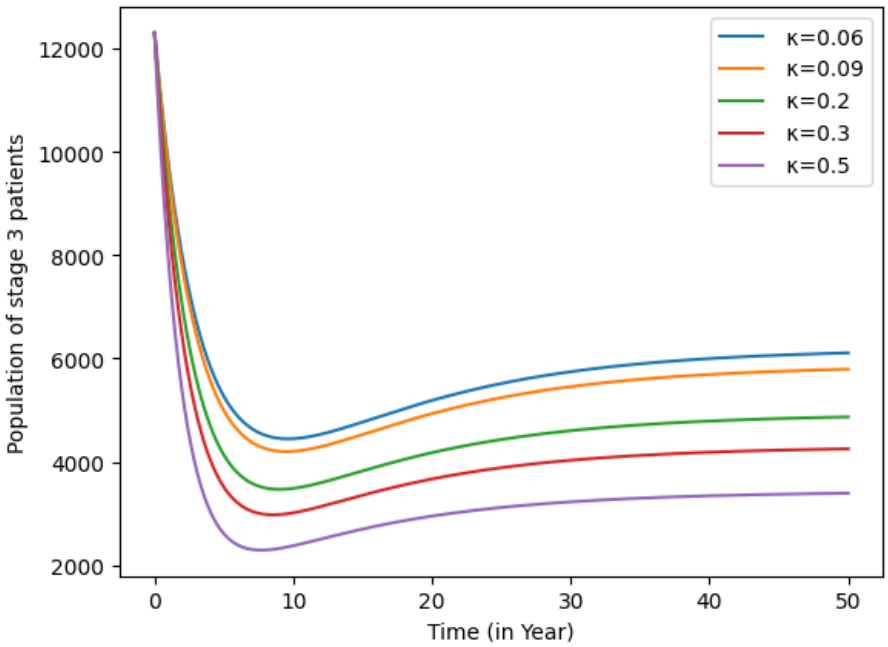

Figure 3.14: Effect of κ on stage 3 patients.

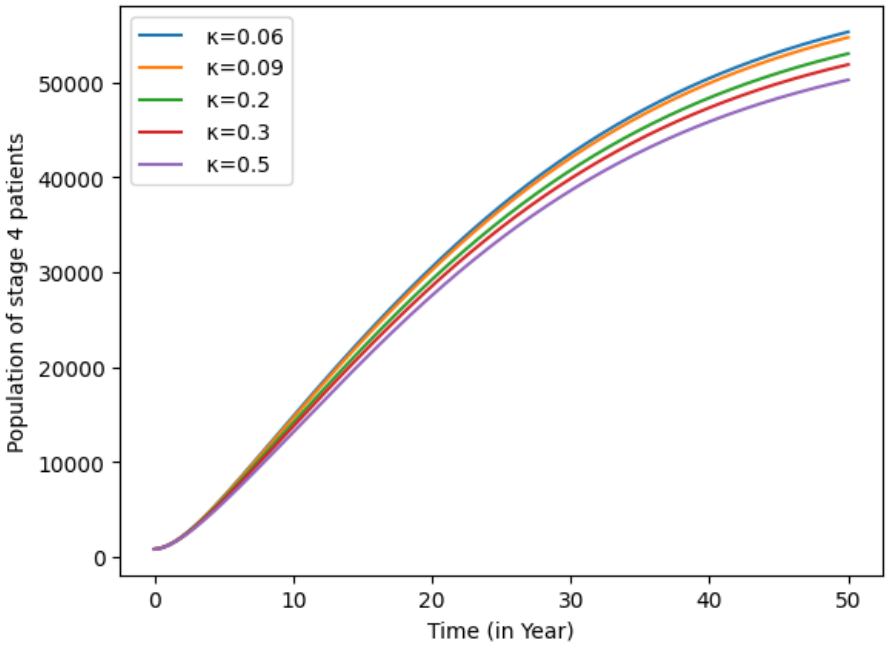

Figure 3.15: Effect of κ on stage 4 patients.

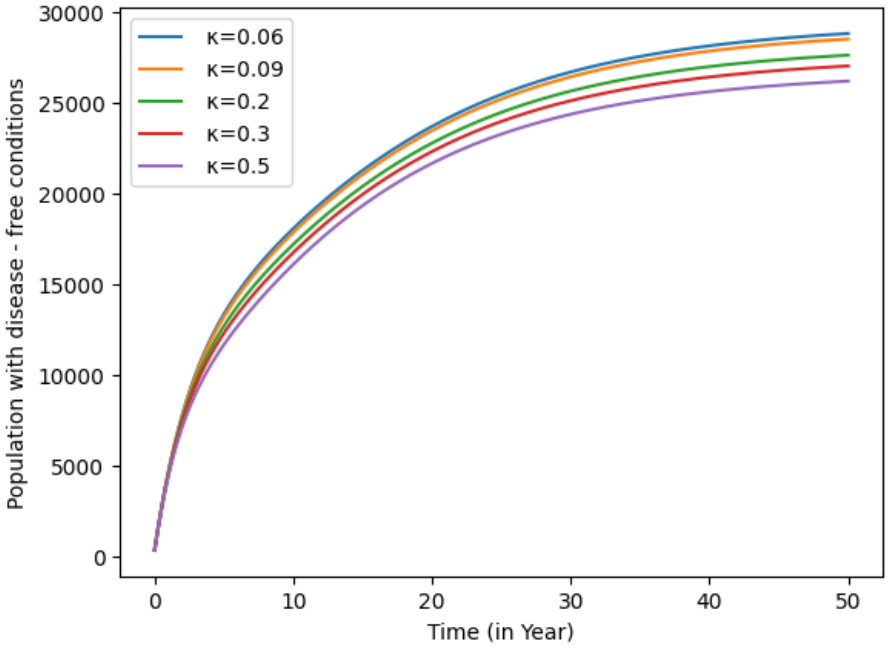

Figure 3.16: Effect of κ on patients at disease free state.

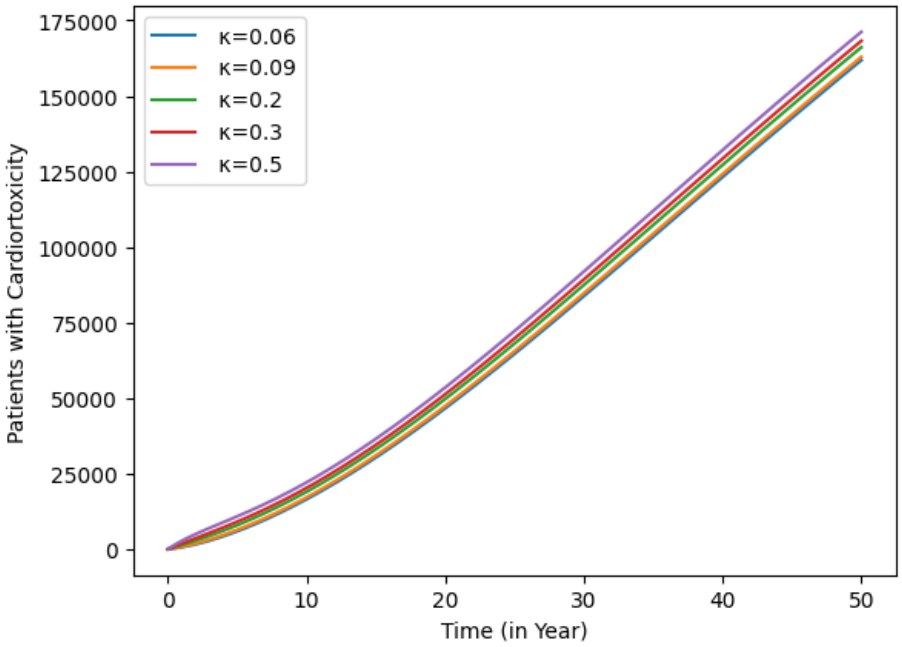

Figure 3.17: Effect of κ on cardiortoxicity patients.

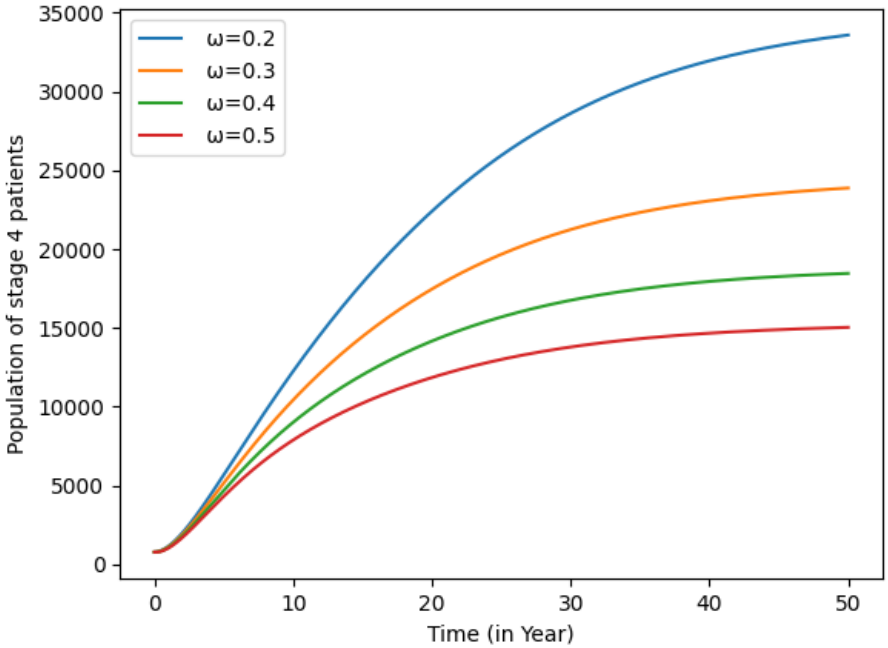

Figure 3.18: Effect of ω on stage 4 patients.

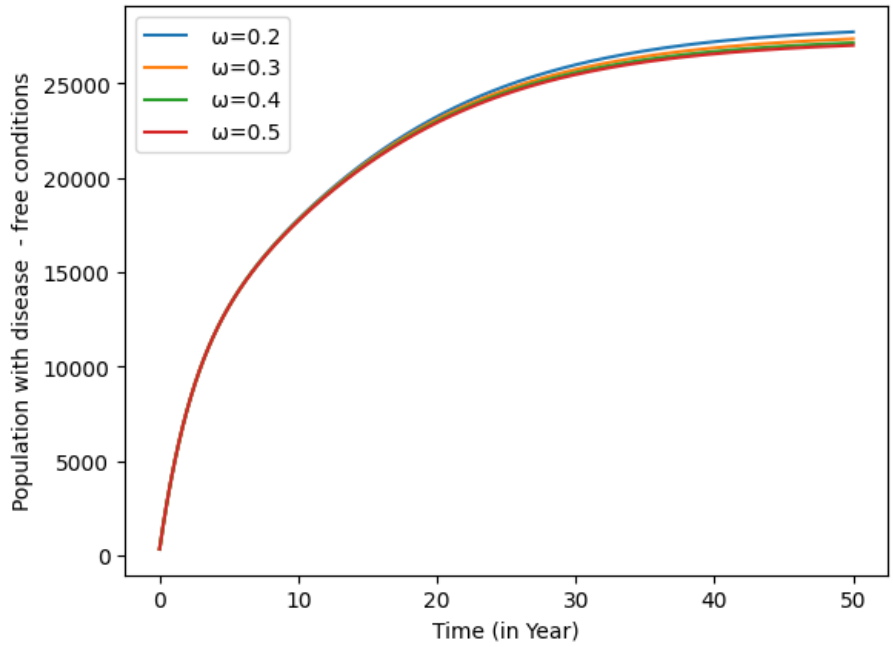

Figure 3.19: Effect of ω on patients at disease free state.

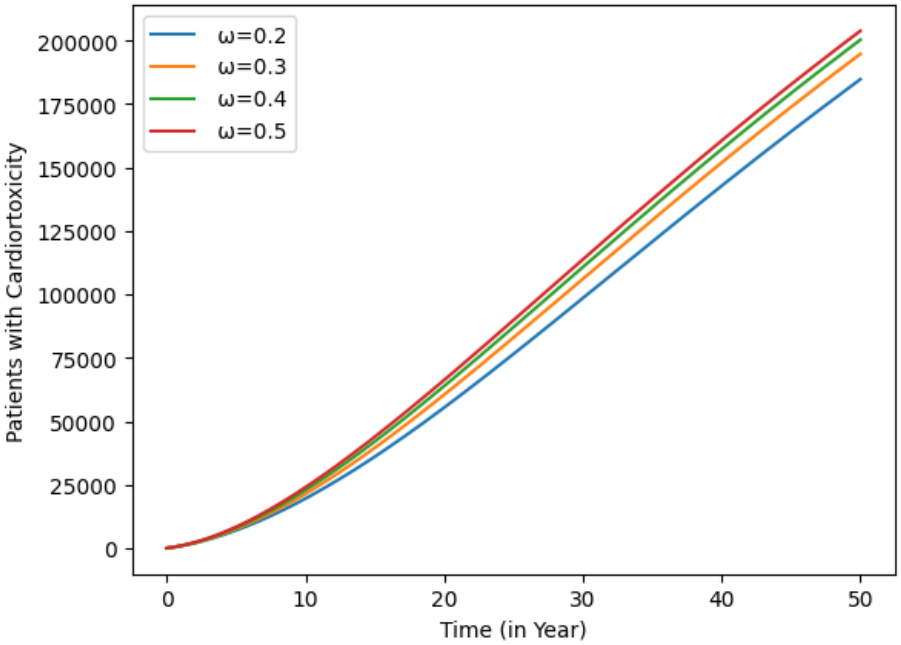

Figure 3.20: Effect of ω on cardiortoxicity patients.

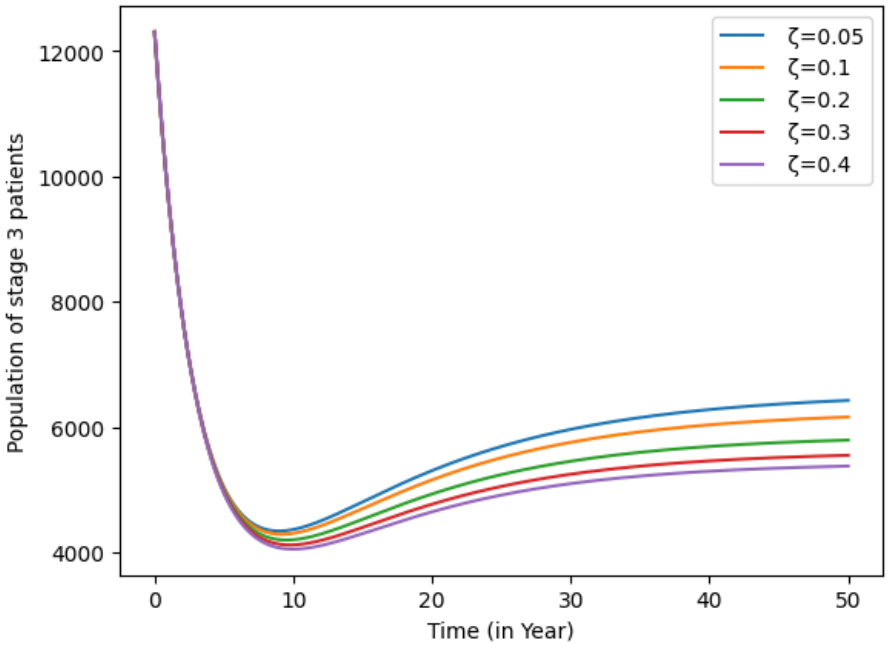

Figure 3.21: Effect of ζ on stage 3 patients.

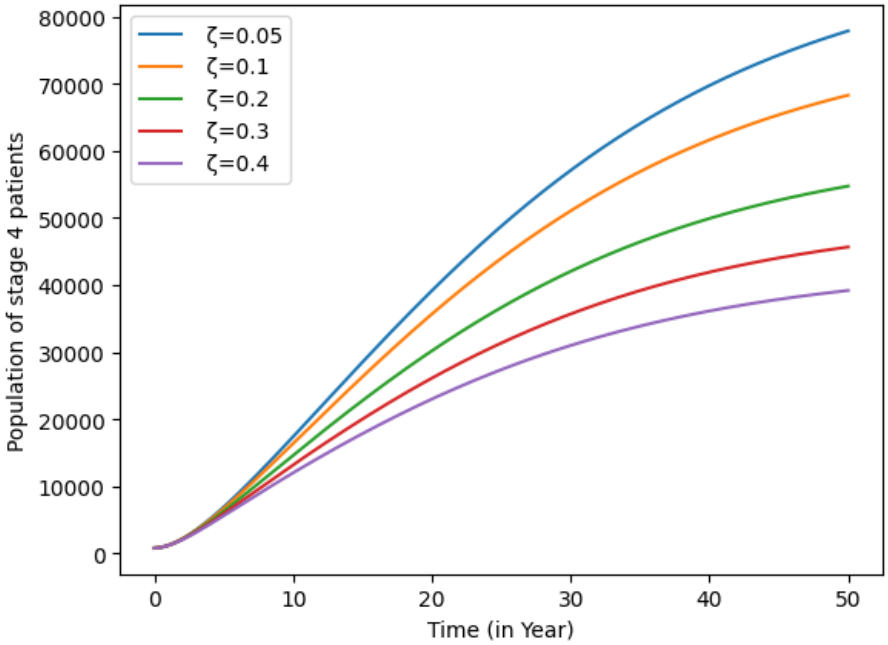

Figure 3.22: Effect of ζ on stage 4 patients.

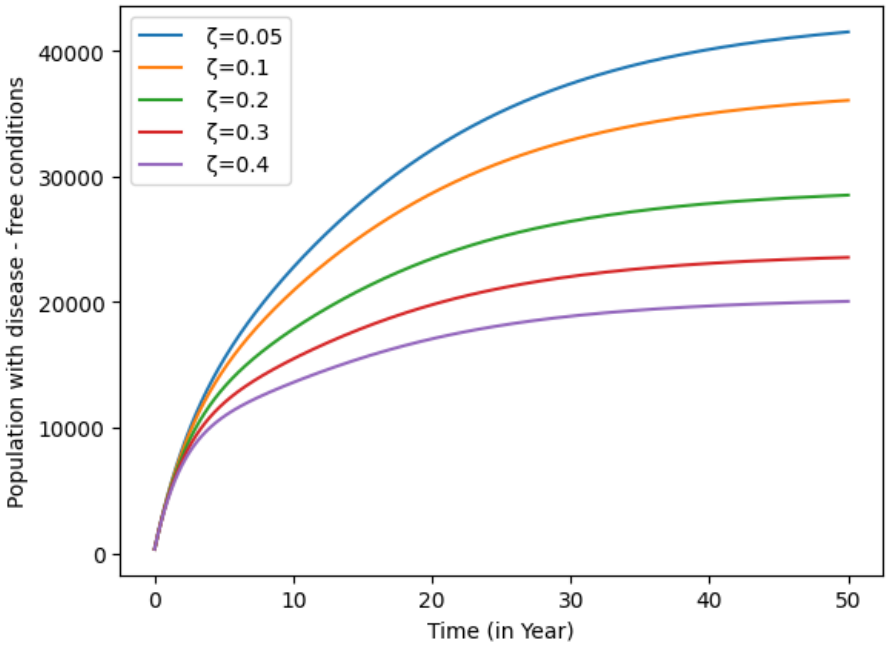

Figure 3.23: Effect of ζ on disease free state patients.

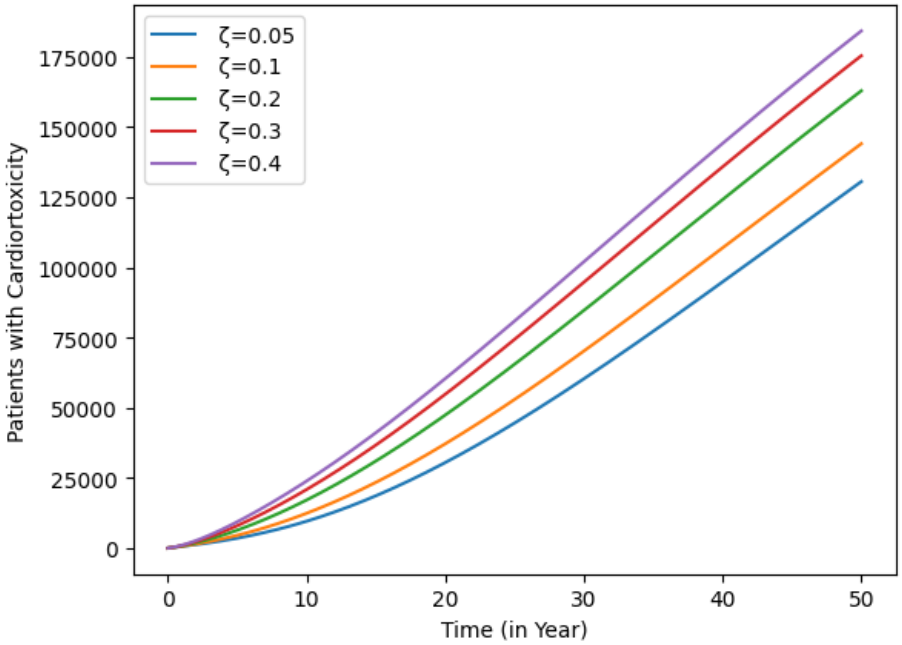

Figure 3.24: Effect of ζ on cardiortoxicity patients.

3.3.8 Conclusion

We developed a mathematical model in a fractional framework for Breast cancer in this research to study the impact of treatment at various phases,incorporating the Caputo-Fabrizio derivative and various chemotherapy rates. The Picard-Lindelof technique is established for the system's existence and uniqueness. We have constructed some results for Ulam-Hyers stability and have shown that our proposed model is UH stable. The numerical simulations supported our approach using the two-step Adams-Bashforth algorithm. Through graphical representations, we illustrated the impact of fractional order and effect of chemotherapy rates on Breast cancer dynamics. Using real incidence data, The CF operator demonstrates a 66.64% improvement in the accuracy of estimating actual data compared to the classical order model. Notably, we identified effective parameters (κ, ω, and ζ) associated with reduced occurrences of stages 3 and 4 as well as disease-free states in Breast cancer modelling. Our results emphasized the increased risk of cardiotoxicity linked with chemotherapy indicating that pre-treatment may be beneficial in mitigating such risks. Our research seeks to reduce cardiotoxicity prevalence among chemotherapy patients and improve their recovery rates, with implications for public health decision-making. Furthermore, by elucidating Breast cancer mechanisms through the Caputo-Fabrizio operator, our study paves the way for targeted therapies to minimize cardiotoxicity, thereby improving patient outcomes and guiding future Breast cancer treatment strategies. In future work, we want to leverage our actual data-oriented estimated parameter values to anticipate Breast cancer patients utilizing various models and fractional derivative operators. Using the provided data, certain optimal controls may also be added in the same model.

3.4 Fractional mathematical modelling of Breast cancer stages with true data from Saudi Arabia

3.4.1 Introduction

In this part, we develop and analyze fractional mathematical models to investigate the transmission dynamics of Breast cancer. The current study investigation is driven by the presence of authentic statistical data, which serves as a means to verify the suggested fractional-order models using the Caputo, Caputo-Fabrizio-Caputo(CFC), and Atangana-Baleanu-Caputo (ABC) operators. In contrast to previous investigations on fractional modelling in the field of epidemiology, the present study incorporates all temporal characteristics.The fractional models being examined in the current research project exhibit balance. The current work has shown that the error norm calculated for all models examined indicates that the model including the ABC approach has the lowest error norm when compared to other models.

The structure of the section 3.4 is as follows: Section 3.4.2 presents some basic definitions of fractional calculus. In section 3.4.3, the model is formulated using both integer and fractional-order operators. Section 3.4.4 involves the equilibria of the system. In section 3.4.5, we offer a comprehensive discussion on the existence and uniqueness of the solution to the ABC model which is based on the fixed-point theory. In section 3.4.8, the discussion focuses on the numerical findings as well as a comparison of the models. The last portion 3.4.9 is dedicated to closing comments, which are delivered there.

3.4.2 Preliminaries

Definition 3.4.1. *[106].The derivative of $N(t)$ under the Caputo operator of order r is defined by*

$$ {}_0^C D_{\mathsf{t}}^r N(\mathsf{t}) = \frac{1}{\Gamma(q-r)} \int_0^{\mathsf{t}} (\mathsf{t}-\delta)^{q-r-1} N^r(\delta) d\delta, \qquad \mathsf{t} > 0, \tag{3.31} $$

where, $q-1 < r \leq q, \qquad q \in \mathbb{N}$.

Definition 3.4.2. *[106] For $N : \mathbb{R}^+ \to \mathbb{R}$ and $r \in (0,1)$, the Riemann-Liouville fractional integration is defined as*

$$ {}^{RL}_{0}I^{r}_{\mathsf{t}}N(\mathsf{t}) = \frac{1}{\Gamma(r)}\int_0^{\mathsf{t}}(\mathsf{t}-\delta)^{r-1}N(\delta)d\delta, \qquad \mathsf{t} > 0. \tag{3.32} $$

Definition 3.4.3. *Let $N \in \mathbb{H}^1(\iota_1, \iota_2)$ and $0 < r < 1$, then the CF fractional derivative [25] defined as follows:*

$$ {}^{\mathsf{CFC}}_{0}D^{r}_{\mathsf{t}}N(\mathsf{t}) = \frac{P(r)}{1-r}\int_0^{\mathsf{t}}N^{'}(\delta)\exp\left[-\frac{r(\mathsf{t}-\delta)}{1-r}\right]d\delta \tag{3.33} $$

Where, $P(r)$ is the normalization function such that with $P(0) = P(1) = 1$.

Definition 3.4.4. *For $0 < r < 1$, the CF fractional integral of order r of the function $N(\mathsf{t})$ is[87]:*

$$ {}^{CF}_{0}I^{r}_{\mathsf{t}}N(\mathsf{t}) = \frac{2(1-r)}{(2-r)P(r)}N(\mathsf{t}) + \frac{2r}{(2-r)P(r)}\int_0^{\mathsf{t}}N(\delta)d\delta. \tag{3.34} $$

Definition 3.4.5. *[14] Let $N \in \mathbb{H}^1(\iota_1, \iota_2), \iota_1 > \iota_2$, then the ABC fractional derivative is given as*

$$ {}^{\mathsf{ABC}}_{0}D^{r}_{\mathsf{t}}N(\mathsf{t}) = \frac{Q(r)}{1-r}\int_a^{\mathsf{t}}E_r\left[-\frac{r(\mathsf{t}-\delta)^r}{1-r}\right]N^{'}(\delta)d\delta, \tag{3.35} $$

where, $Q(r)$ has the same properties as $P(r)$.

Definition 3.4.6. *[14] The AB fractional integral of order r is defined as:*

$$ {}^{\mathsf{AB}}_{0}I^{r}_{\mathsf{t}}N(\mathsf{t}) = \frac{1-r}{Q(r)}N(\mathsf{t}) + \frac{r}{Q(r)\Gamma(r)}\int_0^{\mathsf{t}}N(\delta)(\mathsf{t}-\delta)^{r-1}d\delta. \tag{3.36} $$

3.4.3 Model formulation in fractional frameworks

Authors in [44] classified the Breast cancer model into five epidemiological categories. During the initial medical report, the overall population of Breast cancer patients was divided into phases 1 and 2 ($\mathbb{S}_{12}$), phase 3 ($\mathbb{S}_3$), phase 4($\mathbb{S}_4$), disease-free state ($\mathbb{S}_R$), and cardiotoxic ($\mathbb{S}_E$)

sub populations. The traditional system is described as

$$\begin{aligned}
\frac{d\mathbb{S}_{12}}{dt} &= \Delta - (\rho + \nu)\mathbb{S}_{12}, \\
\frac{d\mathbb{S}_3}{dt} &= \Gamma + \nu\mathbb{S}_{12} + \psi\mathbb{S}_R - (\sigma + \mu + \kappa + \chi)\mathbb{S}_3, \\
\frac{d\mathbb{S}_4}{dt} &= \Omega + \mu\mathbb{S}_3 + \phi\mathbb{S}_R - (\tau + \omega + \delta)\mathbb{S}_4, \\
\frac{d\mathbb{S}_R}{dt} &= \rho\mathbb{S}_{12} + \sigma\mathbb{S}_3 + \tau\mathbb{S}_4 - (\psi + \phi + \zeta)\mathbb{S}_R, \\
\frac{d\mathbb{S}_E}{dt} &= \zeta\mathbb{S}_R + \omega\mathbb{S}_4 + \kappa\mathbb{S}_3 - \eta\mathbb{S}_E,
\end{aligned} \tag{3.37}$$

where, the system's (3.37) parameters are detailed as follows: Δ : Individuals diagnosed with cancer in stages I and II, Γ : People who have stage III cancer, Ω : Patients in the fourth stage of cancer, ρ : Recovery after chemotherapy in stages I and II, σ : Stage III chemotherapy recovery, ϕ_3 : Stage IV chemotherapy recovery, μ : People in poor health are admitted to the stage IV population, ν : People in poor health enroll in $\mathbb{S}_3$ class, κ : Patients receiving life-threatening therapy that causes cardiotoxicity, ω : People suffering from cardiotoxicity as a result of stage IV cancer therapy, ζ : Patients in the disease-free stage who have received substantial treatment that causes cardiotoxicity, χ : Stage III cancer-related death, δ : Stage IV cancer-related death, η : The mortality rate of cardiotoxic patients, ψ :Patient fall back to stage III, ϕ : People fall back to stage IV.

Now, to better approximate the spread of Breast cancer with varying treatment rates into various compartments and to quantitatively demonstrate the influence of the above-mentioned parameters, the integer order model must be replaced by a fractional order model. The goal of this research is to extend the traditional system (3.37) by adding a fractional time derivative operator that allows for the analysis of memory effects in an arbitrary-order system.

The proposed Breast cancer transmission model, which includes the Caputo derivative, is offered as

$$
\begin{aligned}
{}^{\mathsf{c}}_{0}D^{r}_{t}\mathbb{S}_{12} &= \Delta^{r} - (\rho^{r} + \nu^{r})\mathbb{S}_{12},\\
{}^{\mathsf{c}}_{0}D^{r}_{t}\mathbb{S}_{3} &= \Gamma^{r} + \nu^{r}\mathbb{S}_{12} + \psi^{r}\mathbb{S}_{R} - (\sigma^{r} + \mu^{r} + \kappa^{r} + \chi^{r})\mathbb{S}_{3},\\
{}^{\mathsf{c}}_{0}D^{r}_{t}\mathbb{S}_{4} &= \Omega^{r} + \mu^{r}\mathbb{S}_{3} + \phi^{r}\mathbb{S}_{R} - (\tau^{r} + \omega^{r} + \delta^{r})\mathbb{S}_{4},\\
{}^{\mathsf{c}}_{0}D^{r}_{t}\mathbb{S}_{R} &= \rho^{r}\mathbb{S}_{12} + \sigma^{r}\mathbb{S}_{3} + \tau^{r}\mathbb{S}_{4} - (\psi^{r} + \phi^{r} + \zeta^{r})\mathbb{S}_{R},\\
{}^{\mathsf{c}}_{0}D^{r}_{t}\mathbb{S}_{E} &= \zeta^{r}\mathbb{S}_{R} + \omega^{r}\mathbb{S}_{4} + \kappa^{r}\mathbb{S}_{3} - \eta^{r}\mathbb{S}_{E}.
\end{aligned}
\tag{3.38}
$$

Similarly, the proposed Breast cancer transmission model, which includes the CF derivative as:

$$
\begin{aligned}
{}^{\mathsf{CFC}}_{0}D^{r}_{t}\mathbb{S}_{12} &= \Delta^{r} - (\rho^{r} + \nu^{r})\mathbb{S}_{12},\\
{}^{\mathsf{CFC}}_{0}D^{r}_{t}\mathbb{S}_{3} &= \Gamma^{r} + \nu^{r}\mathbb{S}_{12} + \psi^{r}\mathbb{S}_{R} - (\sigma^{r} + \mu^{r} + \kappa^{r} + \chi^{r})\mathbb{S}_{3},\\
{}^{\mathsf{CFC}}_{0}D^{r}_{t}\mathbb{S}_{4} &= \Omega^{r} + \mu^{r}\mathbb{S}_{3} + \phi^{r}\mathbb{S}_{R} - (\tau^{r} + \omega^{r} + \delta^{r})\mathbb{S}_{4},\\
{}^{\mathsf{CFC}}_{0}D^{r}_{t}\mathbb{S}_{R} &= \rho^{r}\mathbb{S}_{12} + \sigma^{r}\mathbb{S}_{3} + \tau^{r}\mathbb{S}_{4} - (\psi^{r} + \phi^{r} + \zeta^{r})\mathbb{S}_{R},\\
{}^{\mathsf{CFC}}_{0}D^{r}_{t}\mathbb{S}_{E} &= \zeta^{r}\mathbb{S}_{R} + \omega^{r}\mathbb{S}_{4} + \kappa^{r}\mathbb{S}_{3} - \eta^{r}\mathbb{S}_{E}.
\end{aligned}
\tag{3.39}
$$

Finally, The proposed Breast cancer transmission model, which includes the ABC derivative is as follows:

$$
\begin{aligned}
{}^{\mathsf{ABC}}_{0}D^{r}_{t}\mathbb{S}_{12} &= \Delta^{r} - (\rho^{r} + \nu^{r})\mathbb{S}_{12},\\
{}^{\mathsf{ABC}}_{0}D^{r}_{t}\mathbb{S}_{3} &= \Gamma^{r} + \nu^{r}\mathbb{S}_{12} + \psi^{r}\mathbb{S}_{R} - (\sigma^{r} + \mu^{r} + \kappa^{r} + \chi^{r})\mathbb{S}_{3},\\
{}^{\mathsf{ABC}}_{0}D^{r}_{t}\mathbb{S}_{4} &= \Omega^{r} + \mu^{r}\mathbb{S}_{3} + \phi^{r}\mathbb{S}_{R} - (\tau^{r} + \omega^{r} + \delta^{r})\mathbb{S}_{4},\\
{}^{\mathsf{ABC}}_{0}D^{r}_{t}\mathbb{S}_{R} &= \rho^{r}\mathbb{S}_{12} + \sigma^{r}\mathbb{S}_{3} + \tau^{r}\mathbb{S}_{4} - (\psi^{r} + \phi^{r} + \zeta^{r})\mathbb{S}_{R},\\
{}^{\mathsf{ABC}}_{0}D^{r}_{t}\mathbb{S}_{E} &= \zeta^{r}\mathbb{S}_{R} + \omega^{r}\mathbb{S}_{4} + \kappa^{r}\mathbb{S}_{3} - \eta^{r}\mathbb{S}_{E},
\end{aligned}
\tag{3.40}
$$

with initial conditions: $\mathbb{S}_{12}(0) = \mathbb{S}_{120}, \mathbb{S}_{3}(0) = \mathbb{S}_{30}, \mathbb{S}_{4}(0) = \mathbb{S}_{40}, \mathbb{S}_{R}(0) = \mathbb{S}_{R0}, \mathbb{S}_{E}(0) = \mathbb{S}_{E0}$.

3.4.4 Equilibria

For the equilibrium points of the system (3.40), we put
${}_0^{\mathsf{ABC}}D_t^r\mathbb{S}_{12} = {}_0^{\mathsf{ABC}}D_t^r\mathbb{S}_3 = {}_0^{\mathsf{ABC}}D_t^r\mathbb{S}_4 = {}_0^{\mathsf{ABC}}D_t^r\mathbb{S}_R = {}_0^{\mathsf{ABC}}D_t^r\mathbb{S}_E = 0.$

After solving, we get the equilibrium point given by $S_{equi} = (\mathbb{S}_{12}^*, \mathbb{S}_3^*, \mathbb{S}_4^*, \mathbb{S}_R^*, \mathbb{S}_E^*)$,
where, $\mathbb{S}_{12}^* = \dfrac{\Delta^r}{f_1}, \mathbb{S}_3^* = \dfrac{\Theta_1}{f_1\theta_5}, \mathbb{S}_4^* = \dfrac{\Theta_2}{f_1\theta_5}, \mathbb{S}_R^* = \dfrac{\Theta_3}{f_1\theta_5}, \mathbb{S}_E^* = \dfrac{\Theta_4}{f_1\theta_5 f_5}$
where,

$$\begin{aligned}\Theta_1 = {} & \left\{f_3\psi^r + (\xi^r + \phi^r)(\delta^r + \omega^r) + \xi^r\tau^r\right\}\Gamma^r\nu^r + (f_3\Delta^r + \tau^r\Omega^r)\psi^r \\ & + \nu^r\Delta^r\left\{(\xi^r + \phi^r)(\delta^r + \omega^r) + \xi^r\tau^r\right\},\end{aligned}$$

$$\begin{aligned}\Theta_2 = {} & \left\{f_2\phi^r + (\psi^r + \xi^r)\mu^r + (\chi^r + \sigma^r + \kappa^r)\xi^r + \psi^r(\chi^r + \kappa^r)\right\} f_1\Omega^r \\ & + \left[\left\{(\Delta^r + \Gamma^r)\mu^r + (\chi^r + \sigma^r + \kappa^r)\Delta^r + \sigma^r\Gamma^r\right\}\phi^r\right. \\ & \left.+(\Gamma^r\xi^r + \psi^r(\Delta^r + \Gamma^r)\mu^r)\right]\rho^r + \left\{(\mu^r + \sigma^r)\phi^r + (\psi^r + \xi^r)\mu^r\right\}(\Delta^r + \Gamma^r)\nu^r,\end{aligned}$$

$$\begin{aligned}\Theta_3 = {} & \left\{f_2\Delta^r + (\Gamma^r + \Omega^r)\sigma^r + \mu^r\Gamma^r + \Omega^r(\chi^r + \mu^r + \kappa^r)\tau^r\right. \\ & \left.+(f_2\Delta^r + \sigma^r\Gamma^r)(\delta^r + \omega^r)\right\}\rho^r + \nu^r\left\{(\mu^r + \sigma^r)\Delta^r + (\Gamma^r + \Omega^r)\sigma^r\right. \\ & \left.+\mu^r\sigma^r + \Omega^r\tau^r(\chi^r + \mu^r + \kappa^r) + \sigma^r(\Delta^r + \Gamma^r)(\delta^r + \omega^r)\right\},\end{aligned}$$

$$\begin{aligned}\Theta_4 = {} & \left\{(\Delta^r + \Gamma^r + \Omega^r)\kappa^r + (\chi^r + \mu^r + \sigma^r)\Delta^r + (\mu^r + \sigma^r)\Gamma^r\right. \\ & \left.+(\chi^r + \mu^r + \kappa^r)\Omega^r\right\}\xi^r\rho^r\omega^r + (\psi^r + \phi^r)(\Delta^r + \Gamma^r + \Omega^r)\kappa^r \\ & + \left\{(\psi^r + \phi^r)\mu^r + (\chi^r + \sigma^r)\right\}\Delta^r + \left\{(\psi^r + \phi^r)\mu^r + \sigma^r\phi^r\right\}\Gamma^r \\ & + \left\{((\psi^r + \phi^r)\mu^r + \chi^r\psi^r + (\chi^r + \sigma^r)\phi^r)\right\}\Omega^r\rho^r\omega^r \\ & + \left\{(\Delta^r + \Gamma^r + \Omega^r)\kappa^r + (\mu^r + \sigma^r)(\Delta^r + \Gamma^r) + \Omega^r(\chi^r + \mu^r + \sigma^r)\right\}\xi^r\gamma^r\omega^r \\ & + \left\{(\psi^r + \phi^r)(\Delta^r + \Gamma^r + \Omega^r)\kappa^r + ((\psi^r + \phi^r)\mu^r + \sigma^r\phi^r)\,\Delta^r\right\}\gamma^r\omega^r\end{aligned}$$

$$
\begin{aligned}
&+\left\{((\psi^r+\phi^r)\mu^r+\sigma^r\phi^r)\Gamma^r+((\psi^r+\phi^r)\mu^r+\chi^r\psi^r+\phi^r(\chi^r+\sigma^r))\Omega^r\right\}\gamma^r\omega^r\\
&+\left\{((\delta^r+\tau^r)\Delta^r+(\delta^r+\tau^r)\Gamma^r+\Omega^r\tau^r)\kappa^r+(\delta^r+\tau^r)(\chi^r+\mu^r+\sigma^r)\right\}\Delta^r\xi^r\rho^r\\
&+\left\{((\mu^r+\sigma^r)\tau^r+\delta^r\sigma^r)\Gamma^r+\Omega^r\tau^r(\chi^r+\mu^r+\sigma^r)\right\}\xi^r\rho^r\\
&+\kappa^r\rho^r\left\{(\delta^r+\tau^r)\psi^r\Delta^r+(\psi^r\tau^r+\delta^r(\psi^r+\phi^r))\Gamma^r+\Omega^r\tau^r\phi^r\right\}\\
&+\nu^r\xi^r\left\{((\delta^r+\tau^r)(\Delta^r+\Gamma^r)+\Omega^r\tau^r)\kappa^r\Delta^r((\mu^r+\sigma^r)\tau^r+\delta^r\sigma^r)\right\}\\
&+\nu^r\xi^r\left\{((\mu^r+\sigma^r)\tau^r+\delta^r\sigma^r)\Gamma^r+\Omega^r\tau^r(\xi^r+\mu^r+\sigma^r)\right\}\\
&+\kappa^r\nu^r\left\{(\psi^r\tau^r+\delta^r(\psi^r+\phi^r))\Delta^r+(\psi^r\tau^r+\delta^r(\psi^r+\phi^r))\Gamma^r+\Omega^r\tau^r\psi^r\right\},
\end{aligned}
$$

$$
\begin{aligned}
\Theta_5 = {} & f_2f_3\xi^r+\left\{(\psi^r+\phi^r)(\chi^r+\kappa^r)+\mu^r\psi^r+(\mu^r+\sigma^r)\phi^r\right\}\delta^r\\
&+\left\{(\psi^r+\phi^r)(\chi^r+\kappa^r)+\mu^r\psi^r+(\mu^r+\sigma^r)\phi^r\right\}\omega^r+\tau^r\psi^r(\chi^r+\kappa^r),
\end{aligned}
$$

and $f_1=\rho^r+\gamma^r, f_2=\sigma^r+\mu^r+\kappa^r+\chi^r, f_3=\tau^r+\omega^r+\delta^r, f_4=\psi^r+\phi^r+\xi^r, f_5=\eta^r$.
For stability of equilibrium point, consider the matrix form:

$$\dot{\mathbb{S}}=\mathbb{P}\mathbb{S}+\Theta$$

$$
\begin{bmatrix}\dot{\mathbb{S}}_{12}\\ \dot{\mathbb{S}}_3\\ \dot{\mathbb{S}}_4\\ \dot{\mathbb{S}}_R\\ \dot{\mathbb{S}}_E\end{bmatrix}=\begin{bmatrix}-f_1 & 0 & 0 & 0 & 0\\ \nu & -f_2 & 0 & \psi & 0\\ 0 & \mu & -f_3 & \phi & 0\\ \rho & \sigma & \tau & -f_4 & 0\\ 0 & \kappa & \omega & \xi & -f_5\end{bmatrix}\begin{bmatrix}\mathbb{S}_{12}\\ \mathbb{S}_3\\ \mathbb{S}_4\\ \mathbb{S}_R\\ \mathbb{S}_E\end{bmatrix}+\begin{bmatrix}\Delta\\ \Gamma\\ \Omega\\ 0\\ 0\end{bmatrix}
$$

The Characteristic equation is

$$
\left|\mathbb{P}-\lambda I\right|=\begin{vmatrix}-f_1-\lambda & 0 & 0 & 0 & 0\\ \nu & -f_2-\lambda & 0 & \psi & 0\\ 0 & \mu & -f_3-\lambda & \phi & 0\\ \rho & \sigma & \tau & -f_4-\lambda & 0\\ 0 & \kappa & \omega & \xi & -f_5-\lambda\end{vmatrix}
$$

Using Routh-Hurwitz criterion, the Routh table is obtained as follows:

$$\begin{bmatrix} \lambda^5 & 1 & + & + \\ \lambda^4 & + & + & 0 \\ \lambda^3 & + & + & 0 \\ \lambda^2 & + & + & 0 \\ \lambda & + & 0 & 0 \\ 1 & + & 0 & 0 \end{bmatrix}$$

The positive nature of the elements in the Routh array is indicated by the "+" symbol. The Routh array exhibits a condition where all elements are positive and zero, signifying that every real eigenvalue is negative. Consequently, it is possible to deduce that the equilibrium point of this system exhibits asymptotic stability.

Remark 3.4.1. *The following result applies to the equilibrium of our fractional order breast cancer model. The disease-free equilibrium point may be readily identified by observing our system's steady state in the absence of infection. These equilibrium points are significant for analyzing the suggested fractional model of cancer with chemotherapy treatment, as they may forecast suitable conditions for infection control and spread.*

Based on the findings of the aforementioned investigation, we can arrive at the following conclusion.

Lemma 3.4.1. *The suggested fractional model of breast cancer has an unconstrained equilibrium.*

Theorem 3.4.1. *The breast cancer model* (3.40) *is locally asymptotically stable.*

Proof. The proof is similar to given in [9]. □

3.4.5 Qualitative analysis

In this section, we will discuss the existence and uniqueness of the considered model (3.40) using Krasnoselskii's and banach fixed point theorem. Let us rewrite the considered model (3.40) in the following form:

$$\begin{aligned}
{}^{\mathsf{ABC}}_{0}D^{r}_{t}\mathbb{S}_{12} &= g_1(t,\mathbb{S}_{12},\mathbb{S}_3,\mathbb{S}_4,\mathbb{S}_R,\mathbb{S}_E),\\
{}^{\mathsf{ABC}}_{0}D^{r}_{t}\mathbb{S}_{3} &= g_2(t,\mathbb{S}_{12},\mathbb{S}_3,\mathbb{S}_4,\mathbb{S}_R,\mathbb{S}_E),\\
{}^{\mathsf{ABC}}_{0}D^{r}_{t}\mathbb{S}_{4} &= g_3(t,\mathbb{S}_{12},\mathbb{S}_3,\mathbb{S}_4,\mathbb{S}_R,\mathbb{S}_E),\\
{}^{\mathsf{ABC}}_{0}D^{r}_{t}\mathbb{S}_{R} &= g_4(t,\mathbb{S}_{12},\mathbb{S}_3,\mathbb{S}_4,\mathbb{S}_R,\mathbb{S}_E),\\
{}^{\mathsf{ABC}}_{0}D^{r}_{t}\mathbb{S}_{E} &= g_5(t,\mathbb{S}_{12},\mathbb{S}_3,\mathbb{S}_4,\mathbb{S}_R,\mathbb{S}_E),
\end{aligned} \tag{3.41}$$

where,

$$\begin{aligned}
g_1(t,\mathbb{S}_{12},\mathbb{S}_3,\mathbb{S}_4,\mathbb{S}_R,\mathbb{S}_E) &= \Delta^r-(\rho^r+\nu^r)\mathbb{S}_{12},\\
g_2(t,\mathbb{S}_{12},\mathbb{S}_3,\mathbb{S}_4,\mathbb{S}_R,\mathbb{S}_E) &= \Gamma^r+\nu^r\mathbb{S}_{12}+\psi^r\mathbb{S}_R-(\sigma^r+\mu^r+\kappa^r+\chi^r)\mathbb{S}_3,\\
g_3(t,\mathbb{S}_{12},\mathbb{S}_3,\mathbb{S}_4,\mathbb{S}_R,\mathbb{S}_E) &= \Omega^r+\mu^r\mathbb{S}_3+\phi^r\mathbb{S}_R-(\tau^r+\omega^r+\delta^r)\mathbb{S}_4,\\
g_4(t,\mathbb{S}_{12},\mathbb{S}_3,\mathbb{S}_4,\mathbb{S}_R,\mathbb{S}_E) &= \rho^r\mathbb{S}_{12}+\sigma^r\mathbb{S}_3+\tau^r\mathbb{S}_4-(\psi^r+\phi^r+\zeta^r)\mathbb{S}_R,\\
g_5(t,\mathbb{S}_{12},\mathbb{S}_3,\mathbb{S}_4,\mathbb{S}_R,\mathbb{S}_E) &= \zeta^r\mathbb{S}_R+\omega^r\mathbb{S}_4+\kappa^r\mathbb{S}_3-\eta^r\mathbb{S}_E.
\end{aligned}$$

For the sake of simplicity we consider the proposed model (3.41) as:

$$\begin{aligned}
{}^{\mathsf{ABC}}_{0}D^{r}_{t}\mathbb{G}(t) &= \Theta\left(t,\mathbb{G}(t)\right),\\
\mathbb{G}(0) &= \mathbb{G}_0\geq 0,
\end{aligned} \tag{3.42}$$

where,

$$\begin{aligned}
\mathbb{G}(t) &= \left(\mathbb{S}_{12}(t),\mathbb{S}_3(t),\mathbb{S}_4(t),\mathbb{S}_R(t),\mathbb{S}_E(t)\right)^T,\\
\mathbb{G}_0 &= \left(\mathbb{S}_{12_0},\mathbb{S}_{3_0},\mathbb{S}_{4_0},\mathbb{S}_{R_0},\mathbb{S}_{E_0}\right)^T,\\
\Theta(t,\mathbb{G}(t)) &= \left(g_1,g_2,g_3,g_4,g_5\right)^T.
\end{aligned}$$

Applying fractional AB integral (3.36) on (5.9), we get

$$\mathbb{G}(t) = \mathbb{G}_0 + \frac{(1-r)}{Q(r)}\Theta(t, \mathbb{G}(t)) + \frac{r}{Q(r)\Gamma(r)}\int_0^t (t-\delta)^{r-1}\Theta(\delta, \mathbb{G}(\delta))d\delta. \tag{3.43}$$

Let us define Banach space by using $\Pi = [0, T]$ as $\Phi = \mathsf{C}(\Pi, \mathbb{R}^7)$ under the norm defined as:

$$\|\mathbb{G}\| = \sup_{t\in\chi}\{\mathbb{G}(t) : \mathbb{G} \in \Phi\}.$$

Suppose for each $\mathbb{G} \in \Phi$ and $t \in [0, T]$, the function $\Theta(t, \mathbb{G}(t))$ satisfies some of the following growth and Lipschitz condition for existence and uniqueness respectively.

- $\exists$ constants μ_Δ and ν_Δ such that $|\Theta(t, \mathbb{G}(t))| \leq \mu_\Delta |\mathbb{G}| + \nu_\Delta$,
- $\exists$ constant $\lambda_\Delta > 0$ such that $|\Theta(t, \mathbb{G}_1(t)) - \Theta(t, \mathbb{G}_2(t))| \leq \lambda_\Delta |\mathbb{G}_1 - \mathbb{G}_2|$.

Now, we define the operators Λ_1 and Λ_2 such that:

$$\Lambda_1\mathbb{G} = \mathbb{G}_0 + \frac{(1-r)}{Q(r)}\Theta(t, \mathbb{G}(t)),$$
$$\Lambda_2\mathbb{G} = \frac{r}{Q(r)\Gamma(r)}\int_0^t (t-\delta)^{r-1}\Theta(\delta, \mathbb{G}(\delta))d\delta,$$

where, $\Lambda_1 + \Lambda_2 = \Phi$

Theorem 3.4.2. *Assume that the growth and Lipschitz conditions hold. Then* (5.10) *has at least one solution if the following conditions hold:*

1. $\frac{(1-r)}{Q(r)}\lambda_\Delta < 1$.
2. $\Psi_1 = \left[\frac{(1-r)}{Q(r)} + \frac{T^r}{Q(r)\Gamma(r)}\right]\nu_\Delta < 1$.
3. $\Psi_2 = \left[\frac{(1-r)}{Q(r)} + \frac{T^r}{Q(r)\Gamma(r)}\right]\mu_\Delta < 1$.

Proof. * Let $B_\tau = \{\mathbb{G} \in \Phi : \|\mathbb{G}\| \leq \tau\}$ be a closed convex set. First we will prove that for

any $\mathbb{G}_1$, $\mathbb{G}_2 \in B_\tau$, $\Lambda_1\mathbb{G}_1 + \Lambda_2\mathbb{G}_2 \in B_\tau$. Using growth condition, we get

$$\begin{aligned}
&\|\Lambda_1\mathbb{G}_1 + \Lambda_2\mathbb{G}_2\| \\
&\leq \sup_{t\in\Pi}\left\{|\mathbb{G}_0| + \frac{(1-r)}{Q(r)}|\Theta(t,\mathbb{G}(t))| + \frac{r}{Q(r)\Gamma(r)}\int_0^t (t-\delta)^{r-1}|\Theta(\delta,\mathbb{G}(\delta))|d\delta\right\} \\
&\leq \left\{|\mathbb{G}_0| + \frac{(1-r)}{Q(r)}(\mu_\Delta\|\mathbb{G}\| + \nu_\Delta) + \frac{r}{Q(r)\Gamma(r)}\int_0^t (t-\delta)^{r-1}(\mu_\Delta\|\mathbb{G}\| + \nu_\Delta)d\delta\right\} \\
&= |\mathbb{G}_0| + \left\{\frac{(1-r)}{Q(r)} + \frac{T^r}{Q(r)\Gamma(r)}\right\}\nu_\Delta + \left\{\frac{(1-r)}{Q(r)} + \frac{T^r}{Q(r)\Gamma(r)}\right\}\mu_\Delta\tau \\
&= \Psi_1 + \Psi_2\tau \leq \tau.
\end{aligned}$$

This shows that $\Lambda_1\mathbb{G}_1 + \Lambda_2\mathbb{G}_2 \in B_\tau$.

Next to show that Λ_1 is contraction. For any $\mathbb{G}_1$, $\mathbb{G}_2 \in B_\tau$, using Lipschitz condition, we get :

$$\begin{aligned}
\|\Lambda_1\mathbb{G}_1 + \Lambda_2\mathbb{G}_1\| &= \sup_{t\in[0,\mathsf{T}]}\frac{(1-r)}{Q(r)}\left|\Theta(t,\mathbb{G}_1(t)) - \Theta(t,\mathbb{G}_2(t))\right| \\
&\leq \frac{(1-r)}{Q(r)}\lambda_\Delta \sup_{t\in[0,\mathsf{T}]}|\mathbb{G}_1 - \mathbb{G}_2| \\
&\leq \frac{(1-r)}{Q(r)}\lambda_\Delta\left\|\mathbb{G}_1 - \mathbb{G}_2\right\|,
\end{aligned}$$

where $\frac{(1-r)}{Q(r)}\lambda_\Delta < 1$. Hence, Λ_1 is a contraction.

Now to show that Λ_2 is relatively compact. For this let $\mathbb{G} \in B_\tau$, consider,

$$\begin{aligned}
\|\Lambda_2\mathbb{G}\| &\leq \sup_{t\in[0,\mathsf{T}]}\frac{r}{Q(r)\Gamma(r)}\int_0^t (t-\delta)^{r-1}|\Delta(\delta,\mathbb{G}(\delta))|d\delta \\
&\leq \frac{r}{Q(r)\Gamma(r)}\int_0^t (t-\delta)^{r-1}\sup_{t\in[0,\mathsf{T}]}[\mu_\Delta|\mathbb{G}| + \nu_\Delta]d\delta \\
&\leq \frac{r}{Q(r)\Gamma(r)}\int_0^t (t-\delta)^{r-1}[\mu_\Delta\|\mathbb{G}\| + \nu_\Delta]d\delta \\
&\leq \frac{T^r}{Q(r)\Gamma(r)}[\mu_\Delta\tau + \nu_\Delta].
\end{aligned}$$

Hence, Λ_2 is uniformly bounded on B_τ. Finally, to show that Λ_2 is equicontinuous. Let

$\mathbb{G} \in B_\tau$ and t_1, $t_2 \in [0, T]$ such that $t_1 < t_2$. Then,

$$\begin{aligned}
&\|\Lambda_2\mathbb{G}(t_1) - \Lambda_2\mathbb{G}(t_2)\| \\
&\leq \frac{r}{Q(r)\Gamma(r)} \int_{t_1}^{t_2} (t_2 - \delta)^{r-1} |\Theta(\delta, \mathbb{G}(\delta))| d\delta \\
&\quad + \frac{r}{Q(r)\Gamma(r)} \int_0^{t_2} [(t_1 - \delta)^{r-1} - (t_2 - \delta)^{r-1}] |\Theta(\delta, \mathbb{G}(\delta))| d\delta \\
&\leq \frac{2[\mu_\Delta \tau + \nu_\Delta]}{Q(r)\Gamma(r)} [(t_2 - t_1)^r].
\end{aligned}$$

Thus, $\|\Lambda_2\mathbb{G}(t_1) - \Lambda_2\mathbb{G}(t_2)\| \to 0$ as $t_2 \to t_1$. By Arzela-Ascoli theorem, the operator Λ_2 is relatively compact, so is equicontinuous. Thus, Eq. (5.10) has at least one solution. Since, the proposed model is equivalent to Eq. (5.10), therefore, the considered model has at least one solution. □

Theorem 3.4.3. *Assume that the Lipschitz condition holds and if*

$$\left\{ \frac{(1-r)}{Q(r)} + \frac{T^r}{Q(r)\Gamma(r)} \right\} \lambda_\Delta < 1,$$

then the Eq. (5.10) *has unique solution*

Proof. For any $\mathbb{G}$, $\mathbb{G}^* \in \Phi$ and $t \in [, T]$, consider

$$\begin{aligned}
\|\Lambda\mathbb{G}(t) - \Lambda\mathbb{G}^*(t)\| &\leq \max_{t\in[0,\mathsf{T}]} \frac{(1-r)}{Q(r)} |\Theta(t, \mathbb{G}(t)) - \Theta(t, \mathbb{G}^*(t))| \\
&\quad + \max_{t\in[0,\mathsf{T}]} \frac{r}{Q(r)\Gamma(r)} \int_0^t (t-\delta)^{r-1} |\Theta(t, \mathbb{G}(t)) - \Theta(t, \mathbb{G}^*(t))| \, d\delta \\
&\leq \left\{ \frac{(1-r)}{Q(r)} + \frac{T^r}{Q(r)\Gamma(r)} \right\} \lambda_\Delta \|\mathbb{G} - \mathbb{G}^*\|.
\end{aligned}$$

Due to hypothesis $\left\{ \frac{(1-r)}{Q(r)} + \frac{T^r}{Q(r)\Gamma(r)} \right\} \lambda_\Delta < 1$, the operator Λ is contraction. By banach contraction theorem the Eq. (5.10) has unique solution. Consequently, the proposed model (3.40) has a unique solution. □

3.4.6 Global stability analysis

In this section, we discuss the Ulam-Hyres (UH) stabiity of the proposed fractional model (3.40) using the notion of nonlinear functional analysis.

Definition 3.4.7. *The proposed system* (3.40) *is UH stable, if* $\exists\ \bar{a} > 0$ *with the following property. For any* $\epsilon > 0$ *and* $\overline{\mathbb{G}} \in \Phi$*. If*

$$\left|{}_0^{\mathsf{ABC}}D_t^r\overline{\mathbb{G}}(t) - \Theta\left(t, \overline{\mathbb{G}}(t)\right)\right| \leq \epsilon. \tag{3.44}$$

then $\exists\ \mathbb{G} \in \Phi$ *satisfying system* (3.40) *with initial condition* $\mathbb{G}(0) = \overline{\mathbb{G}}(0) = \overline{\mathbb{G}}_0$*, such that* $\left\|\overline{\mathbb{G}} - \mathbb{G}\right\| \leq \bar{a}\epsilon$*, where*

$$\begin{aligned}
\overline{\mathbb{G}}(t) &= \left(\overline{\mathbb{S}}_{12}(t), \overline{\mathbb{S}}_3(t), \overline{\mathbb{S}}_4(t), \overline{\mathbb{S}}_R(t), \overline{\mathbb{S}}_E(t)\right)^T, \\
\mathbb{G}_0 &= \left(\overline{\mathbb{S}}_{12_0}(t), \overline{\mathbb{S}}_{3_0}(t), \overline{\mathbb{S}}_{4_0}(t), \overline{\mathbb{S}}_{R_0}(t), \overline{\mathbb{S}}_{E_0}(t)\right)^T, \\
\Theta(t, \overline{\mathbb{G}}(t)) &= \left(\overline{g}_1, \overline{g}_2, \overline{g}_3, \overline{g}_4, \overline{g}_5\right)^T, \\
\epsilon &= max(\epsilon_j)^T; j = 1, 2, 3, 4, 5, \\
\bar{a} &= max(\bar{a}_j)^T; j = 1, 2, 3, 4, 5.
\end{aligned}$$

Remark 3.4.2. *Consider a small perturbation* $\xi \in \mathsf{C}[0, \mathsf{T}]$ *such that* $\xi(0) = 0$ *along with the following property :* $|\xi(t)| \leq \overline{\epsilon}$*, for* $t \in [0, \mathsf{T}]$ *and* $\overline{\epsilon} > 0$*.*

Lemma 3.4.2. *The solution* $\overline{\mathbb{G}}_\xi(t)$ *of the perturbed system*

$${}_0^{\mathsf{ABC}}D_t^r\overline{\mathbb{G}}(t) = \Theta\left(t, \overline{\mathbb{G}}(t)\right) + \xi(t), \quad \overline{\mathbb{G}}(0) = \overline{\mathbb{G}}_0, \tag{3.45}$$

saisfies the relation:

$$\left|\overline{\mathbb{G}}_\xi(t) - \overline{\mathbb{G}}(t)\right| \leq \left[\frac{(1-r)\Gamma(r) + \mathsf{T}^r}{Q(r)\Gamma(r)}\right]\overline{\epsilon},$$

where, $\xi(t) = (\xi_1(t), \xi_2(t), \xi_3(t), \xi_4(t), \xi_5(t))^T$*.*

Proof. Applying fractional integral (3.36) on (3.45), we get

$$\begin{aligned}\overline{\mathbb{G}}_{\xi}(t) = \overline{\mathbb{G}}_0 + \frac{(1-r)}{Q(r)}\Theta\left(t, \overline{\mathbb{G}}(t)\right) + \frac{r}{Q(r)\Gamma(r)}\int_0^t (t-\delta)^{r-1}\Theta\left(\delta, \overline{\mathbb{G}}(\delta)\right)d\delta \\ + \frac{(1-r)}{Q(r)}\xi(t) + \frac{r}{Q(r)\Gamma(r)}\int_0^t (t-\delta)^{r-1}\xi(\delta)d\delta.\end{aligned} \tag{3.46}$$

Also,

$$\overline{\mathbb{G}}(t) = \overline{\mathbb{G}}_0 + \frac{(1-r)}{Q(r)}\Theta\left(t, \overline{\mathbb{G}}(t)\right) + \frac{r}{Q(r)\Gamma(r)}\int_0^t (t-\delta)^{r-1}\Theta\left(\delta, \overline{\mathbb{G}}(\delta)\right)d\delta. \tag{3.47}$$

Using Remark 3.4.2,

$$\begin{aligned}\left|\overline{\mathbb{G}}_{\xi}(t) - \overline{\mathbb{G}}(t)\right| &\leq \frac{(1-r)}{Q(r)}\left|\xi(t)\right| + \frac{r}{Q(r)\Gamma(r)}\int_0^t (t-\delta)^{r-1}\left|\xi(\delta)\right|d\delta, \\ &\leq \left[\frac{(1-r)\Gamma(r) + \mathsf{T}^r}{Q(r)\Gamma(r)}\right]\overline{\epsilon}.\end{aligned}$$

This complete the proof. □

Theorem 3.4.4. *The proposed fractional system* (3.40) *is UM stable,if*

$$\left\|\overline{\mathbb{G}}(t) - \mathbb{G}(t)\right\| \leq \overline{a}\overline{\epsilon}.$$

Proof. Let $\overline{\mathbb{G}}$ be the solution of (5.14) and due to uniqueness $\mathbb{G}$ be a unique solution of the system (3.45), then

$$\begin{aligned}\left|\overline{\mathbb{G}}(t) - \mathbb{G}(t)\right| &\leq \left|\overline{\mathbb{G}}_{\xi}(t) - \overline{\mathbb{G}}(t)\right| + \left|\overline{\mathbb{G}}_{\xi}(t) - \mathbb{G}(t)\right| \\ &\leq 2\left[\frac{(1-r)\Gamma(r) + \mathsf{T}^r}{Q(r)\Gamma(r)}\right]\overline{\epsilon} + \frac{1-r}{Q(r)}\left|\Theta(t, \overline{\mathbb{G}}(t)) - \Theta(t, \mathbb{G}(t))\right| \\ &\quad + \frac{r}{Q(r)\Gamma(r)}\int_0^t (t-\delta)^{r-1}\left|\Theta(\delta, \overline{\mathbb{G}}(\delta)) - \Delta(\delta, \mathbb{G}(\delta))\right|d\delta \\ &\leq 2\left[\frac{(1-r)\Gamma(r) + \mathsf{T}^r}{Q(r)\Gamma(r)}\right]\overline{\epsilon} + \left[\frac{(1-r)\Gamma(r) + \mathsf{T}^r}{Q(r)\Gamma(r)}\right]\lambda_{\Delta}\left|\overline{\mathbb{G}} - \mathbb{G}\right|.\end{aligned}$$

Which implies that,

$$\left|\overline{\mathbb{G}}(t) - \mathbb{G}(t)\right| \leq \frac{2\xi\overline{\epsilon}}{1-\Xi},$$

where $\xi = 2\left[\frac{(1-r)\Gamma(r)+\mathsf{T}^r}{Q(r)\Gamma(r)}\right]$ and $\Xi = \left[\frac{(1-r)\Gamma(r)+\mathsf{T}^r}{Q(r)\Gamma(r)}\right]\lambda_\Delta$.
For $\bar{a} = \frac{2\xi}{1-\eta}$, then $\left|\overline{\mathbb{G}}(t) - \mathbb{G}(t)\right| \leq \bar{a}\overline{\epsilon}$.
Hence, considered fractional system (3.40) is UM stable. □

3.4.7 Numerical method

The present part of the paper provides an approximate solution for the fractional order models 3.38 - 3.40 using two-step fractional Adams-Bashforth technique [16]. The convergence and accuracy of the schemes are provided in the [16]
We discretized model (3.38) as follows :

$$\begin{aligned}
\mathbb{S}_{12}(t_{n+1}) =& \mathbb{S}_{12}(t_n) + \frac{K_1}{h\Gamma(r)}N_1(t_n, \mathbb{S}_{12n}, \mathbb{S}_{3n}, \mathbb{S}_{4n}, \mathbb{S}_{Rn}, \mathbb{S}_{En}) \\
&+ \frac{K_2}{h\Gamma(r)}N_1(t_{n-1}, \mathbb{S}_{12n-1}, \mathbb{S}_{3n-1}, \mathbb{S}_{4n-1}, \mathbb{S}_{Rn-1}, \mathbb{S}_{En-1}), \\
\mathbb{S}_{3}(t_{n+1}) =& \mathbb{S}_{3}(t_n) + \frac{K_1}{h\Gamma(r)}N_2(t_n, \mathbb{S}_{12n}, \mathbb{S}_{3n}, \mathbb{S}_{4n}, \mathbb{S}_{Rn}, \mathbb{S}_{En}) \\
&+ \frac{K_2}{h\Gamma(r)}N_2(t_{n-1}, \mathbb{S}_{12n-1}, \mathbb{S}_{3n-1}, \mathbb{S}_{4n-1}, \mathbb{S}_{Rn-1}, \mathbb{S}_{En-1}), \\
\mathbb{S}_{4}(t_{n+1}) =& \mathbb{S}_{4}(t_n) + \frac{K_1}{h\Gamma(r)}N_3(t_n, \mathbb{S}_{12n}, \mathbb{S}_{3n}, \mathbb{S}_{4n}, \mathbb{S}_{Rn}, \mathbb{S}_{En}) \\
&+ \frac{K_2}{h\Gamma(r)}N_3(t_{n-1}, \mathbb{S}_{12n-1}, \mathbb{S}_{3n-1}, \mathbb{S}_{4n-1}, \mathbb{S}_{Rn-1}, \mathbb{S}_{En-1}), \\
\mathbb{S}_{R}(t_{n+1}) =& \mathbb{S}_{R}(t_n) + \frac{K_1}{h\Gamma(r)}N_4(t_n, \mathbb{S}_{12n}, \mathbb{S}_{3n}, \mathbb{S}_{4n}, \mathbb{S}_{Rn}, \mathbb{S}_{En}) \\
&+ \frac{K_2}{h\Gamma(r)}N_4(t_{n-1}, \mathbb{S}_{12n-1}, \mathbb{S}_{3n-1}, \mathbb{S}_{4n-1}, \mathbb{S}_{Rn-1}, \mathbb{S}_{En-1}), \\
\mathbb{S}_{E}(t_{n+1}) =& \mathbb{S}_{E}(t_n) + \frac{K_1}{h\Gamma(r)}N_5(t_n, \mathbb{S}_{12n}, \mathbb{S}_{3n}, \mathbb{S}_{4n}, \mathbb{S}_{Rn}, \mathbb{S}_{En}) \\
&+ \frac{K_2}{h\Gamma(r)}N_5(t_{n-1}, \mathbb{S}_{12n-1}, \mathbb{S}_{3n-1}, \mathbb{S}_{4n-1}, \mathbb{S}_{Rn-1}, \mathbb{S}_{En-1}),
\end{aligned} \tag{3.48}$$

where,

$$K_1 = \left[\frac{2ht_{n+1}^r}{r} - \frac{t_{n+1}^{r+1}}{r+1} + \frac{ht_n^r}{r} - \frac{t_n^{r+1}}{r+1}\right], \tag{3.49}$$

$$K_2 = \left[-\frac{ht_{n+1}^r}{r} + \frac{t_{n+1}^{r+1}}{r+1} + \frac{t_n^{r+1}}{r+1}\right]. \tag{3.50}$$

Now, we discretized model (3.39) as follows:

$$\begin{aligned}
\mathbb{S}_{12}\left(t_{n+1}\right) &= \mathbb{S}_{12}\left(t_n\right) + M_1(r)N_1(t_n, \mathbb{S}_{12n}, \mathbb{S}_{3n}, \mathbb{S}_{4n}, \mathbb{S}_{Rn}, \mathbb{S}_{En}) - M_2(r) \\
&\quad N_1(t_{n-1}, \mathbb{S}_{12n-1}, \mathbb{S}_{3n-1}, \mathbb{S}_{4n-1}, \mathbb{S}_{Rn-1}, \mathbb{S}_{En-1}), \\
\mathbb{S}_{3}\left(t_{n+1}\right) &= \mathbb{S}_{3}\left(t_n\right) + M_1(r)N_2(t_n, \mathbb{S}_{12n}, \mathbb{S}_{3n}, \mathbb{S}_{4n}, \mathbb{S}_{Rn}, \mathbb{S}_{En}) - M_2(r) \\
&\quad N_2(t_{n-1}, \mathbb{S}_{12n-1}, \mathbb{S}_{3n-1}, \mathbb{S}_{4n-1}, \mathbb{S}_{Rn-1}, \mathbb{S}_{En-1}), \\
\mathbb{S}_{4}\left(t_{n+1}\right) &= \mathbb{S}_{4}\left(t_n\right) + M_1(r)N_3(t_n, \mathbb{S}_{12n}, \mathbb{S}_{3n}, \mathbb{S}_{4n}, \mathbb{S}_{Rn}, \mathbb{S}_{En}) - M_2(r) \\
&\quad N_3(t_{n-1}, \mathbb{S}_{12n-1}, \mathbb{S}_{3n-1}, \mathbb{S}_{4n-1}, \mathbb{S}_{Rn-1}, \mathbb{S}_{En-1}), \\
\mathbb{S}_{R}\left(t_{n+1}\right) &= \mathbb{S}_{R}\left(t_n\right) + M_1(r)N_4(t_n, \mathbb{S}_{12n}, \mathbb{S}_{3n}, \mathbb{S}_{4n}, \mathbb{S}_{Rn}, \mathbb{S}_{En}) - M_2(r) \\
&\quad N_4(t_{n-1}, \mathbb{S}_{12n-1}, \mathbb{S}_{3n-1}, \mathbb{S}_{4n-1}, \mathbb{S}_{Rn-1}, \mathbb{S}_{En-1}), \\
\mathbb{S}_{E}\left(t_{n+1}\right) &= \mathbb{S}_{E}\left(t_n\right) + M_1(r)N_5(t_n, \mathbb{S}_{12n}, \mathbb{S}_{3n}, \mathbb{S}_{4n}, \mathbb{S}_{Rn}, \mathbb{S}_{En}) - M_2(r) \\
&\quad N_5(t_{n-1}, \mathbb{S}_{12n-1}, \mathbb{S}_{3n-1}, \mathbb{S}_{4n-1}, \mathbb{S}_{Rn-1}, \mathbb{S}_{En-1}),
\end{aligned} \tag{3.51}$$

where

$$M_1(r) = \left(\frac{1-r}{P(r)} + \frac{3rh}{2P(r)}\right), \tag{3.52}$$

$$M_2(r) = \left(\frac{1-r}{P(r)} + \frac{rh}{2P(r)}\right). \tag{3.53}$$

Next, we discretized model (3.40) as follows:

$$\begin{aligned}
\mathbb{S}_{12}\left(t_{n+1}\right) &= \mathbb{S}_{12}\left(t_n\right) + N_1(t_n, \mathbb{S}_{12n}, \mathbb{S}_{3n}, \mathbb{S}_{4n}, \mathbb{S}_{Rn}, \mathbb{S}_{En})L_1 \\
&\quad + N_1(t_{n-1}, \mathbb{S}_{12n-1}, \mathbb{S}_{3n-1}, \mathbb{S}_{4n-1}, \mathbb{S}_{Rn-1}, \mathbb{S}_{En-1})L_2, \\
\mathbb{S}_{3}\left(t_{n+1}\right) &= \mathbb{S}_{3}\left(t_n\right) + N_2(t_n, \mathbb{S}_{12n}, \mathbb{S}_{3n}, \mathbb{S}_{4n}, \mathbb{S}_{Rn}, \mathbb{S}_{En})L_1 \\
&\quad + N_2(t_{n-1}, \mathbb{S}_{12n-1}, \mathbb{S}_{3n-1}, \mathbb{S}_{4n-1}, \mathbb{S}_{Rn-1}, \mathbb{S}_{En-1})L_2, \\
\mathbb{S}_{4}\left(t_{n+1}\right) &= \mathbb{S}_{4}\left(t_n\right) + N_3(t_n, \mathbb{S}_{12n}, \mathbb{S}_{3n}, \mathbb{S}_{4n}, \mathbb{S}_{Rn}, \mathbb{S}_{En})L_1 \\
&\quad + N_3(t_{n-1}, \mathbb{S}_{12n-1}, \mathbb{S}_{3n-1}, \mathbb{S}_{4n-1}, \mathbb{S}_{Rn-1}, \mathbb{S}_{En-1})L_2, \\
\mathbb{S}_{R}\left(t_{n+1}\right) &= \mathbb{S}_{R}\left(t_n\right) + N_4(t_n, \mathbb{S}_{12n}, \mathbb{S}_{3n}, \mathbb{S}_{4n}, \mathbb{S}_{Rn}, \mathbb{S}_{En})L_1 \\
&\quad + N_4(t_{n-1}, \mathbb{S}_{12n-1}, \mathbb{S}_{3n-1}, \mathbb{S}_{4n-1}, \mathbb{S}_{Rn-1}, \mathbb{S}_{En-1})L_2, \\
\mathbb{S}_{E}\left(t_{n+1}\right) &= \mathbb{S}_{E}\left(t_n\right) + N_5(t_n, \mathbb{S}_{12n}, \mathbb{S}_{3n}, \mathbb{S}_{4n}, \mathbb{S}_{Rn}, \mathbb{S}_{En})L_1 \\
&\quad + N_5(t_{n-1}, \mathbb{S}_{12n-1}, \mathbb{S}_{3n-1}, \mathbb{S}_{4n-1}, \mathbb{S}_{Rn-1}, \mathbb{S}_{En-1})L_2,
\end{aligned} \tag{3.54}$$

where,

$$L_1 = \frac{1-r}{Q(r)} + \frac{r}{hQ(r)\Gamma(r)}\left[\frac{2ht_{n+1}^r}{r} - \frac{t_{n+1}^{r+1}}{r+1} - \frac{ht_n^r}{r} + \frac{t_n^{r+1}}{r+1}\right], \tag{3.55}$$

$$L_2 = \frac{r-1}{Q(r)} - \frac{r}{hQ(r)\Gamma(r)}\left[\frac{ht_{n+1}^r}{r} - \frac{t_{n+1}^{r+1}}{r+1} + \frac{t_n^{r+1}}{r+1}\right]. \tag{3.56}$$

3.4.8 Numerical simulation and Disucssion

This section focuses on numerical simulations conducted to comprehend the dynamic behavior of the Breast cancer model created utilizing classical system (3.37) and fractional order systems (3.38 - 3.40).The actual statistical data given in Table 3.2 are utilized to compare systems (3.37 - 3.40).The explicit fourth order Runge-Kutta technique [26] is utilized for simulation of the system (3.37), while numerical methods in [15] are used for fractional-order models (3.38 - 3.40). We take the initial values into account as $\mathbb{S}_{12}(0) = 30000, \mathbb{S}_3(0) =$

$12300, \mathbb{S}_4(0) = 783, \mathbb{S}_R(0) = 334, \mathbb{S}_E(0) = 10$ and parameters values: $\Delta = 14000, \Gamma = 80, \Omega = 90, \mu = 0.01, \nu = 0.034, \psi = 0.03, \phi = 0.3, \omega = 0.1, \zeta = 0.2, \chi = \delta = \eta = 0.0256$ in [10],$\kappa = 0.09, \rho = 0.03$ and $\tau = 0.01$ as fitted with true data. In addition, we used the least squares optimization approach to get the optimum values of the parameter r and σ as shown in Table 3.3. Furthermore, the evaluation of the system (3.37 - 3.40) is accomplished (See table 3.4) by calculating the error norm $= \sqrt{\sum_{a=1}^{13}(\text{Real data}_a - \text{Numerical data}_a)^2}$.Compared to the integer order system (3.37), the efficiency rate of the fractional system (3.38) is 46.13%, (3.39) is 52.93%, and (3.40) is 74.23%. The CFC (3.39) and ABC(3.40) models exhibit improvements of 12.61% and 52.16% respectively compared to the Caputo (3.38) model. The ABC model(3.40) exhibits a 45.26% improvement in performance compared to the CFC model (3.39).

The provided graphical illustration depicts a comparison between the supplied empirical data and the outcomes derived from both the classical and fractional order models.Figure 3.25 illustrates the contrast between the authentic data (Table 3.2) and the classical model (3.37), revealing a significant discrepancy in the biggest deviation. In Figure 3.26, the data points derived using the Caputo model exhibit a closer proximity to the true data points, as opposed to those shown in figure 3.25. The CFC model (3.39) has a similar pattern, as seen in figure 3.27. Nevertheless, upon careful examination of figure 3.28, it becomes apparent that there exists a minimal difference between the different points of the actual data and the data acquired using the system (3.40). The integer order model (3.37) has been subjected to comparison with fractional order models (3.38-3.40), as well as empirical data (Table 3.2), as seen in figures 3.29 - 3.31. Finally, figure 3.32 illustrates the comprehensive comparison between the true data and both the conventional (3.37) and fractional-order (3.38-3.40) models. It is seen that the majority of the data points generated by the system (3.40) exhibit the closest proximity to the true data points.

Table 3.2: Incidence of Breast cancer stage IV patients [5] in Saudi Arabia (2004–2016)

Year	**Cases**	**Year**	**Cases**
2004	783	2011	9530
2005	1715	2012	11072
2006	2696	2013	12925
2007	3935	2014	14751
2008	5087	2015	16730
2009	6467	2016	18970
2010	7940		

Table 3.3: Best estimated parameters for Mathematical models

Parameter	**Integer**	**Caputo**	**CF**	**ABC**
order	1	0.73	0.77	0.81
σ	0.4	0.35	0.48	0.38

Table 3.4: Comparison of the incidence of stage IV Breast cancer patients with data obtained under integer (3.37) and fractional order (3.38 - 3.40) systems and the respective norm values

Incidence	**Integer**	**Caputo**	**CF**	**ABC**
783	783	783	783	783
1715	1589	982	883	1110
2696	3021	2625	2096	2810
3935	4620	4413	3338	4015
5087	6226	5147	4805	4950
6467	7800	6538	6359	6460
7940	9353	8961	7982	7939
9530	10904	9379	9641	9468
11072	12469	11833	11319	11215
12925	14060	12340	13003	12454
14751	15677	14904	14683	14722
16730	17320	16516	16353	16642
18970	18982	18166	18006	18599
Norm	3.463e+03	1.865e+03	1.629e+03	0.892e+03

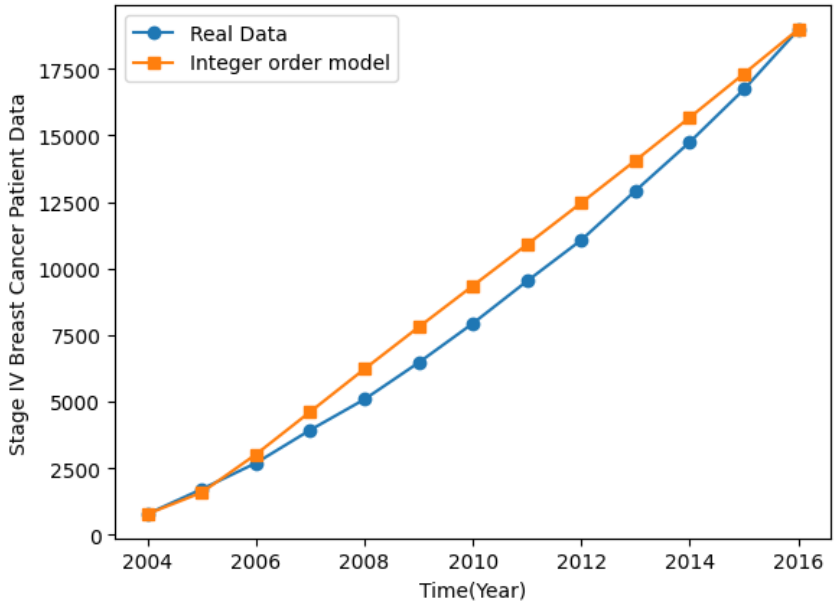

Figure 3.25: Comparison of the stage - IV Breast cancer patient incidences with the integer order model

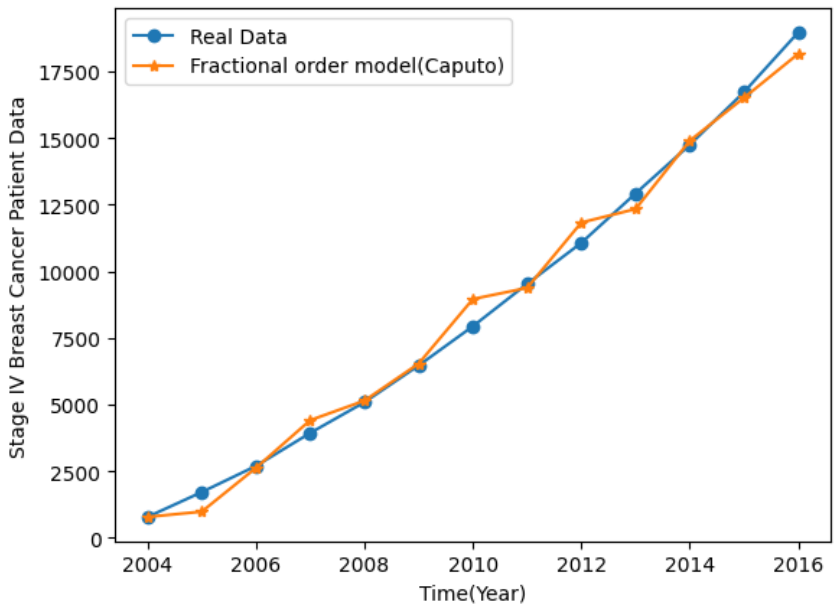

Figure 3.26: Comparison of the stage - IV Breast cancer patient incidences with Caputo model

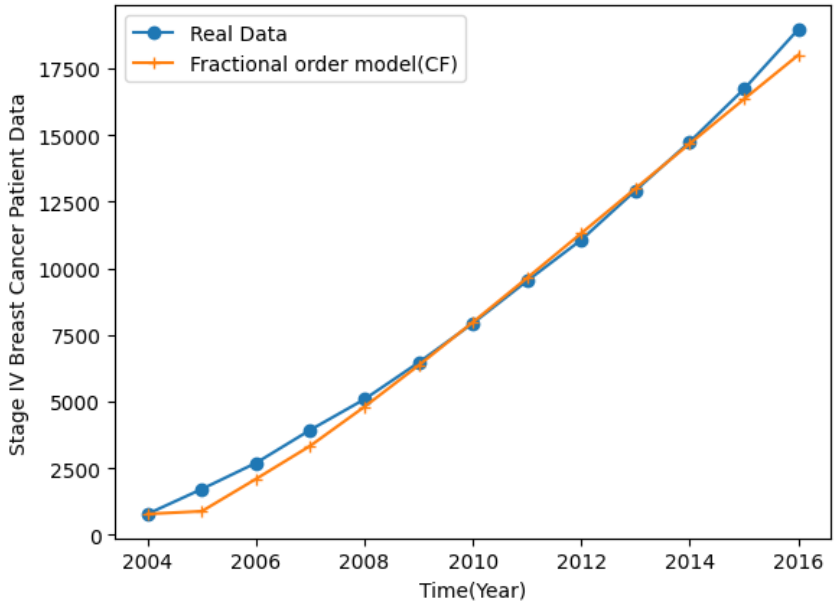

Figure 3.27: Comparison of the stage - IV Breast cancer patient incidences with CFC model

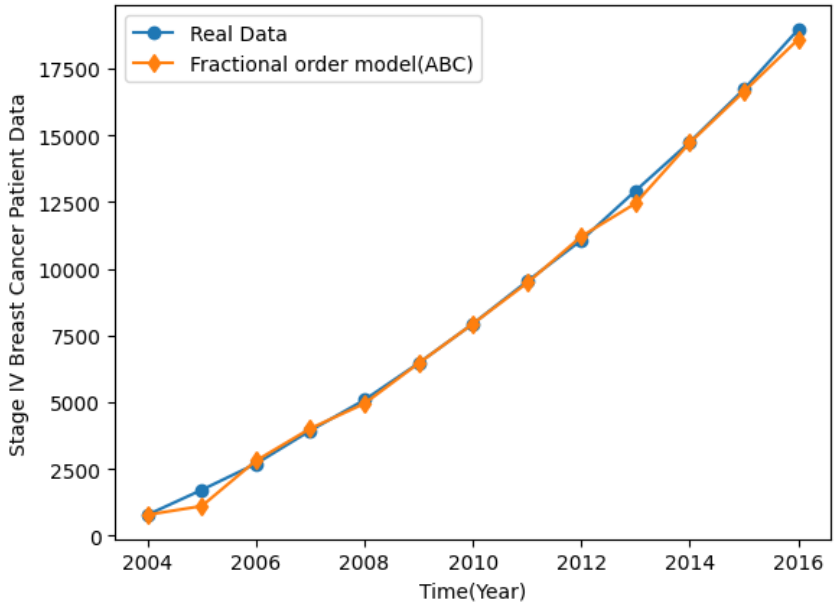

Figure 3.28: Comparison of the stage - IV Breast cancer patient incidences with ABC model

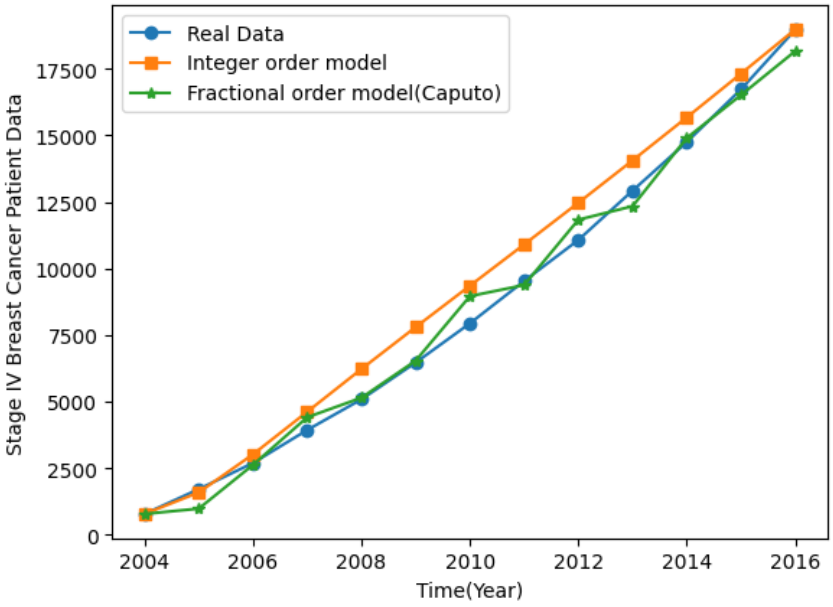

Figure 3.29: Comparison of the stage - IV Breast cancer patient incidences with the integer and the Caputo model

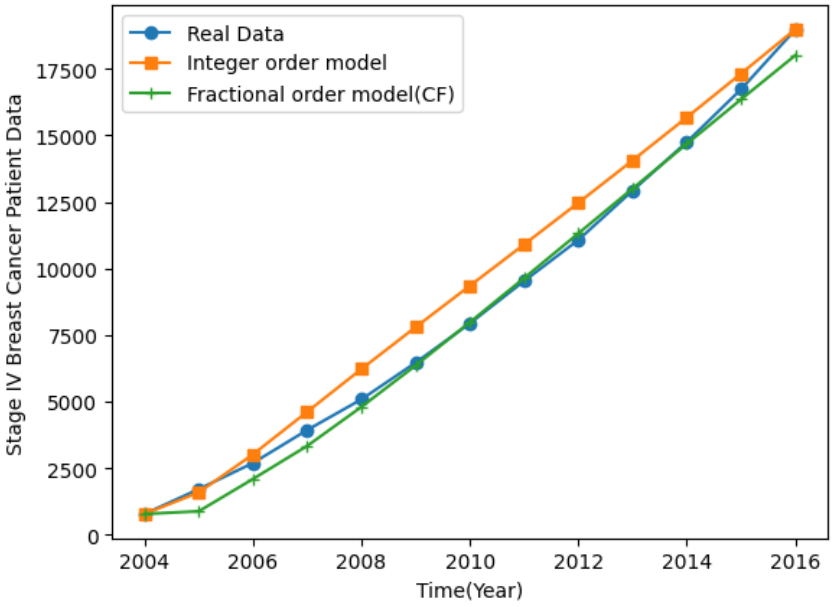

Figure 3.30: Comparison of the stage - IV Breast cancer patient incidences with the integer and the CFC model

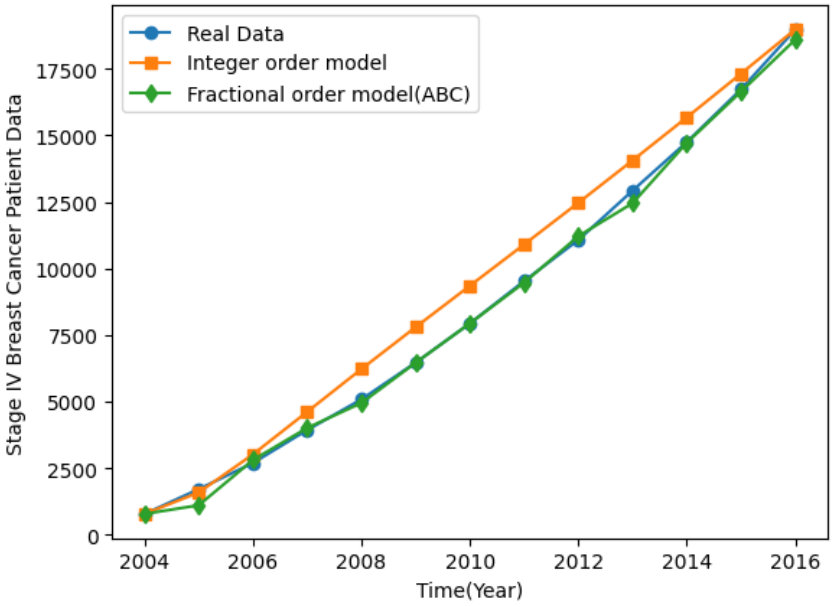

Figure 3.31: Comparison of the stage - IV Breast cancer patient incidences with the integer and the ABC model

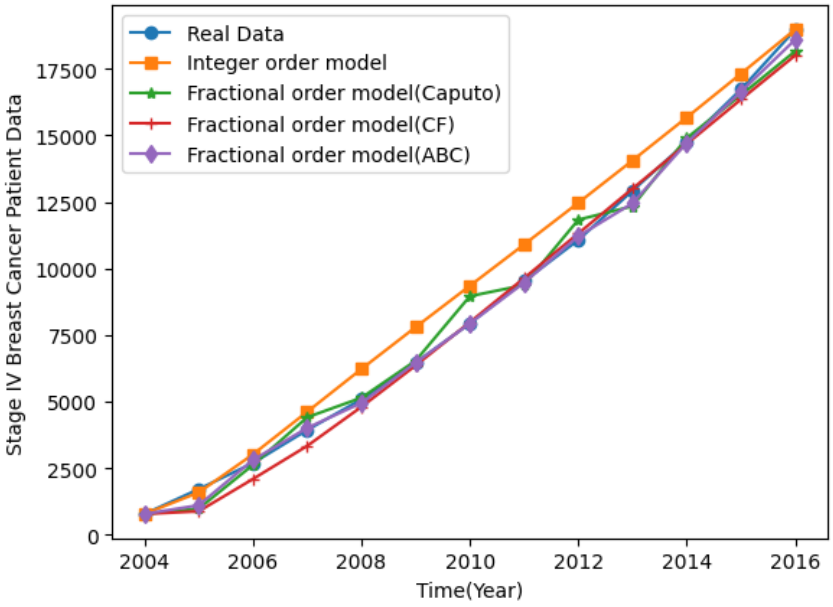

Figure 3.32: Collective comparison of the stage - IV Breast cancer patient incidences with the integer and the fractional order systems

3.4.9 Conclusion

In this study, we developed and analyzed fractional mathematical models to investigate the transmission dynamics of breast cancer, demonstrating the impact of various chemotherapy rates at different stages. We employed Caputo, CFC, and ABC operators commonly used in epidemiology, and validated our models using real statistical data. The research established the existence and uniqueness of solutions for the ABC fractional-order system using Krasnoselskii's and Banach fixed-point theory. Equilibrium points were analyzed for stability using the Routh-Hurwitz criterion. We also derived results for Ulam-Hyres stability and demonstrated that our proposed model is UH stable. System parameters were estimated using least squares error minimization. The results indicated that the ABC fractional-order system exhibited the highest performance rate (74.23 %) compared to the integer-order model, as well as the Caputo and CFC fractional-order models. Numerical simulations of both conventional and fractional-order systems were conducted using established convergent numerical schemes. Through graphical representations, we illustrated the impact of fractional order and the effect of chemotherapy rates on breast cancer dynamics.

The major findings of the present research analysis show that the ABC fractional-order operator, with its non-local and non-singular kernel in this particular epidemiological model, is one of the best choices among other existing fractional-order operators. This is attributed to its crossover behavior which surpasses index and power law, as well as the stretched exponential kernel. Our research aims to reduce the prevalence of cardiotoxicity among chemotherapy patients and improve their recovery rates, with implications for public health decision-making. Furthermore, by elucidating breast cancer mechanisms through the ABC operator, our study paves the way for targeted therapies to minimize cardiotoxicity, thereby improving patient outcomes and guiding future breast cancer treatment strategies. In future work, we aim to leverage our actual data-oriented estimated parameter values to anticipate breast cancer patients utilizing various models and fractional derivative operators. Using the provided data, certain optimal controls may also be added to the same model. Additionally, one can train the model using a machine learning approach.