Modelling the dynamics of Breast Cancer disease with hormone therapy and surgery controls

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Modelling the dynamics of Breast Cancer disease with hormone therapy and surgery controls

By

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Declaration

I, Akhona Ngalo 219751994, hereby declare that the dissertation for Master of Science in Applied Mathematics is my own work and that it has not previously been submitted for assessment or completion of any postgraduate qualification to another University or for another qualification.

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Abstract

In this study, we discussed a mathematical model that incorporates important interactions between normal cells, tumor cells, immune cells, and estrogen. The mathematical model was revised to include two control measures; namely surgery and hormone therapy to minimize the number of tumor cells. The model was mathematically analyzed with the premise that the two control measures are positive constants. Locally and globally analyses were performed using a variety of analytical methods to investigate the stability of the breast cancer model. Furthermore, an optimal control problem was formulated and used to determine the best strategy for reducing the number of tumor cells by incorporating hormone therapy and surgery, based on the well-known Pontryagin's Maximum Principle. The numerical results indicates combining both optimal control measures (surgery and hormone therapy) simultaneously is more efficacious than using single control measure separately in decreasing the number of tumor cells.

Acknowledgements

First and foremost, I would like to thank my supervisors, Dr W. Mbava and Mr P. Zembe, for their invaluable advice, ongoing support, and patience throughout my master's studies. Their vast knowledge and plenteous experience have constantly encouraged me in my academic research and daily life. I am eternally grateful to NRF funding for supporting me throughout my studies.

Dedications

I dedicate my dissertation work to all women who have died of breast cancer as well as those who are still battling with the disease. May God provide them with the strength they need to fight and win the battle against breast cancer. I pay special tribute to my grandmother Audrey Dladla and my aunt Lindiwe Luswazi, who died as a result of breast cancer. May their souls continue to rest in peace. A special gratitude to my family, whose words of encouragement and support kept me going. My sisters, Asavela, Amanda, Zanele, Mbali, and Nwabisa, who have never left my side and are very special to me, deserve special recognition. I also dedicate this to my friends who have supported me throughout the process.

Abbreviations

NTIE	:	**N**ormal **T**umor **I**mmune **E**strogen.
TFE	:	**T**umor **F**ree **E**quilibrium.
PMP	:	**P**ontryagin's **M**aximum **P**rinciple.
OCP	:	**O**ptimal **C**ontrol **P**roblem.
DCIS	:	**D**uctal **C**arcinoma **I**n **S**itu.
IDC	:	**I**nvasive **D**uctal **C**arcinoma.
ILS	:	**L**obular **C**arcinoma **I**nvasive.

Symbols

α_1	:	Per capita growth rate of normal cells.
α_2	:	Per capita growth rate of tumor cells.
ϕ_1	:	Natural death rate of normal cells.
ϕ_2	:	Natural death rate of tumor cells.
σ_1	:	Tumor formation rate as a result of DNA damage by excess estrogen.
σ_2	:	Immune suppression rate due to excess estrogen.
γ_1	:	Tumor cells death rate due to immune response.
γ_2	:	Interaction coefficient rate with immune response.
β	:	Rate of inhibition of normal cells.
δ	:	Natural death rate of estrogen.
Λ	:	Source rate of estrogen.
ρ	:	Immune response rate.
ω	:	Immune threshold rate.
ν	:	Assume constant of value of decay factor.
μ	:	Natural death rate of immune cells.
s	:	Source rate of immune cells.
$u_1(t)$	:	Control function (Surgery).
$u_2(t)$	:	Control function (Hormone therapy).
Ω	:	Model domain.
R_0	:	Basic reproduction number.
$\rho(A)$	:	Spectral radius of matrix A.
$\mathcal{J}$	:	Jacobian matrix.
λ	:	Eigenvalues of $\mathcal{J}$.
$\lambda(t)$	:	Adjoint variable.

Symbols (Continued)

$\mathcal{H}$	:	Hamiltonian.
U	:	Control set.
A	:	Control parameter associated with $u_1(t)$.
B	:	Control parameter associated with $u_2(t)$.
t_f	:	Final time.

Contents

List of Figures

Chapter 1

Introduction

1.1 Background

A disease can be either infectious or non-infectious. Infectious diseases are contagious illnesses that can spread from one person to the next. Non-infectious diseases are illnesses that do not spread to others and they restrain an individual who has contracted them. An example of a non-infectious disease is cancer.

Cancer is a genetic disease caused by changes in genes that controls how our cells function, specifically how they grow and divide. Cancer is defined the unmanageable growth of abnormal cells everywhere in the body. These abnormal cells are termed cancer cells [1]. Cancer cells can move from the location of formation in the body to distant locations in the body via the blood vessels or lymph system, where they exit the vessels to form a new tumor mass. This is referred to as Metastasis [2]. According to Discovery Health Medical Scheme [3], cancer causes more deaths in South Africa than HIV/AIDS, Tuberculosis and Malaria combined. The most common types of cancer include: breast cancer, lung cancer, prostate cancer, and skin cancer among others.

Among many cancer types, breast cancer is the second most common cancer in women, exceeded only by skin cancer. Breast cancer is the most common cancer in women around the world, accounting for 1.7 million cases in 2012 [4]. Breast cancer is a malignant (cancerous) tumor that begins in the breast cells, a group of cancer cells that can grow into surrounding tissues or spread (metastasize) to distant areas of the body.

There are several types of breast cancer, some of which are extremely rare. The vast majority of breast cancers are carcinomas, which are tumors that begin in the epithelial cells that line organs and tissues throughout the body. The type of breast cancer can also indicate whether or not the cancer has spread. Breast cancer is frequently divided into two types: non-invasive and invasive breast cancer. Non-invasive breast cancers are those that have not spread or invaded the normal breast tissues and are contained within the milk ducts or lobules. There are two types of non-invasive breast cancer: ductal carcinoma in situ and lobular carcinoma in situ. Ductal carcinoma in situ develops in the milk ducts of the breast and is non-invasive because it has not spread into the surrounding breast tissue. Lobular carcinoma in situ is a type of non-invasive breast cancer that develops in the lobules and it is non-invasive as it has not spread into any surrounding breast tissue [5]. The term "invasive breast cancer" refers to any type of breast cancer that has spread into the surrounding breast tissue [6]. There are two types of invasive breast cancer: invasive ductal carcinoma and invasive lobular carcinoma. The term "invasive" refers to cancer that has invaded or spread to the surrounding breast tissues. The most common type of breast cancer is invasive ductal carcinoma (IDC) . About 80% of all breast cancers are invasive ductal carcinomas (IDC) [5]. Invasive ductal carcinoma is a type of cancer that begins in the milk ducts of the breast, spreads through the duct lining, and spreads into the surrounding breast tissues. Invasive lobular carcinoma (ILC) is the second most common type after IDC. Invasive lobular carcinoma occurs when a cancer that begin in the milk-producing lobules of the breast has broken through the lining and spread into surrounding breast tissue[5].

The precise cause of breast cancer is unknown, but some factors make it more likely. Breast cancer is caused by three widely accepted phenomena: hormonal imbalance (excess estrogen and progesterone exposure appears to increase the risk of breast cancer), genetics (those with a family history of breast cancer) ,and environmental factors (alcohol consumption, poor diet, smoking, exposure to toxins, and so forth) [7]. The body uses estrogen to form the breast tissue, but too much estrogen causes cells to multiply out of control, leading to breast cancer [8].

The first symptoms of breast cancer usually appear as an area of thickened tissue in the breast or lump in the breast or armpit, sore breast, itchiness, and nipple discharge. Systemic therapies are drugs that can reach cancer cells through out the body and are used to treat breast cancer. Depending on the type of breast cancer, various drug treatments such as, hormone therapy, chemotherapy, immunotherapy, targeted therapy, and radiation therapy may be used. Although

we have treatments for breast cancer, they are not without side effects such as hair loss, vomiting, nausea, mouth sores, constipation, and fatigue. Surgery is an important component of breast cancer treatment because it removes the tumor with an operation known as breast conserving surgery or mastectomy [9]. Breast conserving surgery removes only the cancerous cells from the breast, whereas mastectomy removes the entire breast, including all of the breast tissue and, in some cases, other surrounding tissues. Although surgery is expensive, in South Africa it ranges from R50000 to R140000 and is the best treatment possible because it removes the entire breast or take out the potion with cancer cells [10]. Enderling *et al* [11] demonstrated that surgery alone will result in a tumor recurrence within medically reasonable time period of 5-10 years and they also predicted that the strayed tumor cells can be eradicated by an adjuvant. Adjuvant hormone therapy is now part of the standard treatment because surgery alone results in tumor recurrence in less than 10 years in 30% of cases. Adjuvant hormone therapy is frequently used to help reduce the risk of cancer following surgery. Hormone therapy is also used in breast cancer as anti-hormone or anti-estrogen to lower hormone levels in the body or to block hormone actions. Hormone therapy costs less than any other systematic therapy and it ranges from R650- R2500 per month [10].

Mathematical modeling can be used to analyze disease dynamics [12]. Kermack and McKendrick [13] demonstrated that mathematical modeling can be used solve epidemiology problems. The course of mathematical modeling of cancer was explained by Byrne [14]. Byrne's article shows charts progress in mathematical modeling of cancer over the past 50 years, highlighting the different theories that have been used to dissect and the insights that have arisen. Some studies specifically discussing mathematical model of breast cancer are as follows. De Pillis *et al* [15] presented a tumor growth competition model that includes both immune system response and drug therapy. They also used optimal control problem to find the best cancer treatment. Mufudza *et al* [16], investigated the role of estrogen as a risk factor on the dynamics of breast cancer. They created a probabilistic mathematical model to demonstrate the general dynamics of breast cancer with immune response. They developed a four-population model that incorporates tumor cells, host cells, immune cells and estrogen. In their study, they concluded that taking hormonal birth controls increases the possibility of breast cancer development and their results shows the negative relationship of estrogen and tumor cell development. Segun *et al* [17] used nutritious diet as a control on tumor cells and implementing time-dependent control parameters predicted on the premise

that there is an interaction between normal cells and tumor cells caused by mutation in DNA as a result of excess estrogen in the body. They used optimal control to investigate the effects of ketogenic diet and anti-cancer drugs on tumor cells. Their findings revealed that the development of tumor cells is influenced by the ammount of excess estrogen in the body.

In this study, we will extend the models of Mufudza *et al* [16] and Segun *et al* [17] by incorporating time-dependent control parameters (hormone therapy and surgery) based on the assumption that there is an interaction between normal cells and tumor cells that is due to mutated DNA in the body as a result of excess estrogen. Though Mufudza *et al* demonstrated that high estrogen levels have effects on breast cancer development when they are high and Segun *et al* used chemotherapy to reduce tumor cells and ketogenic diet to control estrogen levels, our model differs from their models because it incorporates surgery and hormone therapy to control the tumor cell growth. We will use the control surgery to remove cancer cells and hormone therapy as adjuvant to kill any remaining cancer cells and prevent the disease from returning. To control estrogen levels we will use hormone therapy. The goal is to keep the patient healthy while killing tumor cells. We will apply Optimal Control Problem to surgery and hormone therapy to investigate if they can assist in minimizing the tumor population and estrogen levels by the end of the treatment period while maintaining the normal cells and immune cells above the required level.

1.2 Problem statement

Breast cancer is a worldwide problem and the most common cancer amongst women comprising 23% of the female cancer [18]. Breast cancer is the leading cause of death in women worldwide and is expanding especially in developing countries where most of cases are discovered in late stages[19]. Breast cancer malignant growth influences roughly 27 out of 100 000 women in South Africa and record for 16% of disease passing against women [20]. In spite of the fact that various treatments are accessible for battling cancer, a mix of medication might be an answer for this issue. It is well known that surgery can not treat breast cancer alone but it needs systemic therapies. In this study we will investigate the use of optimal controls surgery and hormone therapy to reduce tumor cells and estrogen levels.

1.3 Aim

The aim of this study is to investigate if hormone therapy and surgery as control strategies can reduce breast cancer.

1.4 Research objectives

The following are the primary objectives of this study:

1. To formulate the Normal cells, Tumor cells, Immune response and Estrogen (NTIE) model for breast cancer, incorporating surgery and hormone therapy as interventions.
2. To perform mathematical analysis of the NTIE model and obtain epidemic thresholds.
3. To formulate NTIE optimal control problem and investigate the best way to apply hormone therapy and surgery in order to reduce the cancer cells at minimal cost.

1.5 Methodology

A normal cells (N), tumor cells (T), immune cells (I), and estrogen (E) model would be formulated, and it is one of the models used to describe the epidemiology of non-infectious diseases. This computes the number of normal cells, tumor cells, immune cells, and estrogen in a volume(cm^3). The model represented by a dynamical system of non-linear ordinary differential equations will be analyzed numerically to find the epidemic threshold and equilibrium points. The proposed model will then be reformulated in the optimal control framework to select the best control strategy for breast cancer in order to reduce the tumor cells at minimal cost. Finally, numerical simulations will be carried out in MATLAB.

1.6 Justification

There have been mathematical models of breast cancer, and in this study we will extend the existing model of Mufudza *et al* and Segun *et al* [16, 17]. This study, combined with other breast cancer models, will pave the way for broader attempts to reduce tumor growth and prevent this disease in our communities. Death as a result of breast cancer may hamper the country's productivity and hence is a threat to socio-economic development. This study will therefore be of paramount importance in aiding in the control of breast cancer.

Chapter 2

Literature review

In this chapter, we review the literature on breast cancer and intervention measures for combating breast cancer such as surgery and hormone therapy. We also review mathematical models of breast cancer including optimal control models involving the interventions and cancer research papers that are relevant to this dissertation.

2.1 Biology of normal breast and breast cancer

In this section, we consider the anatomy of the breast as well as the position of the cancer when it develops within the breast. This is bound to give a clearer understanding of the cells involved when breast cancer develops.

The mammary glands, which are positioned on the front of the chest, are medically known as the breasts. The breast is made up of connective tissue, fat, and breast tissue, which contains the milk-producing glands [21]. Each breast has 15 to 20 sections called lobes arranged in a circular fashion. The breast's size and shape are determined by the fat (subcutaneous adipose tissue) that covers the lobes. Each lobe is made up of several lobules, each of which has a little bulb-like gland or sac at the end that produces milk in response to hormonal signals. Ducts connect the lobes, lobules, and glands in nursing mothers. The darker pigmented area around the nipple is known as the areola. The gaps between lobules and ducts are filled with fat. There are no muscles in the breast, but muscles lie under each breast and cover the ribs [22]. The following image

is the anatomy of a normal breast [23]:

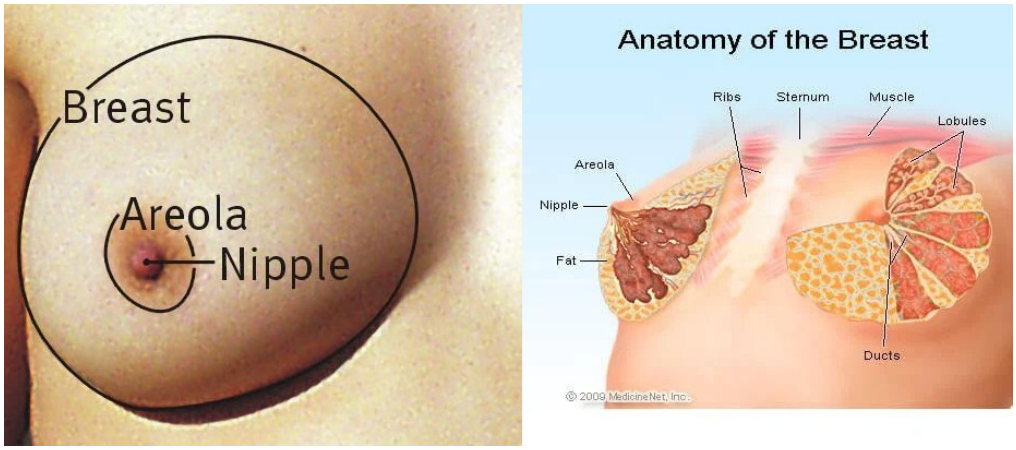

Figure 2.1: Anatomy of the breast [5]

The breast is responsive to a complex interplay of hormones that cause the tissue to develop, enlarge and produce milk. Estrogen, progesterone, and prolactin are the three principal hormones that affect the breast and cause glandular tissue in the breast and uterus to change over the menstrual cycle [23]. Some types of breast cancer are caused by hormones such as estrogen and progesterone. Breast cancer start when cells in the breast (such as ducts and lobules) begin to grow abnormally.

There are various forms of breast cancer that are named after the parts of the breast where they begin. The type of breast cancer might also indicate whether or not the cancer has spread. In situ breast cancer (ductal carcinoma in situ, or DCIS) is a type of cancer that begins in a milk duct but does not spread to the rest of the breast tissue. Any sort of breast cancer that has expanded (invaded) into the surrounding breast tissue is referred to as invasive breast cancer. DCIS is the earliest form of breast cancer. DCIS occurs when abnormal cells are found in the milk ducts. DCIS is non-invasive, which implies it has not spread outside of the milk ducts to any surrounding breast tissue [24]. The most frequent kind of breast cancer is Invasive Ductal Carcinoma (IDC). Invasive indicates that the abnormal cells have migrated beyond the ducts (small tubes that carry milk to the nipples during nursing) and into the surrounding breast tissue. Invasive Lobular Carcinoma (ILC) is a type of breast cancer in which abnormal cells have grown outside the walls of the lobules, which generate milk that empties into the milk ducts and the surrounding breast tissue. Metastatic breast cancer is the breast cancer that has spread to other parts of the body. The brain, liver, bones and lungs are the common organs where breast cancer metastasizes. Breast cancer cells spread from the original tumor through the blood stream and the lymphatic sys-

tem. Inflammatory Breast Cancer is a type of aggressive breast cancer that normally presents as skin reddening and swelling rather than a recognizable tumor. This kind of breast cancer is extremely rare, accounting for about 1% of all breast cancer incidences in the United States [25]. The graphic below depicts the various forms of breast cancer [26]:

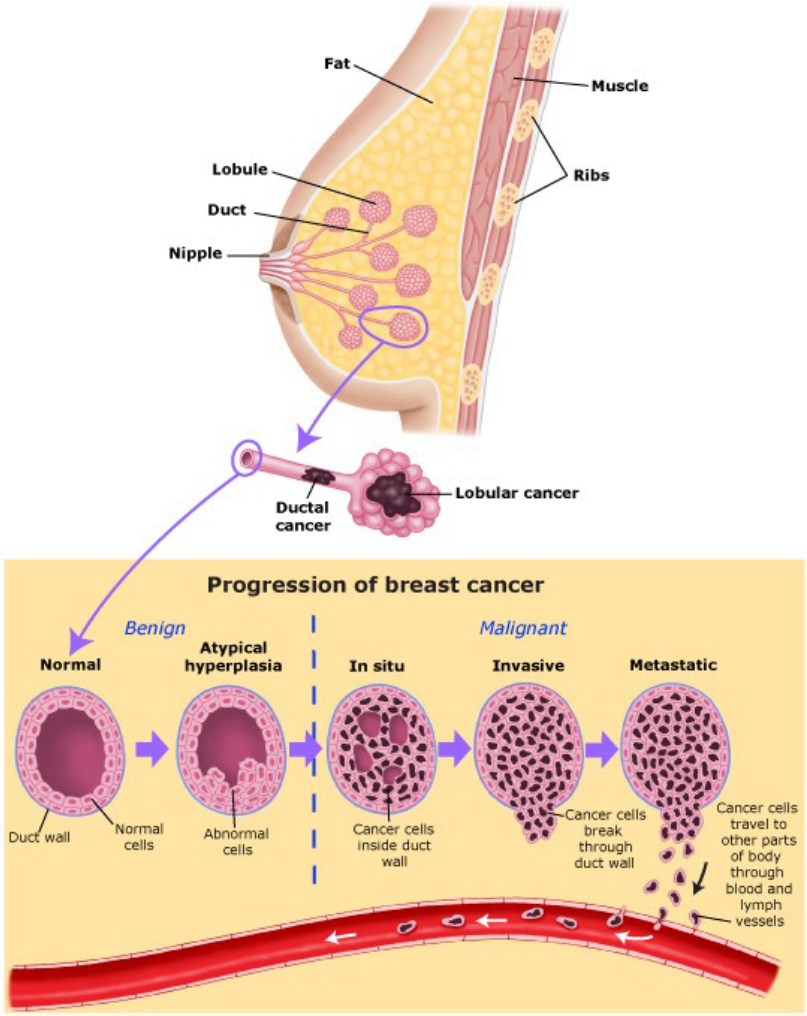

Figure 2.2: A biological scenario of breast cancer progression [5]

2.2 Interventions of breast cancer

The function of all cancer treatments is to destroy cancer cells while also distinguishing between cancerous and healthy cells. There are several types of cancer treatments that includes: surgery, chemotherapy, hormone therapy, and so on. Here we give a review of surgery and hormone therapy as they are the most relevant to the aims of this study [27].

Surgery is a type of medical treatment in which an individual's body is cut open so that a doctor can repair, remove, or replace a diseased or damaged part. Breast cancer surgery is an important part of breast cancer treatment that involves surgically removing the cancer [28]. For several decades, surgery has been the primary treatment for breast cancer. Breast cancer surgery includes a variety of procedures, including:

- Surgical removal of the entire breast (mastectomy)
- A portion of the breast tissue is removed during surgery (lumpectomy)
- Surgical removal of nearby lymph nodes

The best breast cancer surgery is determined by the size and stage of the cancer [29]. Several trials over the last several decades have resulted in a shift away from radical approaches and toward less extreme, breast-conserving procedures. Adjuvant or neoadjuvant therapy, such as hormonal therapy, chemotherapy, and or radiation therapy, is frequently used in conjunction with surgical treatment of breast cancer [30].

Hormone therapy is a cancer treatment that slows or stops the the reproduction cancer cells that use hormones. Hormone therapy is frequently used as an adjuvant therapy to help reduce the risk of cancer recurrence after surgery, but it can also be used as a neoadjuvant treatment. Neoadjuvant therapy is a treatment used to shrink a tumor before the main treatment, which is usually surgery. The variety of methods for blocking estrogen's effect or lowering estrogen levels are used to treat hormone receptor-positive breast cancers [31]. Hormonal therapy, on the other hand, is ineffective in patients whose tumors are both estrogen receptor (ER) and progestin receptor (PR) negative. According to studies, women who receive at least 5 years of adjuvant tamoxifen therapy after surgery for early-stage ER-positive breast cancer have a lower risk of breast cancer recurrence, including a new breast cancer in the opposite breast, and a lower risk of death at 15 years [32].

2.3 A review of mathematical models

Kermack and McKendrick [16] showed that mathematical modeling is useful in solving the problem of epidemiology. Models in mathematics are frequently coupled systems of governing differential equations that describe the dynamics of each of the interacting component cells. Specifically, the interactions between tumor growth and the immune system is often described using a system of coupled differential equations with formulated initial conditions. These equations include nonlinear interactions and do not often admit an exact solution, so they require computational methods to solve them [33].

Pranav *et al* [34] developed a mathematical model that combines an important interactions between tumor cells and cells in the immune systems including natural killer cells, dendritic cells, and cytotoxic $CD8^{+}T$ cells combined with drug delivery to these cell sites. They described these interactions via system of ordinary differential equations that are solved numerically. They also performed a stability analysis to determine conditions for tumor-free equilibrium to be stable. They also studied the influence of proliferation rates and drug interventions in the dynamics of all the cells involved. Their finding showed that the combination of chemotherapy and immunotherapy intervention reduces tumor growth greatly after 10-20 days.

In order to investigate the efficacy of chemotherapy in eradicating cancer cells, Phino *et al* [35] created a mathematical model of chemotherapy for tumor treatment. In their analysis, they demonstrated the parameter space region in which cancer cells can be eliminated. They also proved the effects of varying drug infusion rates on cell concentration levels. They presented their numerical results in the bifurcation diagram in terms of infusion rate and the tumor cells were eradicated at the end of the treatment.

Tian [36] created and examined a basic mathematical model of virotherapy. They considered a tumor populations that were not infected, tumor cell populations that were infected, and free virus populations. Their study discovered two threshold burst size values: below one, the tumor always develops to its maximum size, whereas above the other, one or three families of periodic solutions arising from Hopf bifurcations exist. The study's findings confirmed that when the burst size is large enough, a tumor's cell count can be reduced to undetectable levels.

Manju emph *et al* [37] proposed a framework for describing the interaction of cancer and immune cells during immunotherapy based on a qualitative analysis of a system of nonlinear ordinary differential equations. Their mathematical analysis of the model equation was performed in terms of the boundedness of solutions, the nature of equilibria, and their local and global study. They used numerical analysis to back up their analytic findings. They discovered that immunotherapy-treated lymphocyte proliferation significantly reduces the cancer cell population. They concluded that if cancer is immunogenic, that is, if cancer cells have distinct surface markers known as tumor specific antigens, the cancer cell population can be easily managed. In addition, the presence of antigenic cancer cells causes a time delay in the production of immuno-agents, and the critical value of the delay for which the stability switch occurs is determined.

Sharma *et al* [38] investigated a tumor growth model that includes tumor immune interactions as well as chemotherapeutic drugs. They investigated two types of immune cells: helper (resting) T-cells, which stimulate CTLs and convert them into active (hunting) CTL cells, and active (hunting) CT cells, which attack, destroy, or ingest tumor cells. Tumor cells, active CTL cells, helper T-cells, and chemotherapeutic drugs are divided into four compartments in their model. In relation to the model, they devised an optimal control problem in order to reduce the number of tumor cells and the administration of chemotherapeutic drugs. They discovered that the best control is far more effective at reducing tumor cell counts to near zero. Overall, their numerical analysis indicates that a burst of treatment at the start is beneficial.

De Pillis *et al* [15] presented a tumor growth competition model that incorporates both immune system response and drug therapy. Their research is based on a four-population model, which includes tumor cells, host cells, immune cells, and drug interaction. They looked for target basins of attraction by analyzing the stability of the drug-free equilibrium in relation to the immune response. The goal was to simulate the asynchronous tumor-drug interaction known as "Jeff's phenomenon" qualitatively. This asynchronous response behavior is successfully generated by the developed model. Another goal was to find treatment protocols that could be used to improve standard pulsed chemotherapy regimens. They used optimal control theory with constraints and numerical simulations to develop new therapy protocols, which they then compared to traditional pulsed for periodic treatment. Over time, the optimal control-generated therapies cause larger oscillations in the tumor population. However, by the end of the treatment period, the total tumor size is smaller than with traditional pulsed therapy, and the normal cell population experiences

almost no oscillations. The reviewed studies has given insight into the modeling of breast cancer and that there are methods that can be used to develop breast cancer model. Overall, mathematical modeling is a valuable tool for studying breast cancer and developing new treatments. Mathematical models helps to understand the complex dynamics of tumor growth and interactions between cancer cells and the normal cells in the body. While there are still many challenges to overcome in the study of breast cancer, mathematical modeling offers a promising avenue for advancing our understanding of this disease and improving patient outcomes.

Chapter 3

NTIE Model formulation

3.1 Introduction

In this chapter, we present a mathematical model that extends existing breast cancer models [16, 17] to discuss the cell population interaction. The mathematical model subdivides the total population $H(t)$ of cells into four compartments: normal cells (N), tumor cells (T), immune cells (I) and estrogen (E). The normal cells compartment (N) is a type of epithelial cell that makeups breast tissue. The cells separate and die naturally as they have unaltered DNA which controls all cells activities. The tumor cells compartment (T) represents a class of breast cancer cells with damaged DNA. The immune cells compartment (I) represents the natural killer and CD+8 T cells. Estrogen is a natural steroid hormone, found in both women and men. Estrogen also helps in development of breasts, but an increase of estrogen levels can lead to growth of tumor cells. Estrogen goes about as a cancer-causing agent by legitimately harming DNA, driving solid epithelial cells to have a higher probability of malignant conversion.

3.2 Mathematical model

The $NTIE$ breast cancer model is proposed, the total population is divided into four compartments as normal cells (N), tumor cells (T), immune cells (I) and estrogen cells (E).

3.2.1 Model assumptions

We consider the following assumptions when developing the proposed model:

1. In this model, breast cancer is assumed to be non-invasive.
2. The tumor cells are caused by excess estrogen in the body and damaged cells.
3. Estrogen cells are produced by the ovaries and consumption of birth controls.

3.2.2 Model description

The variable $N(t)$ is used to denote normal cells. Normal cells can either be destroyed or grown utilizing the stable DNA that precludes all activities of the cell. We also assume that normal cells and tumor cells compete for space, nutrients and other resources. The normal cells are represented by the non-linear differential equation:

$$\frac{dN}{dt} = (\alpha_1 - \phi_1 N)N - \beta NT - (1-k)\sigma_1 NE.$$

The first term represents the logistic growth of normal cells, with α_1 representing the intrinsic rate of growth of normal cells and ϕ_1 is a measure of the effect of interaction of normal cells (fighting for space, nutrients, etc). β represents the rate at which normal cells interact with tumor cells, causing normal cells to be inhibited. The last term represents normal cell reduction due to estrogen interaction, where k denotes the efficacy of hormone therapy with $0 \leq k < 1$ if $k = 0$ denotes no intervention. σ_1 denotes the reduction of normal cells as a results of an encounter with estrogen.

The dependent variable $T(t)$ shows how tumor cells emerge; the tumor cell population is assumed to grow logistically in the absence of immune cells and estrogen. The tumor cells are represented by the non-linear differential equation:

$$\frac{dT}{dt} = ((1-d)(1-k)\alpha_2 - \phi_2 T)T + (1-k)\sigma_1 NE - \gamma_1 IT.$$

The first term represents tumor cell growth that is limited by the rate of parameter d and k (surgery and hormone therapy respectively), ϕ_2 denotes death rate of tumor cell due to competition among

themselves, while γ_1 is the rate of loss of tumor cells due to an encounter with immune cells. Excess estrogen causes DNA mutations, which populate the tumor cells $\sigma_1 NE$.

The dependent variable $I(t)$ is represented in the form of NK cells and CD8+ T cells. The growth of immune cells may be stimulated by the presence of the tumor, and they can destroy tumor cells via kinetics process. The immune cells are presented by the non-linear differential equation:

$$\frac{dI}{dt} = s + \rho\frac{IT}{\omega + T} - \gamma_2 IT - \mu I - (1-k)\sigma_2\frac{IE}{\upsilon + E}.$$

The first term represents the constant source of immune system. The second term represents non-linear growth for immune response, where ρ is the rate of immune response and ω is the immune threshold. The parameter γ_2 is the rate at which immune response is inactivated due to interacting with tumor cells, and μ represents the natural death rate of immune cells. The last term denotes a limited rate at which estrogen suppresses immune cells activation, σ_2 is the rate of immune suppression due to estrogen presente and υ is the estrogen threshold rate.

The ovaries produce estrogen, and more estrogen is introduced into the body through birth controls. The estrogen compartment is represented by the non-linear differential equation:

$$\frac{dE}{dt} = (1-k)\Lambda - \delta E.$$

Λ denote constantly replenishing excess estrogen and δ is the rate at which estrogen is being washed out of the body system.

3.2.3 Model equations

The following figure is a flow diagram for the model mentioned above:

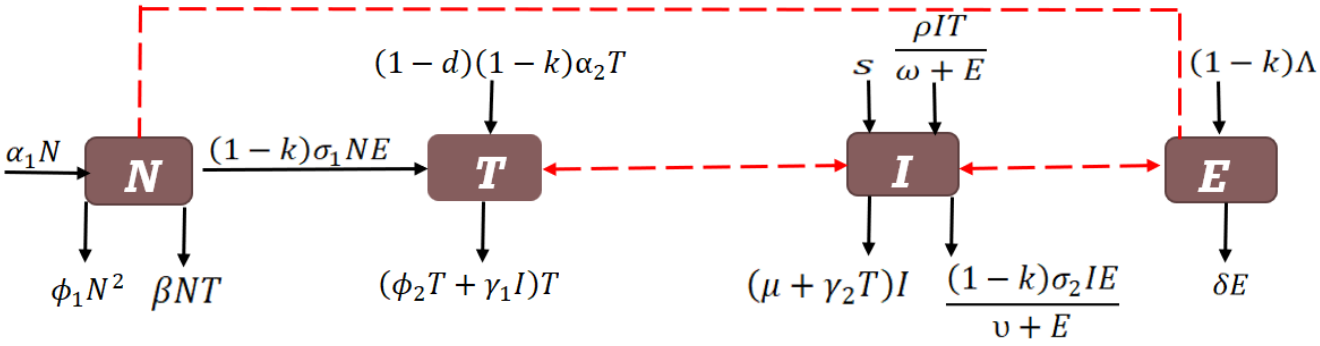

Figure 3.1: Schematic diagram for breast cancer model

Dashed red arrow in the above represents the interactions between compartments and black lines represents addition and also subtraction from the compartment respectively. For simplicity the independent variable t shall be omitted for all the states, thus for example $N(t) = N$. The model depicted in Figure 3.1 is described by the following system of differential equations:

$$\frac{dN}{dt} = (\alpha_1 - \phi_1 N)N - \beta NT - (1-k)\sigma_1 NE, \tag{3.1}$$

$$\frac{dT}{dt} = ((1-d)(1-k)\alpha_2 - \phi_2 T)T + (1-k)\sigma_1 NE - \gamma_1 IT, \tag{3.2}$$

$$\frac{dI}{dt} = s + \rho\frac{IT}{\omega + T} - \gamma_2 IT - \mu I - (1-k)\sigma_2\frac{IE}{\upsilon + E}, \tag{3.3}$$

$$\frac{dE}{dt} = (1-k)\Lambda - \delta E, \tag{3.4}$$

where $N(0) = N_0 \geq 0, T(0) = T_0 \geq 0, I(0) = I_0 \geq 0, E(0) = E_0 \geq 0$.

3.3 Model Analysis

3.3.1 Positivity and boundedness of solutions

In order to retain the biological validity of the model, we must prove that solutions to the system of differential equations are positive and bounded for all values of time. Since the human body is

made up of a finite number of cells, the population must remain limited. Furthermore, boundedness and positivity outline that once tumor started, it is conceivable that the population of the cancer cells will proceed to exist beneath the detectable threshold without doing critical harm [39]. The next step in analyzing our model will be to prove positivity and boundedness for the system of differential equation.

The model equations (3.1)-(3.4) describe cell population and therefore, it is very important to prove that all state variables $N(t), T(t), I(t)$, and $E(t)$ are non-negative for all time t. The system of equations (3.1)-(3.4) has an initial condition by $N(0) = N_0 \geq 0, T(0) = T_0 \geq 0, I(0) = I_0 \geq 0, E(0) = E_0 \geq 0$. Based on the biological finding, the system of equation (3.1)-(3.4) will be studied in the following region such as:

$$\Omega = \left\{(N, T, I, E) \in \mathbb{R}^4_+\right\}. \tag{3.5}$$

The following theorem assures that the system of equation is well posed such that solutions with non-negative initial conditions remain non-negative for all $0 < t < \infty$ and therefore makes the variable biological meaningful. Hence, we have the following results:

Theorem 3.1 *The solution of the system with initial conditions* $N(0) = N_0 > 0, T(0) = T_0 \geq 0, I(0) = I_0 > 0, E(0) = E_0 \geq 0$ *is bounded for all* $t > 0$.

Proof. We must prove that for all $t > 0$, $N(t), T(t), I(t)$, and $E(t)$ will be bounded and we know that all constants used in the system are positive. We begin by writing the equation (3.1) as follows, without losing it's generality:

$$\frac{dN}{dt} \leq N(\alpha_1 - \phi_1 N),$$
$$\frac{dN}{N(\alpha_1 - \phi_1 N)} \leq dt.$$

Solving the above ordinary differential inequality expression using partial fractions, we get this,

$$\int \left(\frac{\frac{1}{\alpha_1}}{N} + \frac{\frac{\phi_1}{\alpha_1}}{\alpha_1 - \phi_1 N} \right) dN = \int dt.$$

Integration and using the initial condition we get,

$$N(t) \leq \frac{\alpha_1}{\phi_1 + \frac{\alpha_1 - \phi_1 N_0}{N_0} e^{-\alpha_1 t}}, \forall t \geq 0.$$

Thus

$$\lim_{t\longrightarrow\infty} N(t) \leq \frac{\alpha_1}{\phi_1}, \tag{3.6}$$

hence, $N(t)$ is bounded at $\frac{\alpha_1}{\phi_1}$. Writing the equation (3.2) without losing it's generality as follows:

$$\frac{dT}{dt} \leq (1-d)(1-k)\alpha_2 T - \phi_2 T^2$$

The method in the first differential inequality can be used to solve the above inequality. As a result, we have:

$$T(t) \leq \frac{(1-d)(1-k)\alpha_2}{\phi_2 + \frac{(1-d)(1-k)\alpha_2 - \phi_2 T_0}{T_0} e^{-(1-d)+(1-k)\alpha_2 t}}, \forall t \geq 0.$$

Thus

$$\lim_{t\to\infty} T(t) \leq \frac{(1-d)(1-k)\alpha_2}{\phi_2}, \tag{3.7}$$

hence, $T(t)$ is bounded at $\frac{(1-d)(1-k)\alpha_2}{\phi_2}$. Once more, we present the equation (3.3) as follows:

$$\frac{dI}{dt} \leq s + \frac{\rho I T}{\omega + T} - \mu I,$$

applying proper fraction, give $\rho\frac{T}{\omega+T} \leq \rho \times 1$ then

$$\frac{dI}{dt} + (\mu - \rho)I \leq s,$$

solving using integrating factor $H = e^{\int(\mu-\rho)dt}$, we have

$$I(t) \leq \frac{s}{\mu-\rho} + I_0 e^{-(\mu-\rho)t},$$

thus

$$\lim_{t\to\infty} I(t) \leq \frac{s}{\mu-\rho}, \tag{3.8}$$

hence, $I(t)$ is bounded at $\frac{s}{\mu-\rho}$ under the condition that $\mu > \rho$, when $\mu <= \rho$ there is negative population which is unrealistic. Finally, we solve the equation (3.4),

$$\frac{dE}{dt} = (1-k)\Lambda - \delta E,$$
$$\frac{dE}{dt} + \delta E = (1-k)\Lambda,$$

integrating using factor, with $X = e^{\delta t}$, we have

$$E(t) = \frac{(1-k)\Lambda}{\delta} + Ce^{-\delta t},$$

from the initial condition we have $E(0) = E_0$ and solving for C we get,

$$E(t) = \frac{(1-k)\Lambda}{\delta} + E_0 e^{-\delta t},$$

thus

$$\lim_{t\to\infty} E(t) \leq \frac{(1-k)\Lambda}{\delta}, \tag{3.9}$$

hence, $E(t)$ is bounded by $\frac{(1-k)\Lambda}{\delta}$, hence all solutions in the system are bounded. □

Theorem 3.2 *Let the state variables be such that* $N(0) = N_0 \geq 0, T(0) = T_0 \geq 0, I(0) = I_0 \geq 0$, $E(0) = E_0 \geq 0$ *All solutions* $N(t), T(t), I(t), E(t)$ *of the system (3.1)-(3.4) are non-negative in* $\mathbb{R}^4_+$ *for all* $t \geq 0$. *For the model system (3.1)-(3.4), the region* Ω *is positively invariant and all solutions starting in* Ω *remain in* Ω.

Proof. The equation (3.1) can be expressed as a differential inequality without losing it's generality,

$$\frac{dN}{dt} \geq -(\phi_1 N + \beta T + (1-k)\sigma_1 E)N.$$

Since $T(t)$ and $E(t)$ are bounded, let

$$\sup T(t) = \frac{(1-d)(1-k)\alpha_2}{\phi_2} \text{ and } \sup E(t) = \frac{(1-k)\Lambda}{\delta}$$

respectively. Taking $\beta(\frac{(1-d)(1-k)\alpha_2}{\phi_2}) + (1-k)^2\sigma_1\frac{\Lambda}{\delta} = C$ proven in the previous theorem. Then we have

$$\frac{dN}{dt} \geq -(\phi_1 N + C)N.$$

Using partial fractions to solve the above expression, we get:

$$\int \left(\frac{\frac{1}{C}}{N} - \frac{\frac{\phi_1}{C}}{\phi_1 N + C} \right) \geq -\int dt.$$

By integrating over $[0, t]$, we obtain

$$N(t) \geq \frac{C}{\frac{C+\phi_1 N_0}{N_0} e^{-Ct} - \phi_1} \tag{3.10}$$

since $N(0) \geq 0$, we have $N(t) \geq 0$ for all $t \geq 0$ and $C = \beta(\frac{(1-d)(1-k)\alpha_2}{\phi_2}) + \frac{(1-k)^2\sigma_1\Lambda}{\delta}$. After removing the positive terms from the differential equation (3.2), we obtain the following differential inequality,

$$\frac{dT}{dt} \geq -(\phi_2 T + \gamma_1 I)T$$

Since $I(t)$ bounded, let $\sup I(t) = \frac{s}{\mu-\rho}$. Taking $\frac{\gamma_1 s}{\mu-\rho} = K$. Hence

$$\frac{dT}{dt} \geq -(\phi_2 T + K)T$$

Integration over $[0,t]$ and also using the statement in the solution above gives

$$T(t) \geq \frac{K}{\frac{K+\phi_2 T_0}{T_0} e^{-Kt} - \phi_2},$$

if $T(0) \geq 0$, then we have $T(t) \geq 0$ for all $t \geq 0$, $\frac{K+\phi_2 T_0}{T_0} e^{-Kt} > \phi_2$ and $K = \frac{\gamma_1 s}{\mu - \rho}$. The equation (3.3) can be expressed as a differential inequality without losing generality and is written as

$$\frac{dI}{dt} \geq -\Big(\mu + \gamma_2 T + \frac{(1-k)\sigma_2 E}{\nu + E}\Big) I.$$

Since E and T are bounded, let $\sup E(t) = \frac{(1-k)\Lambda}{\delta}$ and $\sup T(t) = \beta(\frac{(1-d)(1-k)\alpha_2}{\phi_2})$ respectively. Let $A = \mu + \gamma_2 \frac{(1-d)(1-k)\alpha_2}{\phi_2}) + \frac{(1-k)\sigma_2 e}{\nu+e} \frac{(1-d)(1-k)\alpha_2}{\phi_2})$, then we have

$$\frac{dI}{dt} \geq -AI.$$

By integrating over$[0,t]$, we obtain

$$I(t) \geq I_0 e^{-At},$$

again if $I(0) \geq 0$, then we have $I(t) \geq 0$ for all $t \geq 0$ and $A = \mu + \gamma_2 \frac{(1-d)(1-k)\alpha_2}{\phi_2}) + \frac{(1-k)\sigma_2 e}{\nu+e} \frac{(1-d)(1-k)\alpha_2}{\phi_2})$. Finally, after removing the positive term that appears on the right hand side of the equation (3.4), can be expressed as a differential inequality without losing generality,

$$\frac{dE}{dt} \geq -\delta E,$$
$$\frac{dE}{E} \geq -\delta.$$

Integration over $[0,t]$ gives,

$$E(t) \geq E_0 e^{-\delta t}.$$

Also, since $E(0) \geq 0$, we have $E(t) \geq 0$ for all $t \geq 0$. Hence, the solution $(N(t), T(t), I(t), E(t))$ is non-negative for non-negative initial conditions. Thus, all solutions of model (3.1)-(3.4) are non-negative and bounded in the following region:

$$\Omega = \left\{(N,T,I,E) \in \mathbb{R}^4_+ : N \leq \frac{\alpha_1}{\phi_1}, T \leq \frac{(1-d)(1-k)\alpha_2}{\phi_2}, I \leq \frac{s}{\mu - \rho}, E \leq \frac{(1-k)\Lambda}{\delta}\right\}, \qquad (3.11)$$

Ω is positively invariant. This means that every solution with initial conditions in Ω remains Ω $\forall t \geq 0$ that is, the model (3.1)-(3.4) is well posed. □

3.3.2 The equilibrium points of the system

A stable condition that does not change over time is referred to as an equilibrium point. The equilibrium point occurs when all of the ordinary differential equations in the system are simultaneously zero, that is, when:

$$\frac{dN}{dt} = \frac{dT}{dt} = \frac{dI}{dt} = \frac{dE}{dt} = 0.$$

The model system concedes six equilibrium points, in which there are four dead equilibria, one tumor-free equilibrium point, and one co-existing equilibrium point, and since cell populations are non-negative and real, therefore, all parameters and variables are positive.

- Tumor-free equilibrium (TFE) point: in this category , the tumor cell population is zero, but other cells survive. To find TFE, we let $T = 0$, and we have the following system of equations:

$$\begin{aligned} &(\alpha_1 - \phi_1 N)N - (1-k)\sigma_1 NE = 0, \\ &s - \mu I - (1-k)\sigma_2 \frac{IE}{\nu + E} = 0, \\ &(1-k)\Lambda - \delta E = 0. \end{aligned} \tag{3.12}$$

  Solving these system of equations simultaneously from the third equation in the system (3.12) solving for E we get

$$E = \frac{(1-k)\Lambda}{\delta}. \tag{3.13}$$

  Solving the first equation in the system (3.12), we have

$$\begin{aligned} (\alpha_1 - \phi_1 N)N - (1-k)\sigma_1 NE = 0, \\ N = 0, N = \frac{\alpha_1 - (1-k)\sigma_1 E}{\phi_1}. \end{aligned}$$

  Substituting for E in the above equation we get

$$N = \frac{\alpha_1 \delta - (1-k)^2 \sigma_1 \Lambda}{\delta \phi_1}. \tag{3.14}$$

  Solving the second equation in the system (3.12)

$$\begin{aligned} s = \mu I + (1-k)\sigma_2 \frac{IE}{\nu + E}, \\ I = \frac{s(\nu + E)}{\mu(\nu + E) + (1-k)\sigma_2 E}. \end{aligned}$$

Substituting E in the above equation we get,

$$I = \frac{s(\nu\delta + (1-k)\Lambda)}{\mu(\nu\delta + (1-k)\Lambda) + (1-k)^2\sigma_2\Lambda}. \tag{3.15}$$

The Tumor-free equilibrium (TFE) point is given by:

$$\mathcal{E}_0 = \left(\frac{\alpha_1\delta - (1-k)^2\sigma_1\Lambda}{\delta\phi_1}, 0, \frac{s(\nu\delta + (1-k)\Lambda)}{\mu(\nu\delta + (1-k)\Lambda) + (1-k)^2\sigma_2\Lambda}, \frac{(1-k)\Lambda}{\delta}\right), \tag{3.16}$$

tumor-free equilibrium $\mathcal{E}_0$ is positive if $\alpha_1\delta > (1-k)^2\sigma_1\Lambda$.

- Case (i) A dead equilibrium point exists when both normal and tumor cell populations have died off and then we left with the following system of equations,

$$\begin{aligned} &s - \mu I - (1-k)\sigma_2\frac{IE}{\nu + E} = 0, \\ &(1-k)\Lambda - \delta E = 0. \end{aligned} \tag{3.17}$$

Solving the equations in (3.17) simultaneous, we obtain case (i) equilibrium as follows,

$$\mathcal{E}_{d1} = \left(0, 0, \frac{s(\nu\delta + (1-k)\Lambda)}{\mu(\nu\delta + (1-k)\Lambda) + (1-k)^2\sigma_2\Lambda}, \frac{(1-k)\Lambda}{\delta}\right). \tag{3.18}$$

- Case (ii), (iii), (iv) The dead equilibrium point is reached when all of the normal cells have died, leaving only the tumor cells to survive. We call this "dead" because there is no recovery of damaged normal cells because they have been forced to extinction. The following systems of equations are solved simultaneously,

$$\begin{aligned} &(1-d)(1-k)\alpha_2 T - \phi_2 T^2 - \gamma_1 IT = 0, \\ &s + \frac{\rho IT}{\omega + T} - \mu I - (1-k)\sigma_2\frac{IE}{\nu + E} = 0, \\ &(1-k)\Lambda - \delta E = 0. \end{aligned} \tag{3.19}$$

Solving the first differential equation in the system (3.19), we have

$$T = 0, T = \frac{(1-d)(1-k)\alpha_2 - \gamma_1 I}{\phi_2}.$$

Solving the second differential equation in the system (3.19), and substituting for the value

of T, we obtain the following

$$\begin{aligned}
& \frac{\gamma_1\gamma_2(\nu+E)}{\phi_2}I^3 \\
- & \left(\frac{2\mu\gamma_1}{\phi_2} - \frac{\gamma_1}{\phi+2}(\gamma_2\omega + \frac{2(1-d)(1-k)\gamma_2}{\phi_2})(\nu+E) - \frac{(1-k)\sigma_2\gamma_1 E}{\phi 2}\right) \\
- & \left(\frac{(1-d)(1-k)\alpha_2\mu}{\phi_2} - (\frac{\gamma_1\mu}{\phi_2} + \frac{\gamma_1\gamma_2\omega(1-d)(1-k)\alpha_2}{\phi_2} - \mu\omega\right) I \\
- & \left(\frac{\gamma_2((1-d)(1-k))\alpha_2)^2}{\phi_2^2})(\nu+E) + \frac{s\gamma_1}{\phi_2}(\nu+E) + (1-k)\sigma_2\omega E + \frac{(1-k)^2(1-d)\sigma_2\gamma_1 E}{\phi_2}\right) I \\
+ & \ s(\nu\omega + \omega E + \frac{\nu\gamma_1}{\phi_2} + E).
\end{aligned}$$

Substituting for E in the above differential equation and solving for I, yields a cubic function and following are the equilibrium points obtained when solving the system (3.19):

Case (ii)

$$\mathcal{E}_{d2} = \left(0, \frac{(1-d)(1-k)\alpha_2 - \gamma_1 I_1^*}{\phi_2}, I_1^*, \frac{(1-k)\Lambda}{\delta}\right) \tag{3.20}$$

Case (iii)

$$\mathcal{E}_{d3} = \left(0, \frac{(1-d)(1-k)\alpha_2 - \gamma_1 I_2^*}{\phi_2}, I_2^*, \frac{(1-k)\Lambda}{\delta}\right) \tag{3.21}$$

Case (iv)

$$\mathcal{E}_{d4} = \left(0, \frac{(1-d)(1-k)\alpha_2 - \gamma_1 I_3^*}{\phi_2}, I_3^*, \frac{(1-k)\Lambda}{\delta}\right) \tag{3.22}$$

- Co-existing equilibrium point state exists when all cell populations would have survived the competition. To find co-existing equilibrium point, we solve the following system of differential equations simultaneously:

$$\begin{aligned}
& (\alpha_1 - \phi_1 N)N - \beta NT - (1-k)\sigma_1 NE = 0, \\
& ((1-d)(1-k)\alpha_2 - \phi_2 T)T + (1-k)\sigma_1 NE - \gamma_1 IT = 0, \\
& s + \rho\frac{IT}{\omega+T} - \gamma_2 IT - \mu I - (1-k)\sigma_2\frac{IE}{\upsilon+E} = 0, \\
& (1-k)\Lambda - \delta E = 0,
\end{aligned} \tag{3.23}$$

then the equilibrium point is given by:

$$\mathcal{E}_e = (N_e, T_e, I_e, E_e)$$

where

$$N_e = \frac{\alpha_1 - \beta Te - (1-k)\sigma_1 E_e}{\phi_1}, \tag{3.24}$$

$$T_e = \frac{1}{2\phi_1\phi_2}\left(-A + \sqrt{A^2 + 4\phi_1\phi_2(\sigma_1^2 E_e - \alpha_1\sigma_1 E_e)}\right), \tag{3.25}$$

$$I_e = \frac{s(\omega + T_e)(\nu + E_e)}{\rho T_e(\nu + E_e) - (\mu + \gamma_2 T_e)(\omega + T_e)(\nu + E_e) - (1-k)(\omega + T_e)\sigma_2 E_e}, \tag{3.26}$$

$$E_e = \frac{(1-k)\Lambda}{\delta}, \tag{3.27}$$

where

$$A = -\sigma_2\phi_1 + \phi_1\gamma_1 I_e + \beta\sigma_1 E_e.$$

We need $\alpha_1 \geq \beta Te + (1-k)\sigma_1 E_e$ for N_e to be feasible at this equilibrium state. The value of $T_e > 0$ at the equilibrium when

$$E_e(\sigma_1^2 E_e - \alpha_1\sigma_1) \geq 0.$$

Therefore we have $E_e \neq 0$ and $E_e \geq \frac{\alpha_1}{\sigma_1}$. The value of I_e exist at the equilibrium state, when

$$\mu + (1-k)\frac{\sigma_2 E_e}{\nu + E_e} > \frac{\rho T_e}{\omega + T_e} - \gamma_2 T_e.$$

3.3.3 The Basic Reproduction number

The basic reproduction number (R_0) is the number of newly infected cells produced by one infected cell during it's life time, assuming all other cells are susceptible [39]. R_0 can also be interpreted as the minimum absolute elimination or eradication effort, if we are dealing with a homogenous population and a control method which affects every body in a non-selective way [40]. It is one of the most important threshold parameters in mathematical epidemiology. It has a significant implication on epidemiological trend in such a way that if each infective can produce less than one new infective, (when $R_0 < 1$), then the epidemic will die out; and if each infective individual can produce more than one infective during the individual's lifetime as an infective (when $R_0 > 1$), then the epidemic will develop in the population. The basic reproduction number for the model is computed using the next generation method proposed by Van den Driesshe and Watmough [41].

The description of this method is as follows:

Assume that there are n compartments so that upon rearrangement the first m compartments correspond to infected cells. Let $\mathcal{F}_i(x)$ be the rate of appearance of new infections in compartment i, $V_i^+(x)$ be the rate of transfer of cells into compartment i by all other means, other than the epidemic and $V_i^-(x)$ be the rate of transfer of individuals out of compartment i. The disease transmission model consists of the system of equations

$$x_i = g_i(x) = \mathcal{F}_i(x) - \mathcal{V}_i(x),$$

where

$$\mathcal{V}_i^-(x) - \mathcal{V}_i^+(x)$$

One other important step is to obtain the tumor-free equilibrium point x_0. The $m \times m$ matrices F and V are then computed, where m represents the number infected classes, defined by

$$F = \left[\frac{\partial \mathcal{F}_i}{\partial x_j}(x_0)\right],$$

and

$$V = \left[\frac{\partial \mathcal{V}_i}{\partial x_j}(x_0)\right] \text{ with } 1 \leq i, j \leq m$$

F is non-negative and V is a non-singular M-matrix (a matrix with inverse, belonging to the class of positive matrices). Since F is non-negative and V is non-singular, then V^{-1} is non-negative and also FV^{-1} is non-negative. The matrix FV^{-1}, defined as the *the next generation matrix* , is then computed [27].

The basic reproduction number (reproduction ratio) R_0 is then defined as

$$R_0 = \rho(FV^{-1}), \tag{3.28}$$

where $\rho(A)$ is the *spectral radius of matrix* A, (or the maximum modulus of the eigenvalues of A). The method described above is now used to establish local stability of the basic model using R_0 as follows:

Rewriting the equations (3.1)-(3.4) so that those representing infected classes are written first and the rest follow, yields :

$$\frac{dT}{dt} = ((1-d)(1-k)\alpha_2 - \phi_2 T)T + (1-k)\sigma_1 NE - \gamma_1 IT, \tag{3.29}$$

$$\frac{dN}{dt} = (\alpha_1 - \phi_1 N)N - \beta NT - (1-k)\sigma_1 NE, \tag{3.30}$$

$$\frac{dI}{dt} = s + \rho\frac{IT}{\omega + T} - \gamma_2 IT - \mu I - (1-k)\sigma_2\frac{IE}{\upsilon + E}, \tag{3.31}$$

$$\frac{dE}{dt} = (1-k)\Lambda - \delta E, \tag{3.32}$$

From system (3.29)-(3.32), $\mathcal{F}_i$ and $\mathcal{V}_i$ are defined as:

$$\mathcal{F}_i = \begin{pmatrix} (1-k)\sigma_1 NE \\ 0 \\ 0 \\ 0 \end{pmatrix}, \tag{3.33}$$

and

$$\mathcal{V}_i = \begin{pmatrix} \phi_2 T^2 + \gamma_1 IT - (1-r)\alpha_2 T \\ \beta NT + (1-k)\sigma_1 NE - N(\alpha_1 - \phi_1 N) \\ \mu I + \gamma_2 IT + (1-k)\sigma_2\frac{IE}{\nu+E} - s - \frac{\rho IT}{\omega+T} \\ \delta E - (1-k)\Lambda \end{pmatrix}. \tag{3.34}$$

When evaluating the Jacobian of $\mathcal{F}_i$ at tumor free equilibrium $\mathcal{E}_0$, the following is obtained

$$\mathcal{J}_{\mathcal{F}_i} = \begin{pmatrix} 0 & (1-k)\sigma_1 E^* & 0 & (1-k)\sigma_1 N^* \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, \tag{3.35}$$

Also

$$\mathcal{J}_{\mathcal{V}_i} = \begin{pmatrix} -(1-r)\alpha_2 + \gamma_1 I^* & 0 & 0 & 0 \\ \beta N^* & -\alpha_1 + 2\phi_1 N^* + (1-k)\sigma_1 E^* & 0 & (1-k)\sigma_1 N^* \\ \frac{\rho I^*}{\omega} & 0 & \mu + (1-k)\sigma_2\frac{E^*}{\nu+E^*} & (1-k)\sigma_2\frac{\nu I^*}{(\nu+E^*)^2} \\ 0 & 0 & 0 & -\delta \end{pmatrix}, \tag{3.36}$$

Now, we let F and V be as follows:

$$F = \begin{pmatrix} 0 & (1-k)\sigma_1 E^* & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \tag{3.37}$$

and

$$V = \begin{pmatrix} a_{11} & 0 & 0 \\ a_{21} & a_{22} & 0 \\ a_{31} & 0 & a_{33} \end{pmatrix}, \tag{3.38}$$

where

$$\begin{aligned}
a_{11} &= \frac{(\nu\delta + (1-k)\Lambda)(s\gamma_1 - \mu(1-d)(1-k)\alpha_2) - (1-d)(1-k)\alpha_2(1-k)^2\sigma_2\Lambda}{\mu(\nu\delta + (1-k)\Lambda) + (1-k)^2\sigma_2\Lambda}, \\
a_{21} &= \beta\frac{(\alpha_1\delta - (1-k)^2\sigma_1)}{\delta\phi_1}, \\
a_{22} &= \frac{\alpha_1\delta\phi_1 - \phi_1\sigma_1(1-k)^2\Lambda}{\delta\phi_1}, \\
a_{31} &= \frac{\rho s(\nu\delta + (1-k)\Lambda)}{\omega(\mu(\nu\delta + (1-k)\Lambda) + (1-k)^2\sigma_2\Lambda)}, \\
a_{33} &= \frac{\mu(\nu\delta + (1-k)\Lambda) + (1-k)^2\sigma_2\Lambda}{\nu\delta + (1-k)\Lambda}.
\end{aligned}$$

To find the inverse matrix of V, we use minors, co-factors and adjugate method. The inverse matrix is given by:

$$V^{-1} = \begin{pmatrix} 1 & 0 & 0 \\ \frac{a_{21}}{a_{11}a_{22}}(1-k)\sigma_1 E & \frac{1}{a_{22}} & 0 \\ \frac{a_{31}}{a_{11}a_{33}} & 0 & \frac{1}{a_{33}} \end{pmatrix}. \tag{3.39}$$

Now we compute FV^{-1}[28] resulting in

$$FV^{-1} = \begin{pmatrix} \frac{a_{21}}{a_{11}a_{22}}(1-k)\sigma_1 E^* & \frac{1}{a_{22}}(1-k)\sigma_1 E^* & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \tag{3.40}$$

To compute R_0 , the spectral radius of the matrix in (3.40) is required computing this from

$$\Big|FV^{-1} - \lambda D\Big| = 0, \tag{3.41}$$

where the 3×3 identity matrix, the following is obtained

$$\begin{vmatrix} \frac{a_{21}}{a_{11}a_{22}}(1-k)\sigma_1 E^* - \lambda & \frac{1}{a_{22}}(1-k)\sigma_1 E^* & 0 \\ 0 & 0-\lambda & 0 \\ 0 & 0 & 0-\lambda \end{vmatrix} = 0, \tag{3.42}$$

yielding the three eigen values $\lambda_1 = \frac{a_{21}}{a_{11}a_{22}}(1-k)\sigma_1 E^*, \lambda_2 = 0, \lambda_3 = 0$

It follows that λ_1 is the spectral radius and thus the basic reproduction number R_0 is given by:

$$\begin{aligned} R_0 &= \rho(FV^{-1}) = \lambda_1 = \frac{a_{21}}{a_{11}a_{22}}(1-k)\sigma_1 E^*, \\ &= \frac{a_{21}}{a_{11}a_{22}} \times \frac{(1-k)^2\sigma_1\Lambda}{\delta}. \end{aligned}$$

Then the expanded expression of R_0 is given by:

$$R_0 = \frac{\beta\sigma_1\Lambda(1-k)^2\Big(\alpha_1\delta - (1-k)^2\sigma_1\Big)\Big(\mu(\nu\delta + (1-k)\Lambda) + (1-k)^2\sigma_2\Lambda\Big)}{\delta\Big(\alpha_1\delta\phi_1 - \phi_1\sigma_1(1-k)^2\Lambda\Big)\Big((\nu\delta + (1-k)\Lambda)(s\gamma_1 - \mu\alpha_2 r) - r\alpha_2(1-k)^2\sigma_2\Lambda\Big)}, \tag{3.43}$$

where $r = (1-d)(1-k)$. The Basic reproduction number is represented by all parameters that play a role in either controlling or stimulating the growth of breast cancer. As long as σ_1 is negative in the R_0 expression, the growth of cancer cells is controllable, as estrogen hormone stimulates tumor cell growth.

3.4 Local stability of equilibrium points

Now, we will be analysing the system's stability by means of eigenvalues. We say that an equilibrium point is stable if all the eigenvalues have real parts less than zero and unstable if at least one of the eigenvalues has a real part greater than zero, otherwise there is no conclusion. The equilibrium point and it's local stability are examined using linearised stability analysis. The model system (3.1)-(3.4) is thus linearised by computing their Jacobian matrix $\mathcal{J}$, and the general Jacobian matrix is given by:

$$\mathcal{J} = \begin{pmatrix} J_{11} & J_{12} & J_{13} & J_{14} \\ J_{21} & J_{22} & J_{23} & J_{24} \\ J_{31} & J_{32} & J_{33} & J_{34} \\ J_{41} & J_{42} & J_{43} & J_{44} \end{pmatrix} = \begin{pmatrix} J_{11} & -\beta N & 0 & -(1-k)\sigma_1 N \\ (1-k)\sigma_1 E & J_{22} & -\gamma_1 T & (1-k)\sigma_1 N \\ 0 & J_{32} & J_{33} & J_{34} \\ 0 & 0 & 0 & -\delta \end{pmatrix}, \tag{3.44}$$

where

$$\begin{aligned} J_{11} &= \alpha_1 - 2\phi_1 N - \beta T - (1-k)\sigma_1 E, \\ J_{22} &= (1-d)(1-k)\alpha_2 - 2\phi_2 T - \gamma_1 I, \\ J_{32} &= \frac{\rho\omega I}{(\omega+T)^2} - \gamma_2 T, \\ J_{33} &= \frac{\rho T}{\omega+T} - \gamma_2 T - \mu - (1-k)\frac{\sigma_2 E}{\nu+E}, \\ J_{34} &= -(1-k)\frac{\sigma_2 \nu I}{(\nu+E)^2}. \end{aligned}$$

Theorem 3.3 *The tumor-free equilibrium point of the system (3.1)-(3.4) is locally asymptotically stable if this conditions hold* $R_0 < 1, \alpha_1\phi_1\delta < 2\phi_1(\alpha_1\delta - (1-k)^2\sigma_1\Lambda) + (1-k)^2\alpha_1\Lambda$, *(1-d)(1-k)*$\alpha_2 < \frac{s\gamma_1(\nu\delta+(1-k)\Lambda)}{\mu(\nu\delta+(1-k)\Lambda)+(1-k)^2\sigma_2\Lambda}$.

Proof. Linearising the system(3.1)-(3.4) at TFE ($\mathcal{E}_0$), we obtain the following Jacobian matrix $\mathcal{J}(E_0)$

$$\mathcal{J}(\mathcal{E}_0) = \begin{pmatrix} A_0 & A_1 & 0 & -A_2 \\ A_3 & A_4 & 0 & A_2 \\ 0 & A_5 & A_6 & A_7 \\ 0 & 0 & 0 & -\delta \end{pmatrix}, \tag{3.45}$$

$$\begin{aligned}
A_0 &= \frac{\alpha_1\phi_1\delta - (1-k)^2\sigma_1\Lambda}{\delta\phi_1}, \\
A_1 &= \frac{\beta(\alpha_1\delta - (1-k)^2\sigma_1\Lambda)}{\phi_1\delta}, \\
A_2 &= \frac{(1-k)\sigma_1(\alpha_1\delta - (1-k)^2\sigma_1\Lambda)}{\delta\phi_1}, \\
A_3 &= \frac{(1-k)^2\sigma_1\Lambda}{\delta}, \\
A_4 &= \frac{(\nu\delta + (1-k)\Lambda)(s\gamma_1 - \mu(1-d)(1-k)\alpha_2) - (1-d)(1-k)\alpha_2(1-k)^2\sigma_2\Lambda}{\mu(\nu\delta + (1-k)\Lambda) + (1-k)^2\sigma_2\Lambda}, \\
A_5 &= \frac{s\rho(\nu\delta + (1-k)\Lambda) - \gamma_2(\nu\delta + (1-k)\Lambda)}{\omega(\mu(\nu\delta + (1-k)\sigma_2\Lambda) + (1-k)^2\sigma_2\Lambda)}, \\
A_6 &= \frac{-\mu(\nu\delta + (1-k)\Lambda) - (1-k)^2\sigma_2\Lambda}{\nu\delta + (1-k)\Lambda}, \\
A_7 &= \frac{\sigma_2\delta^2 s(1-k)(\nu\delta + (1-k)\Lambda)}{\mu(\nu\delta + (1-k)\Lambda) + ((1-k)^2\sigma_2\Lambda)(\nu\delta + (1-k)\Lambda)^2}.
\end{aligned}$$

Let λ denote the eigenvalues of $\mathcal{J}$, then

$$|\mathcal{J}(\mathcal{E}_0) - \lambda I| = 0 \tag{3.46}$$

where I is a 4×4 identity matrix Using (3.46) we get the following:

$$\begin{vmatrix} A_0 - \lambda & A_1 & 0 & -A_2 \\ A_3 & A_4 - \lambda & 0 & A_2 \\ 0 & A_5 & A_6 - \lambda & A_7 \\ 0 & 0 & 0 & -\delta - \lambda \end{vmatrix} = 0. \tag{3.47}$$

Then the characteristic equation at $\mathcal{E}_0$ of the linearised system of the model (3 1)-(3 4) is given below,

$$(-\delta - \lambda)(A_6 - \lambda)(\lambda^2 - (A_0 + A_4)\lambda + A_0A_4 - A_1A_3) = 0.$$

Therefore, we get two negative characteristic roots,

$$\lambda_1 = -\delta, \lambda_2 = -A_6,$$

Now, we consider the following equation to try and find R_0

$$\lambda^2 - (A_0 + A_4)\lambda + A_0A_4 - A_1A_3 = 0$$
$$\lambda^2 - (A_0 + A_4)\lambda + A_0A_4(1 - \frac{A_1A_3}{A_0A_4}) = 0$$

By simplifying the below expression, we have the basic reproduction number,

$$\frac{A_1A_3}{A_0A_4} = \frac{\beta\sigma_1\Lambda(1-k)^2\Big(\alpha_1\delta - (1-k)^2\sigma_1\Big)\Big(\mu(\nu\delta + (1-k)\Lambda) + (1-k)^2\sigma_2\Lambda\Big)}{\delta\Big(\alpha_1\delta\phi_1 - \phi_1\sigma_1(1-k)^2\Lambda\Big)\Big((\nu\delta + (1-k)\Lambda)(s\gamma_1 - \mu\alpha_2 r) - r\alpha_2(1-k)^2\sigma_2\Lambda\Big)} = R_0, \tag{3.48}$$

where $r = (1-d)(1-k)$. This implies the following equation,

$$\lambda^2 - (A_0 + A_4)\lambda + A_0A_4(1 - R_0) = 0$$

Now we can apply the Routh-Hurwitz criterion in the above equation,

- $Tr(A) < 0$,
- $Det(A) > 0$.

$$a_0 = 1 > 0, a_1 = (A_0 + A_4) < 0, A_0A_4(1 - R_0) > 0,$$

the above conditions are true, when

$$\begin{aligned} \alpha_1\phi_1\delta &< 2\phi_1(\alpha_1\delta - (1-k)^2\sigma_1\Lambda) + (1-k)^2\alpha_1\Lambda, \\ (1-d)(1-k)\alpha_2 &< \frac{s\gamma_1(\nu\delta + (1-k)\Lambda)}{\mu(\nu\delta + (1-k)\Lambda) + (1-k)^2\sigma_2\Lambda} \text{ and } R_0 < 1. \end{aligned} \tag{3.49}$$

Since the Routh-Hurwitz criterion holds, all the eigenvalues are negative. Therefore, the Tumor-free equilibrium point of the system of equation (3.1)-(3.4) is locally asymptotically stable when $R_0 < 1$. □

We now discuss local stability of the system about it's dead equilibrium point. For this, we compute eigenvalues of the jacobian matrix of the linearised system. Negative eigenvalues of the jacobian matrix about the dead equilibrium point implies local stability of the dead equilibrium point.

Theorem 3.4 *The case (i) Dead equilibrium point $\mathcal{E}_{d1}$ of the system (3.1)-(3.4) is locally asymptotically stable if*

$$\frac{(1-k)^2\sigma_1\Lambda}{\alpha_1\delta} > 1,$$
$$\frac{s\gamma_1(\nu\delta+(1-k)\Lambda)}{(1-d)(1-k)\alpha_2(\mu(\nu\delta+(1-k)\Lambda)+(1-k)^2\sigma_2\Lambda)} > 1.$$

.

Proof. When $\mathcal{J}$ is evaluated at dead equilibrium point $\mathcal{E}_{d1}$ is given by,

$$\mathcal{J}(\mathcal{E}_{d1}) = \begin{pmatrix} B_0 & 0 & 0 & 0 \\ B_1 & B_2 & 0 & 0 \\ 0 & B_3 & B_4 & 0 \\ 0 & 0 & 0 & -\delta \end{pmatrix}, \tag{3.50}$$

$$|\mathcal{J}(\mathcal{E}_{d1}) - \lambda I| = 0 \tag{3.51}$$

$$\begin{vmatrix} B_0-\lambda & 0 & 0 & 0 \\ B_1 & B_2-\lambda & 0 & 0 \\ 0 & B_3 & B_4-\lambda & 0 \\ 0 & 0 & 0 & -\delta-\lambda \end{vmatrix} = 0 \tag{3.52}$$

The characteristic polynomial of $\mathcal{J}(\mathcal{E}_{d1})$ is,

$$(-\delta-\lambda_1)(B_0-\lambda_2)(B_2-\lambda_3)(B_4-\lambda_4) = 0$$

where

$$\begin{aligned} B_0 &= \alpha_1 - \frac{(1-k)^2\sigma_2\Lambda}{\delta}, \\ B_2 &= (1-d)(1-k)\alpha_2 - \frac{s\gamma_1(\nu\delta+(1-k)\Lambda)}{\mu(\nu\delta+(1-k)\Lambda)+(1-k)^2\sigma_2\Lambda}, \\ B_4 &= -\mu - \frac{(1-k)^2\sigma_2\Lambda}{\nu\delta+(1-k)\Lambda} \end{aligned}$$

Clearly, two eigenvalues of the system at $\mathcal{E}_{d1}$ are negative and real,

$$\lambda_1 = -\delta, \lambda_4 = -\mu - \frac{(1-k)^2\sigma_2\Lambda}{\nu\delta + (1-k)\Lambda}$$

for dead equilibrium point to be stable all eigenvalues need to be less than zero, for $\lambda_2 < 0, B_0 < 0$

$$\begin{aligned}
\alpha_1 - \frac{(1-k)^2\sigma_2\Lambda}{\delta} &< 0, \\
\alpha_1 &< \frac{(1-k)^2\sigma_2\Lambda}{\delta}, \\
1 &< \frac{(1-k)^2\sigma_2\Lambda}{\delta\alpha_1}, \\
\frac{(1-k)^2\sigma_2\Lambda}{\delta\alpha_1} &> 1
\end{aligned}$$

for $\lambda_3 < 0, B_2 < 0$

$$\begin{aligned}
(1-d)(1-k)\alpha_2 - \frac{s\gamma_1(\nu\delta + (1-k)\Lambda)}{\mu(\nu\delta + (1-k)\Lambda) + (1-k)^2\sigma_2\Lambda} &< 0, \\
(1-d)(1-k)\alpha_2 &< \frac{s\gamma_1(\nu\delta + (1-k)\Lambda)}{\mu(\nu\delta + (1-k)\Lambda) + (1-k)^2\sigma_2\Lambda}, \\
\frac{s\gamma_1(\nu\delta + (1-k)\Lambda)}{(1-d)(1-k)\alpha_2(\mu(\nu\delta + (1-k)\Lambda) + (1-k)^2\sigma_2\Lambda)} &> 1.
\end{aligned}$$

Thus, all eigenvalues are negative and real. Hence, the Dead equilibrium point $\mathcal{E}_{d1}$ of the system (3.1)-(3.4) is locally asymptotically stable. □

Theorem 3.5 *The case (ii) Dead equilibrium point E_{d2} of the system (3.1)-(3.4) is locally asymptotically stable if*

$$\begin{aligned}
\frac{(1-k)^2\sigma_1\Lambda}{\alpha_1\delta} &> 1, \\
\frac{(1-d)(1-k)\alpha_2}{\gamma_1 I_1^*} &> 1, \\
A_0 > 0, 0 < k < 1
\end{aligned}$$

otherwise unstable.

Proof. When $\mathcal{J}$ is evaluated at dead equilibrium point $\mathcal{E}_{d2}$ is given by,

$$\mathcal{J}(\mathcal{E}_{d2}) = \begin{pmatrix} C_0 & 0 & 0 & 0 \\ C_1 & C_2 & C_3 & 0 \\ 0 & C_4 & C_5 & C_6 \\ 0 & 0 & 0 & -\delta \end{pmatrix}, \tag{3.53}$$

$$|\mathcal{J}(\mathcal{E}_{d2}) - \lambda I| = 0 \tag{3.54}$$

$$\begin{vmatrix} C_0 - \lambda & 0 & 0 & 0 \\ C_1 & C_2 - \lambda & C_3 & 0 \\ 0 & C_4 & C_5 - \lambda & 0 \\ 0 & 0 & 0 & -\delta - \lambda \end{vmatrix} = 0 \tag{3.55}$$

Clearly, one of the eigenvalues of the system at $\mathcal{J}(\mathcal{E}_{d2})$ is negative and real, $\lambda_1 = -\delta$. However, the remaining can be analysed by basic calculation

$$(C_0 - \lambda)(C_2 - \lambda)(C_5 - \lambda) = 0,$$
$$\lambda_2 = C_0, \lambda_3 = C_2, \lambda_4 = C_5$$

where

$$\begin{aligned} C_0 &= \frac{\alpha_1 - (1-k)^2\sigma_1\Lambda}{\delta}, \\ C_2 &= \gamma_1 I_1^* - (1-d)(1-k)\alpha_2, \\ C_5 &= \frac{(A_0\rho\phi_2 - A_0A_1\gamma_2)((1-d)(1-k)\alpha_2 - \gamma_1 I_1^* - A_1\phi_1(\mu A_0 + (1-k)^2\sigma_2\Lambda))}{\phi_2 A_0 A_1} \end{aligned}$$

where

$$A_0 = \delta\nu - (1-k)\Lambda, A_1 = \omega\phi_2 + (1-d)(1-k)\alpha_2 - \gamma_1 I_1^*.$$

For dead equilibrium point to be stable all eigenvalues need to be less than zero, the following conditions apply,

1. $C_0 < 0$ if $0 < k < 1$, $\frac{(1-k)^2\sigma_1\Lambda}{\alpha_1\delta} > 1$,
2. $C_2 < 0$ if, $\frac{(1-d)(1-k)\alpha_2}{\gamma_1 I_1^*} > 1$,

3. $C_5 < 0$ given $A_0 > 0, 0 < k < 1$.

Thus, all eigenvalues are negative and real. Hence, the Dead equilibrium point $\mathcal{E}_{d2}$ of the system (3.1)-(3.4) is locally asymptotically stable. □

Theorem 3.6 *The co-existing equilibrium point $\mathcal{E}_e$ of the system (3.1)-(3.4) is stable if the following Routh-Hurwitz criterion is satisfied,*

$$Tr(\mathcal{J}(\mathcal{E}_e)) = (Q_0 + Q_3 + Q_6 - \delta) < 0,$$
$$Det(\mathcal{J}(\mathcal{E}_e)) = (-\delta(Q_0Q_3Q_6 + Q_0Q_4Q_5 + Q_1Q_2Q_6)) > 0.$$

Proof. We examined and Linearized the system (3.1)-(3.4) around the co-existing equilibrium point $\mathcal{E}_e$ and we obtained the Jacobian matrix below $\mathcal{J}(\mathcal{E}_e)$, which represents the co-existing equilibrium values for normal cells, tumor cells, immune cells and estrogen levels

$$\mathcal{J}(\mathcal{E}_e) = \begin{pmatrix} Q_0 & -\beta N_e & 0 & -Q_1 \\ Q_2 & Q_3 & -\gamma_1 T_e & Q_1 \\ 0 & Q_4 & Q_5 & Q_6 \\ 0 & 0 & 0 & -\delta \end{pmatrix}, \tag{3.56}$$

$$|\mathcal{J}(\mathcal{E}_e)| = \begin{vmatrix} Q_0 & -\beta N_e & 0 & -Q_1 \\ Q_2 & Q_3 & -\gamma_1 T_e & Q_1 \\ 0 & Q_4 & Q_5 & Q_6 \\ 0 & 0 & 0 & -\delta \end{vmatrix} = 0 \tag{3.57}$$

where

$$\begin{aligned}
Q_0 &= \alpha_1 - 2\phi_1 N_e - \beta T_e - (1-k)\sigma_1 E_e, \\
Q_1 &= (1-k)\sigma_1 N_e, \\
Q_2 &= (1-k)\sigma_1 E_e, \\
Q_3 &= (1-d)(1-k)\alpha_2 - 2\phi_2 T_e - \gamma_1 I_e, \\
Q_4 &= \frac{\rho\omega I_e}{(\omega+T_e)^2} - \gamma_2 I_e, \\
Q_5 &= \frac{\rho T_e}{\omega+T_e} - \gamma_2 T_e - (1-k)\frac{\sigma_2 E_e}{\nu+E_e}, \\
Q_6 &= (1-k)\frac{\sigma_2 \nu I_e}{(\nu+E_e)^2}.
\end{aligned}$$

We need to show that $Trace(\mathcal{J}(\mathcal{E}_e)) < 0$, that is

$$\begin{aligned}
Trace(\mathcal{J}\mathcal{E}_e) &= (Q_0 + Q_3 + Q_6 - \delta) < 0 \\
&= -(\delta - \alpha_1 - (1-d) + (1-k)\alpha_2) - T_e\left(\beta + 2\phi_2 - \frac{\rho}{\omega+T_e}\right) \\
&- \gamma_1 I_e - 2\phi_1 N_e - E_e\left((1-k)\sigma_1 + (1-k)\sigma_2\frac{\nu I_e}{(\nu+E_e)^2}\right)
\end{aligned}$$

Thus,

$$Tr(\mathcal{J}(\mathcal{E}_e)) < 0, \text{ if } \delta > \alpha_1 + (1-d)(1-k)\alpha_2$$

To show that,

$$Det(\mathcal{J}(\mathcal{E}_e)) = (-\delta(Q_0Q_3Q_6 + Q_0Q_4Q_5 + Q_1Q_2Q_6)) > 0$$
$$\text{let}\tau_1 = -\delta Q_0Q_3Q_6, \tau_2 = -\delta Q_0Q_4Q_5, \tau_3 = -\delta Q_1Q_2Q_6$$

$$\tau_1 = -\delta\left((\alpha_1 - 2\phi_1 N_e - \beta T_e - (1-k)\sigma_1 E_e)((1-d)(1-k)\alpha_2 - 2\phi_2 T_e - \gamma_1 I_e)((1-k)\frac{\sigma_2\nu I_e}{(\nu+E_e)^2})\right)$$

This implies that $\tau_1 > 0$, if $\alpha_1 > 2\phi_1 N_e +_e +(1-k)\sigma_1 E_e$ and $(1-d)(1-k)\alpha_2 < \gamma_1 I_e + 2\phi_2 T_e$

$$\begin{aligned}
\tau_2 &= -\delta Q_0 Q_4 Q_5, \\
&= -\delta\left((\alpha_1 - 2\phi_1 N_e - \beta T_e - (1-k)\sigma_1 E_e)(\frac{\rho\omega I_e}{(\omega+T_e)^2} - \gamma_2 I_e)(\frac{\rho T_e}{\omega+T_e} - \gamma_2 T_e - (1-k)\frac{\sigma_2 E_e}{\nu+E_e})\right).
\end{aligned}$$

This implies that $\tau_2 > 0$, if $\alpha_1 < 2\phi_1 N_e + \beta T_e + (1-k)\sigma_1 E_e$, $\frac{\rho\omega I_e}{(\omega+T_e)^2} < \gamma_2 I_e$ and $\frac{\rho T_e}{\omega+T_e} < \gamma_2 T_e - (1-k)\frac{\sigma_2 E_e}{\nu+E_e}$

$$\tau_3 = \delta_e((1-k)\sigma_1 E_e)((1-k)\frac{\nu I_e}{(\nu+E_e)^2}).$$

This implies that $\tau_3 > 0$ and by Rourth-Hurwitz criterion the co-existing equilibrium point is asymptotically stable. □

3.5 Global stability of equilibrium points

Rantzer [44] presented the concept of global stability and its analysis through the Lyapunov Method in his paper, which opened a new study avenue in nonlinear differential equations analysis. Two well-known approaches (Lyapunov method and Bendixson-Dulac criteria) are used to investigate the requirement of global stability for steady states of nonlinear differential equations.

Solving the global stability, we will make use of Lyapunov function. Lyapunov method is a powerful technique for multidimensional systems. There is no systematic strategy for constructing Lyapunov function for mathematical models. On the other hand the Lyapunov functions for a given system are not unique. It turns out that Lyapunov function can continuously be found for any steady system and thus in the event that a system is stable, a Lyapunov function exists and vice versa[45].

3.5.1 Global stability of Tumor-free equilibrium point

Now we need to show that the tumor-free equilibrium point is globally stable, which means the total eradication of the tumor cells. We will accomplish this objective by the Lyapunov second strategy. The tumor-free equilibrium point for our model, which is locally stable is $\mathcal{E}_0 = (N_0, 0, I_0, E_0)$.

Theorem 3.7 *The tumor-free equilibrium point is globally asymptotically stable in* Ω*, if the following conditions hold:*

$$\alpha_1 > \frac{(1-k)^2\sigma_1\Lambda}{\delta},$$
$$\mu + \frac{\alpha_2\gamma_2(1-d)(1-k)}{\phi_2} + \frac{(1-k)^2\sigma_2\Lambda}{\delta\nu + (1-k)\Lambda} > \frac{\alpha_2\rho}{\delta\omega + (1-d)(1-k)\alpha_2},$$
$$\frac{2\delta}{I_0^2E_0^2}\left\{\gamma_2 T + \mu + (1-k)\sigma_2\frac{E}{\upsilon + E}\right\} > \frac{(1-k)^2\sigma_2^2}{I_0^2(\nu+E)^2(\nu+E_0)^2} + \frac{2\delta\rho T}{I_0^2E_0^2(\omega+T)},$$
$$\frac{2\delta}{N_0^2E_0^2}\left\{\phi_1(N+N_0) + +(1-k)\sigma_1 E\right\} > \frac{(1-k)^2\sigma_1^2}{N_0^2} + \frac{2\delta\alpha_1}{N_0^2E_0^2}$$

Proof. We now consider a Lyapunov function V defined by:

$$V = \left(\frac{N-N_0}{N_0}\right)^2 + \left(\frac{I-I_0}{I_0}\right)^2 + \left(\frac{E-E_0}{E_0}\right)^2 + (T-T_0)^2.$$

In the $NTIE$-plane containing the tumor free equilibrium point $\mathcal{E}_0$, $V(\mathcal{E}_0) = 0$ and $V(\mathcal{E}) > 0$ are evident. As a result, it is a Lyapunov function.

The derivative of V along the system's solution (3.1)-(3.4) is represented as:

$$\begin{aligned}
\frac{dV}{dt} &= \frac{2}{N_0^2}(N-N_0)\frac{dN}{dt} + \frac{2}{I_0^2}(I-I_0)\frac{dI}{dt} + \frac{2}{E_0^2}(E-E_0)\frac{dE}{dt} + 2(T-T_0)\frac{dT}{dt}, \\
&= \frac{2}{N_0^2}(N-N_0)\left\{\alpha_1 N - \phi_1 N^2 - \beta NT - (1-k)\sigma_1 NE\right\} \\
&\quad + \frac{2}{I_0^2}(I-I_0)\left\{s + \rho\frac{IT}{\omega+T} - \gamma_2 IT - \mu I - (1-k)\sigma_2\frac{IE}{\upsilon+E}\right\} \\
&\quad + \frac{2}{E_0^2}(E-E_0)\left\{(1-k)\Lambda - \delta E\right\} \\
&\quad + 2(T-T_0)\left\{((1-d)(1-k)\alpha_2 - \phi_2 T)T + (1-k)\sigma_1 NE - \gamma_1 IT\right\}.
\end{aligned}$$

Since at the tumor free equilibrium point ($\mathcal{E}_0$)

$$\frac{dN}{dt} = \frac{dI}{dt} = \frac{dE}{dt} = 0$$

and $T_0 = 0$, so we have

$$\begin{aligned}
\alpha_1 N_0 - \phi_1 N_0^2 - \beta N_0 T_0 - (1-k)\sigma_1 N_0 E_0 &= 0, \\
s + \rho\frac{I_0 T_0}{\omega+T_0} - \gamma_2 I_0 T_0 - \mu I_0 - (1-k)\sigma_2\frac{I_0 E_0}{\upsilon+E_0} &= 0, \\
(1-k)\Lambda - \delta E_0 &= 0, \\
((1-d)(1-k)\alpha_2 - \phi_2 T_0)T_0 + (1-k)\sigma_1 N_0 E_0 - \gamma_1 I_0 T_0 &= 0.
\end{aligned}$$

Incorporating the above terms in $\frac{dV}{dt}$ and we get

$$\begin{aligned}
\frac{dV}{dt} &= \frac{2}{N_0^2}(N-N_0)\Big(\alpha_1 N - \phi_1 N^2 - \beta NT - (1-k)\sigma_1 NE - (\alpha_1 N_0 - \phi_1 N_0^2 - \beta N_0 T_0 - (1-k)\sigma_1 N_0 E_0)\Big) \\
&\quad + \frac{2}{I_0^2}(I-I_0)\Big(s + \rho\frac{IT}{\omega+T} - \gamma_2 IT - \mu I - (1-k)\sigma_2\frac{IE}{\upsilon+E} \\
&\quad - \Big(s + \rho\frac{I_0 T_0}{\omega+T_0} - \gamma_2 I_0 T_0 - \mu I_0 - (1-k)\sigma_2\frac{I_0 E_0}{\upsilon+E_0}\Big)\Big) \\
&\quad + \frac{2}{E_0^2}(E-E_0)\Big((1-k)\Lambda - \delta E - ((1-k)\Lambda - \delta E_0)\Big) \\
&\quad + 2(T-T_0)\Big(1-d)(1-k)\alpha_2 T - \phi_2 T^2 + (1-k)\sigma_1 NE - \gamma_1 IT \\
&\quad - \Big((1-d)(1-k)\alpha_2 T_0 - \phi_2 T_0^2 + (1-k)\sigma_1 N_0 E_0 - \gamma_1 I_0 T_0\Big)\Big).
\end{aligned}$$

Collecting and canceling terms, yields

$$
\begin{aligned}
= \; & \frac{2}{N_0^2}(N-N_0)\Big(\alpha_1(N-N_0)-\phi_1(N^2-N_0^2)-\beta(NT-N_0T_0)-(1-k)\sigma_1(NE-N_0E_0)\Big) \\
& +\frac{2}{I_0^2}(I-I_0)\Big(\rho(\frac{IT}{\omega+T}-\frac{I_0T_0}{\omega+T_0})-\gamma_2(IT-I_0T_0)-\mu(I-I_0)-(1-k)\sigma_2(\frac{IE}{\upsilon+E}-\frac{I_0E_0}{\upsilon+E_0})\Big) \\
& +\frac{2}{E_0^2}(E-E_0)(-\delta(E-E_0)) \\
& +2(T-T_0)\Big((1-d)(1-k)\alpha_2(T-T_0)-\phi_2(T^2-T_0^2)-\gamma_1(IT-I_0T_0)\Big),
\end{aligned}
$$

which then becomes:

$$
\begin{aligned}
= \; & \frac{2}{N_0^2}(N-N_0)\Big(\alpha_1(N-N_0)-\phi_1(N-N_0)(N+N_0)-\beta(NT-N_0T+N_0T-N_0T_0) \\
& -(1-k)\sigma_1(NE-N_0E+N_0E-N_0E_0)\Big) \\
& +\frac{2}{I_0^2}(I-I_0)\Big(\rho\Big(\frac{IT}{\omega+T}-\frac{I_0T}{\omega+T}+\frac{I_0T}{\omega+T}-\frac{I_0T_0}{\omega+T_0}\Big)-\gamma_2(IT-I_0T+I_0T-I_0T_0) \\
& -\mu(I-I_0)-(1-k)\sigma_2\Big(\frac{IE}{\upsilon+E}-\frac{I_0E}{\upsilon+E}+\frac{I_0E}{\upsilon+E}-\frac{I_0E_0}{\upsilon+E_0}\Big)\Big) \\
& +\frac{2}{E_0^2}(E-E_0)\Big(-\delta(E-E_0)\Big) \\
& +2(T-T_0)\Big((1-d)(1-k)\alpha_2(T-T_0)-\phi_2(T-T_0)(T+T_0)-\gamma_1(IT-T_0I+T_0I-I_0T_0)\Big), \\
= \; & \frac{2}{N_0^2}(N-N_0)\Big(\alpha_1(N-N_0)-\phi_1(N-N_0)(N+N_0)-\beta(T(N-N_0)-N_0(T-T_0) \\
& -(1-k)\sigma_1(E(N-N_0)-N_0(E-E_0))\Big)+\frac{2}{I_0^2}(I-I_0)\Big(\rho(\frac{T}{\omega+T}(I-I_0) \\
& +\frac{I_0}{(\omega+T_0)(\omega+T)}(T(\omega+T_0)-T_0(\omega+T))\Big)-\gamma_2(T(I-I_0)-I_0(T-T_0))\Big) \\
& +\frac{2}{E_0^2}(E-E_0)(-\delta(E-E_0)) \\
& +2(T-T_0)\Big((1-d)(1-k)\alpha_2(T-T_0)-\phi_2(T-T_0)(T+T_0)-\gamma_1(T(T-T_0)-T_0(I-I_0))\Big).
\end{aligned}
$$

Following some algebraic computations, we arrive at

$$\begin{aligned}
\frac{dV}{dt} &= \frac{2}{N_0^2}(N-N_0)^2\Big(\alpha_1-\phi_1(N+N_0)-\beta T-(1-k)\sigma_1 E\Big)+(N-N_0)(I-I_0)\times 0\\
&\quad -\frac{2(1-k)\sigma_1}{N_0}(N-N_0)(E-E_0)-\frac{2\beta}{N_0}(N-N_0)(T-T_0)\\
&\quad +\frac{2}{I_0^2}(I-I_0)^2\left(\rho\frac{T}{\omega+T}-\gamma_2 T-\mu-(1-k)\sigma_2\frac{E}{\upsilon+E}\right)\\
&\quad -\frac{2(1-k)\sigma_2\nu}{I_0(\nu+E)(\nu+E_0)}(I-I_0)(E-E_0)+2\left(\frac{\rho\omega}{I_0(\omega+T)(\omega+T_0)}-\frac{\gamma_2}{I_0}-\gamma_1\right)(I-I_0)(T-T_0)\\
&\quad -\frac{2\delta}{E_0^2}(E-E_0)^2\\
&\quad +2(T-T_0)^2\Big((1-d)(1-k)\alpha_2-\phi_2(T+T_0)-\gamma_1 I\Big)\\
&= -a_{11}(N-N_0)^2-a_{13}(N-N_0)(E-E_0)-2a_{14}(N-N_0)(T-T_0)\\
&\quad -a_{22}(I-I_0)^2-2a_{23}(I-I_0)(E-E_0)-2a_{24}(I-I_0)(T-T_0)\\
&\quad -a_{33}(E-E_0)^2-a_{44}(T-T_0)^2.
\end{aligned}$$

Thus, $\frac{dV}{dt}$ is a quadratic form which can be expressed as

$$\frac{dV}{dt}=-Y^TAY,$$

where $Y^T=(N-N_0,I-I_0,E-E_0,T-T_0)$ and A is a symmetric matrix given by

$$A=\begin{pmatrix} a_{11} & 0 & a_{13} & a_{14}\\ 0 & a_{22} & a_{23} & a_{24}\\ a_{31} & a_{32} & a_{33} & 0\\ a_{41} & a_{42} & 0 & a_{44}\end{pmatrix} \tag{3.58}$$

where

$$\begin{aligned}
a_{11} &= \frac{2}{N_0^2}\left\{-\alpha_1+\phi_1(N+N_0)+\beta T+(1-k)\sigma_1 E\right\},\\
a_{13}=a_{31} &= \frac{(1-k)\sigma_1}{N_0},\\
a_{14}=a_{41} &= \frac{\beta}{N_0},\\
a_{22} &= \frac{2}{I_0^2}\left\{-\rho\frac{T}{\omega+T}+\gamma_2 T+\mu+(1-k)\sigma_2\frac{E}{\upsilon+E}\right\},\\
a_{23}=a_{32} &= \frac{(1-k)\sigma_2\nu}{I_0(\nu+E)(\nu+E_0)},\\
a_{24}=a_{42} &= \frac{\rho\omega}{I_0(\omega+T)(\omega+T_0)}-\frac{\gamma_2}{I_0}-\gamma_1,\\
a_{33} &= \frac{2\delta}{E_0^2},\\
a_{44} &= 2\left\{-(1-d)(1-k)\alpha_2+\phi_2(T+T_0)+\gamma_1 I\right\}
\end{aligned}$$

Now $\frac{dV}{dt}$ can only be negative definite if the matrix A is positive definite i.e all the principal minors of A are positive. Now the first principal minor is given by

$$M_1=|a_{11}|=\frac{2}{N_0^2}\left\{-\alpha_1+\phi_1(N+N_0)+\beta T+(1-k)\sigma_1 E\right\}>0$$

only if

$$-\alpha_1+\phi_1(N+N_0)+\beta T+(1-k)\sigma_1 E>0.$$

Since all the variables are bounded in the region:

$$\Omega=\left\{N\leq\frac{\alpha_1}{\phi_1},T\leq\frac{(1-d)(1-k)\alpha_2}{\phi_2},I\leq\frac{s}{\mu-\rho},E\leq\frac{(1-k)\Lambda}{\delta}\right\},$$

now substituting for the upper bounds of the variables, we get

$$-\alpha_1+\phi_1(\frac{\alpha_1}{\phi_1}+N_0)+\beta\frac{(1-d)(1-k)\alpha_2}{\phi_2}+\frac{(1-k)^2\sigma_1\Lambda}{\delta}\leq 0.$$

Moreover, substituting for $N_0=\frac{\alpha_1\delta-(1-k)^2\sigma_1\Lambda}{\delta\phi_1}$, we have the following comparison:

$$\begin{aligned}
\Rightarrow -\alpha_1+\phi_1(\frac{\alpha_1}{\phi_1}+\frac{\alpha_1\delta-(1-k)^2\sigma_1\Lambda}{\delta\phi_1})+\beta\frac{(1-d)(1-k)\alpha_2}{\phi_2}+\frac{(1-k)^2\sigma_1\Lambda}{\delta}&\geq 0\\
\frac{\alpha_1\delta-(1-k)^2\sigma_1\Lambda}{\delta}+\beta\frac{((1-d)+(-k))\alpha_2}{\phi_2}+\frac{(1-k)^2\sigma_1\Lambda}{\delta}&\geq 0.
\end{aligned}$$

Thus, a sufficient condition for M_1 to be positive definite is that

$$\alpha_1 > \frac{(1-k)^2\sigma_1\Lambda}{\delta}, \tag{3.59}$$

which holds. Therefore, $M_1 > 0$.

For the second principal minor

$$M_2 = \begin{vmatrix} a_{11} & 0 \\ 0 & a_{22} \end{vmatrix} > 0$$

holds if $a_{11}a_{22} > 0$ since $a_{11} > 0$ holds from the first condition, now we need $a_{22} > 0$. Now substituting the upper bounds of the variables, then $a_{22} > 0$ if

$$\mu + \frac{\alpha_2\gamma_2(1-d)(1-k)}{\phi_2} + \frac{(1-k)^2\sigma_2\Lambda}{\delta\nu + (1-k)\Lambda} > \frac{\alpha_2\rho}{\delta\omega + (1-d)(1-k)\alpha_2} \tag{3.60}$$

therefore $M_2 > 0$, with $0 \leq k < 1$ and $0 \leq d < 1$. The third principal minor

$$M_3 = \begin{vmatrix} a_{11} & 0 & a_{13} \\ 0 & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{vmatrix} = a_{11}a_{22}a_{33} - a_{11}a_{23}^2 - a_{13}^2a_{22} > 0$$

holds if

$$a_{11}a_{22}a_{33} - (a_{11}a_{23}^2 + a_{13}^2a_{22}) > 0$$

$$\Rightarrow a_{11}\left\{\frac{a_{22}a_{33}}{2} - a_{23}^2\right\} + a_{22}\left\{\frac{a_{11}a_{33}}{2} - a_{13}^2\right\} > 0$$

Since a_{11} holds from M_1 and a_{22} holds from M_2, then for the above inequality to hold we need the following inequalities to be positive,

$$\frac{a_{22}a_{33}}{2} - a_{23}^2 > 0$$

and

$$\frac{a_{11}a_{33}}{2} - a_{13}^2 > 0$$

Now we have

$$\frac{a_{22}a_{33}}{2} - a_{23}^2 > 0,$$

$$\Rightarrow \frac{2\delta}{I_0^2E_0^2}\left\{-\rho\frac{T}{\omega+T} + \gamma_2T + \mu + (1-k)\sigma_2\frac{E}{\upsilon+E}\right\} - \frac{(1-k)^2\sigma_2^2}{I_0^2(\nu+E)^2(\nu+E_0)^2} > 0,$$

$$\frac{2\delta}{I_0^2E_0^2}\left\{\gamma_2T + \mu + (1-k)\sigma_2\frac{E}{\upsilon+E}\right\} > \frac{(1-k)^2\sigma_2^2}{I_0^2(\nu+E)^2(\nu+E_0)^2} + \frac{2\delta\rho T}{I_0^2E_0^2(\omega+T)}$$

and

$$\frac{a_{11}a_{33}}{2} - a_{13}^2 > 0$$
$$\frac{2\delta}{N_0^2E_0^2}\{-\alpha_1 + \phi_1(N+N_0) + \beta T + (1-k)\sigma_1 E\} - \frac{(1-k)^2\sigma_1^2}{N_0^2} > 0$$
$$\frac{2\delta}{N_0^2E_0^2}\{\phi_1(N+N_0) + \beta T + (1-k)\sigma_1 E\} > \frac{(1-k)^2\sigma_1^2}{N_0^2} + \frac{2\delta\alpha_1}{N_0^2E_0^2}$$

Then $M_3 > 0$ if the following holds,

$$\begin{aligned}\frac{2\delta}{I_0^2E_0^2}\left\{\gamma_2 T + \mu + (1-k)\sigma_2\frac{E}{\upsilon+E}\right\} &> \frac{(1-k)^2\sigma_2^2}{I_0^2(\nu+E)^2(\nu+E_0)^2} + \frac{2\delta\rho T}{I_0^2E_0^2(\omega+T)} \\ \frac{2\delta}{N_0^2E_0^2}\{\phi_1(N+N_0) + \beta T + (1-k)\sigma_1 E\} &> \frac{(1-k)^2\sigma_1^2}{N_0^2} + \frac{2\delta\alpha_1}{N_0^2E_0^2}.\end{aligned} \tag{3.61}$$

Therefore $M_3 > 0$ provided the conditions above.

Lastly, the fourth principal minor

$$M_4 = \begin{vmatrix} a_{11} & 0 & a_{13} & a_{14} \\ 0 & a_{22} & a_{23} & a_{24} \\ a_{31} & a_{32} & a_{33} & 0 \\ a_{41} & a_{42} & 0 & a_{44} \end{vmatrix} > 0$$

$$\begin{aligned} a_{11}\left\{a_{44}(\frac{a_{22}a_{33}}{2} - a_{23}^2) + a_{33}(\frac{a_{22}a_{44}}{2} - a_{24}^2)\right\} \\ +a_{13}\left\{a_{24}^2a_{31} - (a_{24}a_{32}a_{41} + a_{22}a_{41}a_{44})\right\} \\ +a_{14}\left\{a_{41}a_{23}^2 - (a_{22}a_{33}a_{41} + a_{23}a_{31}a_{42})\right\} > 0\end{aligned}$$

M_4 is positive if

$$\begin{aligned}\frac{a_{22}a_{33}}{2} > a_{23}^2, \frac{a_{22}a_{44}}{2} > a_{24}^2 \\ a_{24}^2a_{31} > a_{24}a_{32}a_{41} + a_{22}a_{41}a_{44} \\ a_{41}a_{23}^2 > a_{22}a_{33}a_{41} + a_{23}a_{31}a_{42}.\end{aligned} \tag{3.62}$$

The principal minor M_4 is positive provided all the above conditions are satisfied. Then $\frac{dV}{dt}$ is negative definite if the matrix A is positive definite if all the inequalities (3.49), (3.50), (3.51). Since the model is proven to be bounded and singleton ,LaSalle's Invariance Principle [46] allows us to conclude that the tumor-free equilibrium point ($\mathcal{E}_0$) of the system (3.1)-(3.4) is globally asymptotically stable. □

3.5.2 Global stability of Case (i) dead equilibrium point

Theorem 3.8 *The dead equilibrium point $\mathcal{E}_{d1}$ is globally asymptotically stable in Ω, provided the following conditions holds:*

$$\gamma_2 T + \mu + (1-k)\sigma_2 \frac{E}{\upsilon + E} > \rho \frac{T}{\omega + T},$$
$$\frac{2\delta}{I_1^2 E_1^2}\left(\gamma_2 T + \mu + (1-k)\sigma_2 \frac{E}{\upsilon + E}\right) > \frac{(1-k)^2\sigma_2^2\nu^2}{I_1^2(\nu+E)^2(\nu+E_1)^2} + \frac{2\delta\rho T}{I_1^2 E_1^2(\omega+T)},$$
$$\frac{2\delta}{I_1^2 E_1^2}\left(\gamma_2 T + \mu + (1-k)\frac{\sigma_2 E}{\nu + E}\right) > (1-k)^2\sigma_1^2 + \frac{2\delta\rho T}{I_1^2 E_1^2(\omega+T)}.$$

Proof. Now we will show the equilibrium point

$$\mathcal{E}_{d1} = (N_1, T_1, I_1, E_1) = \left(0, 0, \frac{s(\nu\delta - (1-k)\Lambda)}{\mu(\nu\delta + (1-k)\Lambda) + (1-k)^2\sigma_2\Lambda}, \frac{(1-k)\Lambda}{\delta}\right)$$

is globally stable by constructing a Lyapunov function, which described the total eradication of normal cells and tumor cells. We first define a Lyapunov function of the model as

$$W = \left(\frac{I - I_1}{I_1}\right)^2 + \left(\frac{E - E_1}{E_1}\right)^2 + (N - N_1)^2 + (T - T_1)^2$$

Evidently, we can see that $W(\mathcal{E}_{d1}) = 0$ and $W(\mathcal{E}) > 0\ \forall \mathcal{E} \neq \mathcal{E}_{d1}$ in the $NTIE$-plane containing the equilibrium point $\mathcal{E}_{d1}$ So, it is a Lyapunov function. Now differentiating on both sides with respect to time, yields

$$\begin{aligned}
\frac{dW}{dt} &= \frac{2}{I_1^2}(I - I_1)\frac{dI}{dt} + \frac{2}{E_1^2}(E - E_1)\frac{dE}{dt} + 2(N - N_1)\frac{dN}{dt} + 2(T - T_1)\frac{dT}{dt} \\
\frac{dW}{dt} &= \frac{2}{I_1^2}(I - I_1)\left\{s + \rho\frac{IT}{\omega + T} - \gamma_2 IT - \mu I - (1-k)\sigma_2\frac{IE}{\upsilon + E}\right\} \\
&+ \frac{2}{E_1^2}(E - E_1)\{(1-k)\Lambda - \delta E\} \\
&+ 2(N - N_1)\left\{\alpha_1 N - \phi_1 N^2 - \beta NT - (1-k)\sigma_1 NE\right\} \\
&+ 2(T - T_1)\{((1-d)(1-k)\alpha_2 - \phi_2 T)T + (1-k)\sigma_1 NE - \gamma_1 IT\}.
\end{aligned}$$

Since at the dead equilibrium point $\mathcal{E}_{d1}$

$$\frac{dI}{dt} = \frac{dE}{dt} = 0$$

and $N_1 = T_1 = 0$, then we have

$$\begin{aligned} s + \rho\frac{I_1T_1}{\omega + T_1} - \gamma_2 I_1T_1 - \mu I_1 - (1-k)\sigma_2\frac{I_1E_1}{\upsilon + E_1} &= 0, \\ (1-k)\Lambda - \delta E_1 &= 0, \\ \alpha_1 N_1 - \phi_1 N_1^2 - \beta N_1T_1 - (1-k)\sigma 1 N_1E_1 &= 0, \\ ((1-d)(1-k)\alpha_2 - \phi_2 T_1)T_1 + (1-k)\sigma_1 N_1E_1 - \gamma_1 I_1T_1 &= 0 \end{aligned}$$

Incorporating the above terms in $\frac{dW}{dt}$ and the derivation are the same as in the tumor free global stability proof, yields:

$$\begin{aligned} \frac{dW}{dt} &= \frac{2}{I_1^2}(I-I_1)^2\left\{\rho\frac{T}{\omega+T} - \gamma_2 T - \mu - (1-k)\sigma_2\frac{E}{\upsilon+E}\right\} \\ &\quad -\frac{2(1-k)\sigma_2\nu}{I_1(\nu+E)(\nu+E_0)}(I-I_1)(E-E_1) \\ &\quad +(I-I_1)(N-N_1)\times 0 + 2(\frac{\rho\omega}{I_1(\omega+T)(\omega+T_0)} - \frac{\gamma_2}{I_1} - \gamma_1)(I-I_1)(T-T_1) \\ &\quad -\frac{2\delta}{E_1^2}(E-E_1)^2 \\ &\quad +2(N-N_1)^2\left\{\alpha_1 - \phi_1(N+N_1) - \beta T - (1-k)\sigma_1 E\right\} \\ &\quad -2(1-k)\sigma_1(N-N_1)(E-E_1) - 2\beta(N-N_1)(T-T_1) \\ &\quad +2(T-T_1)^2\left\{(1-d)(1-k)\alpha_2 - \phi_2(T+T_1) - \gamma_1 I\right\}, \\ &= -b_{11}(I-I_1)^2 - 2b_{12}(I-I_1)(E-E_1) - 2b_{14}(I-I_1)(T-T_1) \\ &\quad -b_{22}(E-E_1)^2 - 2b_{23}(N-N_1)(E-E_1) \\ &\quad -b_{33}(N-N_1) - 2b_{34}(N-N_1)(T-T_1) - b_{44}(T-T_1)^2. \end{aligned}$$

As a result, $\frac{dW}{dt}$ is a quadratic form that may be written as

$$\frac{dW}{dt} = -X^TBX$$

where $X^T = (I-I_1, E-E_1, N-N_1, T-T_1)$ and B is a symmetric matrix given by

$$B = \begin{pmatrix} b_{11} & b_{12} & 0 & b_{14} \\ b_{21} & b_{22} & b_{23} & 0 \\ 0 & b_{32} & b_{33} & b_{34} \\ b_{41} & 0 & b_{43} & b_{44} \end{pmatrix}$$

where

$$\begin{aligned}
b_{11} &= \frac{2}{I_1^2}(-\rho\frac{T}{\omega+T}+\gamma_2 T+\mu+(1-k)\sigma_2\frac{E}{\upsilon+E}) \\
b_{12}=b_{21} &= \frac{(1-k)\sigma_2\nu}{I_1(\nu+E)(\nu+E_1)} \\
b_{14}=b_{41} &= \gamma_1+\frac{\gamma_2}{I_1}-\frac{\rho\omega}{I_1(\omega+T)(\omega+T_1)} \\
b_{22} &= \frac{2\delta}{E_1^2} \\
b_{23}=b_{32} &= (1-k)\sigma_1 \\
b_{33} &= 2(-\alpha_1+\phi_1(N+N_1)+\beta T+(1-k)\sigma_1 E) \\
b_{34}=b_{43} &= \beta \\
b_{44} &= 2\left(-(1-d)(1-k)\alpha_2+\phi_2(T+T_1)+\gamma_1 I\right)
\end{aligned}$$

Then $\frac{dW}{dt} < 0$ if the matrix B is positive definite i e all the principal minors of B are positive. Now the first principal minor is given by

$$M_1 = |b_{11}| = \frac{2}{I_1^2}(-\rho\frac{T}{\omega+T}+\gamma_2 T+\mu+(1-k)\sigma_2\frac{E}{\upsilon+E}) > 0$$

only if

$$\begin{aligned}
-\rho\frac{T}{\omega+T}+\gamma_2 T+\mu+(1-k)\sigma_2\frac{E}{\upsilon+E} &> 0 \\
\gamma_2 T+\mu+(1-k)\sigma_2\frac{E}{\upsilon+E} &> \rho\frac{T}{\omega+T}
\end{aligned}$$

with this condition

$$\gamma_2 T+\mu+(1-k)\sigma_2\frac{E}{\upsilon+E} > \rho\frac{T}{\omega+T}, \tag{3.63}$$

therefore $M_1 > 0$. For the second principal minor

$$M_2 = \begin{vmatrix} b_{11} & b_{12} \\ b_{21} & b_{22} \end{vmatrix} > 0$$

holds if $b_{11}b_{22} > 0$ since $b_{11} > 0$ holds from the first condition. Now we need $b_{22} > 0$, then $b_{22} > 0$ if

$$\begin{aligned}
b_{11}b_{22}-b_{12}^2 &> 0 \\
\frac{2\delta}{I_1^2E_1^2}\left(-\rho\frac{T}{\omega+T}+\gamma_2 T+\mu+(1-k)\sigma_2\frac{E}{\upsilon+E}\right)-\frac{(1-k)^2\sigma_2^2\nu^2}{I_1^2(\nu+E)^2(\nu+E_1)^2} &> 0 \\
\frac{2\delta}{I_1^2E_1^2}\left(\gamma_2 T+\mu+(1-k)\sigma_2\frac{E}{\upsilon+E}\right) &> \frac{(1-k)^2\sigma_2^2\nu^2}{I_1^2(\nu+E)^2(\nu+E_1)^2}+\frac{2\delta\rho T}{I_1^2E_1^2(\omega+T)}
\end{aligned} \tag{3.64}$$

Therefore $M_2 > 0$ since the above inequality holds. The third principal minor is given by

$$M_3 = \begin{vmatrix} b_{11} & b_{12} & 0 \\ b_{21} & b_{22} & b_{23} \\ 0 & b_{32} & b_{33} \end{vmatrix} = b_{11}(b_{22}b_{33} - b_{23}^2) - b_{12}b_{21}b_{33} > 0$$

$$\begin{aligned} b_{11}(b_{22}b_{33} - b_{23}^2) - b_{12}b_{21}b_{33} > 0 \\ b_{11}\left(\frac{b_{22}b_{33}}{2} - b_{23}^2\right) + b_{33}\left(\frac{b_{11}b_{22}}{2} - b_{12}^2\right) \end{aligned}$$

This inequality hold if

$$\begin{aligned} \frac{b_{22}b_{33}}{2} - b_{23}^2 > 0, \\ \frac{2\delta}{I_1^2 E_1^2}\left(\gamma_2 T + \mu + (1-k)\frac{\sigma_2 E}{\nu + E}\right) > (1-k)^2\sigma_1^2 + \frac{2\delta\rho T}{I_1^2 E_1^2(\omega + T)}, \\ \frac{b_{11}b_{22}}{2} - b_{12}^2 > 0, \\ \frac{2\delta}{I_1^2 E_1^2}\left(\gamma_2 T + \mu + (1-k)\frac{\sigma_2 E}{\nu + E}\right) > \frac{(1-k)^2\sigma_2^2\nu^2}{I_1^2(\nu + E)^2(\nu + E_1)^2} + \frac{2\delta\rho T}{I_1^2 E_1^2(\omega + T)}. \end{aligned} \tag{3.65}$$

Lastly, the fourth principal minor

$$M_4 = \begin{vmatrix} b_{11} & b_{12} & 0 & b_{14} \\ b_{21} & b_{22} & b_{23} & 0 \\ 0 & b_{32} & b_{33} & b_{34} \\ b_{41} & 0 & b_{43} & b_{44} \end{vmatrix} > 0$$

$$\begin{aligned} b_{11}\left(b_{22}(\frac{b_{33}b_{44}}{2} - b_{34}^2) + b_{44}(\frac{b_{22}b_{33}}{2} - b_{23}^2)\right) \\ +b_{12}\left(b_{21}(\frac{b_{34}^2}{2} - b_{33}b_{44}) + b_{34}(\frac{b_{21}b_{34}}{2} - b_{23}b_{41})\right) \\ +b_{14}\left(b_{23}(\frac{b_{23}b_{41}}{2} - b_{21}b_{43}) + b_{41}(\frac{b_{23}^2}{2} - b_{22}b_{33})\right) > 0. \end{aligned}$$

Then $M_4 > 0$ if

$$\begin{aligned} \frac{b_{33}b_{44}}{2} > b_{34}^2, \frac{b_{22}b_{33}}{2} > b_{23}^2, \frac{b_{34}^2}{2} > b_{33}b_{44} \\ \frac{b_{21}b_{34}}{2} > b_{23}b_{41}, \frac{b_{23}b_{41}}{2} > b_{21}b_{43}, \frac{b_{23}^2}{2} > b_{22}b_{33} \end{aligned} \tag{3.66}$$

Then the principal minor M_4 is positive provided all the above conditions are satisfied. Then $\frac{dW}{dt}$ is negative definite if the matrix B is positive definite if all the inequalities (3.54), (3.55), (3.56), (3.57) are satisfied simultaneously. The tumor-free equilibrium point($\mathcal{E}_{d1}$) of the system (3.1)-(3.4) is globally asymptotically stable, according to LaSalle's Invariance Principle [46]. □

3.5.3 Global stability of Case (ii) dead equilibrium point

Theorem 3.9 *If* $Z = \frac{\alpha_1}{\phi_1 N + \beta T + (1-k)\sigma_1 E} \leq 1$, *then the dead equilibrium point* $\mathcal{E}_{d2}$ *is globally asymptotically stable in* Ω.

Proof. Consider the following Lyapunov function:

$$V(N, T, I, E) = \frac{1}{2}N^2.$$

In the $NTIE$-plane containing the equilibrium point, $V(\mathcal{E}_{d1}) = 0$ and $V(\mathcal{E}) > 0\ \forall \mathcal{E} \neq \mathcal{E}_{d1}$ are evident, as a result, it is a Lyapunov function. The derivative of V along the system's solution (3.1)-(3.4) is represented as

$$\begin{aligned}
\frac{dV}{dt} &= N\frac{dN}{dt}, \\
&= N(\alpha_1 N - \phi_1 N^2 - \beta NT - (1-k)\sigma_1 NE), \\
&= -N^2(\phi_1 N + \beta T + (1-k)\sigma_1 E - \alpha_1), \\
&= -N^2(\phi_1 N + \beta T + (1-k)\sigma_1 E)(1-Z),
\end{aligned}$$

where $Z = \frac{\alpha_1}{\phi_1 N + \beta T + (1-k)\sigma_1 E}$. If $Z \leq 1$ then $\frac{dV}{dt} \leq 0$. Hence, V is a Lyapunov function on Ω. Therefore, it follows from the LaSalle's Invariance Principle [47], that the dead equilibrium point is globally asymptotically stable. □

3.5.4 Global stability of co-existing equilibrium point

Theorem 3.10 *The co-existing equilibrium point $\mathcal{E}_e = (N_e, T_e, I_e, E_e)$ of the system (3.1)-(3.4) is globally asymptotically stable provided the following conditions are satisfied in Ω:*

$$\phi_1 N_e + \frac{\alpha_2\beta(1-d)(1-k)}{\phi_2} + \frac{(1-k^2)\sigma_1\Lambda}{\delta} > 0,$$

$$\frac{2}{N_e^2T_e^2}\left(\phi_1 N_e + \frac{\alpha_2\beta(1-d)(1-k)}{\phi_2} + \frac{(1-k)^2\sigma_1\Lambda}{\delta}\right)\left(\phi_2 T_e + \frac{\gamma_1 s}{\mu-\rho}\right) > \frac{\beta^2}{N_e^2},$$

$$\frac{2}{T_e^2I_e^2}\left(\phi_2 T_e + \frac{\gamma_1 s}{\mu-\rho}\right)\left(\frac{\alpha_2\gamma_2(1-d)(1-k)}{\phi_2} + \mu + \frac{(1-k)^2\sigma_2\Lambda}{\nu\delta+(1-k)\Lambda}\right) + \left(\frac{\rho\omega}{I_e(\omega+T)(\omega+T_e)}\right)^2 >,$$

$$\frac{2}{T_e^2I_e^2}\left(\phi_2 T_e + \frac{\gamma_1 s}{\mu-\rho}\right)\left(\frac{\alpha_2\rho(1-d)(1-k)}{\phi_2\omega+(1-d)(1-k)\alpha_2}\right) + \frac{\gamma_1}{T_e^2} + \frac{\gamma_2}{I_e^2}.$$

The conditions means that even though the cells co-exists, normal and immune cells are still above the equilibria.

Proof. Consider the following Lyapunov function about $\mathcal{E}_e$

$$V = \left(\frac{N-N_e}{N_e}\right)^2 + \left(\frac{T-T_e}{T_e}\right)^2 + \left(\frac{I-I_e}{I_e}\right)^2 + \left(\frac{E-E_e}{E_e}\right)^2$$

Differentiating on both side with respect to time, we get

$$\begin{aligned}
\frac{dV}{dt} &= \frac{2}{N_e^2}(N-N_e)\frac{dN}{dt} + \frac{2}{T_e^2}(T-T_e)\frac{dT}{dt} + \frac{2}{I_e^2}(I-I_e)\frac{dI}{dt} + \frac{2}{E_e^2}(E-E_e)\frac{dE}{dt} \\
&= \frac{2}{N_e^2}(N-N_e)(\alpha_1 N - \phi_1 N^2 - \beta NT - (1-k)\sigma_1 NE) \\
&\quad + \frac{2}{T_e^2}(T-T_e)((1-d)(1-k)\alpha_2 T - \phi_2 T^2 + (1-k)\sigma_1 NE - \gamma_1 IT) \\
&\quad + \frac{2}{I_e^2}(I-I_e)(s + \frac{\rho IT}{\omega+T} - \mu I - \gamma_2 IT - (1-k)\sigma_2\frac{IE}{\nu+E}) \\
&\quad + \frac{2}{E_e^2}(E-E_e)((1-k)\Lambda - \delta E)
\end{aligned}$$

We arrived at this conclusion after some algebraic calculations:

$$\begin{aligned}
= \; & \frac{2}{N_e^2}(N-N_e)^2(\alpha_1 - \phi_1(N+N_e) - \beta T - (1-k)\sigma_1 E) - \frac{2\beta}{N_e}(N-N_e)(T-T_e) + (N-N_e)(I-I_e)\times 0 \\
& -(1-k)\sigma_1(N-N_e)(E-E_e) + \frac{2}{T_e^2}(T-T_e)^2((1-d)(1-k)\alpha_2 - \phi_2(T+T_e) - \gamma_1 I) \\
& +2(\frac{\gamma_1}{T_e} + \frac{\gamma_2}{I_e} - \frac{\rho\omega}{I_e(\omega+T)(\omega+T_e)})(T-T_e)(I-I_e) \\
& +\frac{2}{I_e^2}(I-I_e)^2(\frac{\rho T}{\omega+T} - \mu - \gamma_2 T - (1-k)\sigma_2\frac{E}{\nu+E}) - \frac{2(1-k)\sigma_2\nu}{I_e(\nu+E)(\nu+E_e)} \\
& -\frac{2\delta}{E_e^2}(E-E_e)^2.
\end{aligned}$$

$\frac{dV}{dt}$ can now be written as the sum of the quadratics as follows:

$$\begin{aligned}\frac{dV}{dt} &= -a_{11}(N-N_e)^2 - 2a_{12}(N-N_e)(T-T_e) - 2a_{14}(N-N_e)(E-E_e) - a_{22}(T-T_e)^2 \\ &\quad -2a_{23}(T-T_e)(I-I_e) - a_{33}(I-I_e)^2 - a_{44}(E-E_e)^2 \\ &= -X^T C X\end{aligned}$$

where $X^T = (N-N_e, T-T_e, I-I_e, E-E_e)$ and C is a symmetric matrix given by

$$C = \begin{pmatrix} c_{11} & c_{12} & 0 & c_{14} \\ c_{21} & c_{22} & c_{23} & 0 \\ 0 & c_{32} & c_{33} & c_{34} \\ c_{41} & 0 & c_{43} & c_{44} \end{pmatrix} \tag{3.67}$$

where

$$\begin{aligned} c_{11} &= \frac{2}{N_e^2}(-\alpha_1 + \phi_1(N+N_e) + +(1-k)\sigma_1 E) \\ c_{12} = c_{21} &= \frac{\beta}{N_e} \\ c_{14} = c_{41} &= \frac{(1-k)\sigma_1}{N_e} \\ c_{22} &= \frac{2}{T_e^2}\left(-(1-d)(1-k)\alpha_2 + \phi_2(T+T_e) + \gamma_1 I\right) \\ c_{23} = c_{32} &= \frac{\gamma_1}{T_e} + \frac{\gamma_2}{I_e} - \frac{\rho\omega}{I_e(\omega+T)(\omega+T_e)} \\ c_{33} &= \frac{2}{I_e^2}(-\rho\frac{T}{\omega+T} + \gamma_2 T + \mu + (1-k)\sigma_2\frac{E}{\upsilon+E}) \\ c_{34} = c_{43} &= \frac{(1-k)\sigma_2}{I_e} \\ b_{44} &= \frac{2\delta}{E_e^2}. \end{aligned}$$

Then $\frac{dV}{dt} < 0$ if the matrix C is positive definite *i.e* all the principal minors of C are positive. Now the first principal minor is given by:

$$M_1 = |c_{11}| = \frac{2}{N_e^2}(-\alpha_1 + \phi_1(N+N_e) + \beta T + (1-k)\sigma_1 E) > 0$$

$M_1 > 0$ only if $-\alpha_1 + \phi_1(N+N_e) + \beta T + (1-k)\sigma_1 E > 0$. Since all variables are bounded in the region Ω, now substituting the upper bounds of the variables, yields:

$$\phi_1 N_e + \frac{\alpha_2\beta(1-d)(1-k)}{\phi_2} + \frac{(1-k^2)\sigma_1\Lambda}{\delta} > 0 \tag{3.68}$$

which holds. Therefore $M_1 > 0$. For the second principle minor, repeat the process,

$$M_2 = \begin{vmatrix} c_{11} & c_{12} \\ c_{21} & c_{22} \end{vmatrix} > 0$$

$$c_{11}c_{22} - c_{12}^2 > 0$$

$$c_{11}c_{22} > c_{12}^2.$$

Since all variable are bounded in the region Ω and now substituting the upper bounds of the variables, yields:

$$\frac{2}{N_e^2 T_e^2}\left(\phi_1 N_e + \frac{\alpha_2\beta(1-d)(1-k)}{\phi_2} + \frac{(1-k^2)\sigma_1\Lambda}{\delta}\right)\left(\phi_2 T_e + \frac{\gamma_1 s}{\mu-\rho}\right) > \frac{\beta^2}{N_e^2} \tag{3.69}$$

Since the above inequality holds, then $M_2 > 0$. The third principal minor

$$M_3 = \begin{vmatrix} c_{11} & c_{12} & 0 \\ c_{21} & c_{22} & c_{23} \\ 0 & c_{32} & c_{33} \end{vmatrix} = c_{11}(c_{22}c_{33} - c_{23}^2) - c_{12}c_{21}c_{33} > 0$$

M_3 is positive definite if the following holds,

$$c_{11}\left(\frac{c_{22}c_{33}}{2} - c_{23}^2\right) + c_{33}\left(\frac{c_{11}c_{22}}{2} - c_{12}^2\right) > 0$$

Since all variable are bounded in the region Ω and now substituting the upper bounds of the variables, then the above inequality holds if

$$\begin{aligned} \frac{c_{22}c_{33}}{2} &> c_{23}^2 \\ \frac{2}{T_e^2 I_e^2}\left(\phi_2 T_e + \frac{\gamma_1 s}{\mu-\rho}\right)\left(\frac{\alpha_2\gamma_2(1-d)(1-k)}{\phi_2} + \mu + \frac{(1-k)^2\sigma_2\Lambda}{\nu\delta + (1-k)\Lambda}\right) + \left(\frac{\rho\omega}{I_e(\omega+T)(\omega+T_e)}\right)^2 &> \\ \frac{2}{T_e^2 I_e^2}\left(\phi_2 T_e + \frac{\gamma_1 s}{\mu-\rho}\right)\left(\frac{\alpha_2\rho(1-d)(1-k)}{\phi_2\omega + (1-d)(1-k)\alpha_2}\right) + \frac{\gamma_1}{T_e^2} + \frac{\gamma_2}{I_e^2} & \\ \frac{c_{11}c_{22}}{2} &> c_{12}^2 \\ \frac{2}{N_e^2 T_e^2}\left(\phi_1 N_e + \frac{\alpha_2\beta(1-d)(1-k)}{\phi_2} + \frac{(1-k^2)\sigma_1\Lambda}{\delta}\right)\left(\phi_2 T_e + \frac{\gamma_1 s}{\mu-\rho}\right) &> \frac{\beta^2}{N_e^2} \end{aligned} \tag{3.70}$$

Lastly the fourth principle minor

$$M_4 = \begin{vmatrix} c_{11} & c_{12} & 0 & c_{14} \\ c_{21} & c_{22} & c_{23} & 0 \\ 0 & c_{32} & c_{33} & c_{34} \\ c_{41} & 0 & c_{43} & c_{44} \end{vmatrix} > 0$$

Then

$$\begin{aligned} c_{11}\left(c_{22}(\frac{c_{33}c_{44}}{2}-c_{34}^2)+c_{44}(\frac{c_{22}c_{33}}{2}-c_{23}^2)\right) \\ +c_{12}\left(c_{21}(\frac{c_{34}^2}{2}-c_{33}c_{44})+c_{34}(\frac{c_{21}c_{34}}{2}-c_{23}c_{41})\right) \\ +c_{14}\left(c_{23}(\frac{c_{23}c_{41}}{2}-c_{21}c_{43})+c_{41}(\frac{c_{23}^2}{2}-c_{22}c_{33})\right)>0 \end{aligned}$$

then M_4 is positive definite if the following holds

$$\begin{aligned} \frac{c_{33}c_{44}}{2}>c_{34}^2, \frac{c_{22}c_{33}}{2}>c_{23}^2, \frac{c_{34}^2}{2}>c_{33}c_{44} \\ \frac{c_{21}c_{34}}{2}>c_{23}c_{41}, \frac{c_{23}c_{41}}{2}>c_{21}c_{43}, \frac{c_{23}^2}{2}>c_{22}c_{33} \end{aligned} \tag{3.71}$$

So the matrix C is positive definite if all the inequalities (3.68), (3.69), (3.70), (3.71) are satisfied simultaneously. Thus the co-existing equilibrium point $\mathcal{E}_e$ satisfies all the Lyapunov stability theorem with the conditions in (3.68), (3.69), (3.70), (3.71). Then the co-existing equilibrium point is globally stable. In all aspect the Normal and Immune cells should always be positive, so that the body can fight Tumor cells. □

Chapter 4

NTIE model as an Optimal Control Problem

4.1 Introduction

Optimal Control theory is a branch of mathematical optimization that deals with evaluating a control for a dynamical system over time in order to optimize an objective function[48]. Our aim is use two controls surgery (u_1) and hormone therapy (u_2) to reduce the number of tumor cells and the levels of estrogen cells at a minimal cost.

In this chapter, we use the model system (3.1)-(3.4) in Chapter 3 to formulate a corresponding Optimal Control Problem (OCP). Thus we seek from the OCP, optimal values for the controls $u_1(t)$ (surgery) and $u_2(t)$ (hormone therapy) as well as the optimal trajectories N^*, T^*, I^* and E^* which form the solution to the OCP. The system will be considered in the time interval $[0, t_f]$, where t_f is the final time. The control set is defined as follows:

$$U = \{(u_1(t), u_2(t)) : u_i \text{ Lebesgue measurable }, 0 \leq u_i \leq u_{i\max} < 1, i = 1, 2\} \tag{4.1}$$

where $u_{1\max}$ and $u_{2\max}$ denote the upper bounds for the efforts of respective intervention. These bounds reflect practical limitations on the maximum rates of controls in the given time period [48]. As a result, these will be determined by the budget set aside for the implementation of each of these control measures. The lower bounds for the controls, on the other hand, correspond to the situation in which there is no intervention for the classes T and E.

4.2 Formulation of the optimal control problem

In this section, we formulate an Optimal Control Problem for the model in the systems of differential equations (3.1)-(3.4), using surgery and hormone therapy as control interventions to reduce the tumor burden and estrogen levels at the lowest possible cost at final time. Then, we formulate the objective functional

$$J(u_1, u_2) = \min_{u_1,u_2} \int_0^{t_f} \left(T(t) + E(t) + \frac{1}{2}Au_1^2 + \frac{1}{2}Bu_2^2 \right) dt, \tag{4.2}$$

subject to

$$\begin{aligned}
\frac{dN}{dt} &= (\alpha_1 - \phi_1 N)N - \beta NT - (1-u_2)\sigma_1 NE, \\
\frac{dT}{dt} &= ((1-u_1)(1-u_2)\alpha_2 - \phi_2 T)T + (1-u_2)\sigma_1 NE - \gamma_1 IT, \\
\frac{dI}{dt} &= s + \rho\frac{IT}{\omega + T} - \gamma_2 IT - \mu I - (1-u_2)\sigma_2\frac{IE}{\upsilon + E}, \\
\frac{dE}{dt} &= (1-u_2)\Lambda - \delta E,
\end{aligned} \tag{4.3}$$

where $N(0) = N_0 \geq 0, T(0) = T_0 \geq 0, I(0) = I_0 \geq 0, E(0) = E_0 \geq 0$

$$U = \{0 \leq u_1 \leq u_{1\max}, 0 \leq u_2 \leq u_{2\max}, \forall t \in [0, t_f]\} \tag{4.4}$$

and where the parameters A and B together with appropriate units define the appropriate costs associated with controls $u_1(t)$ and $u_2(t)$ respectively. The quadratic terms are introduced to indicate non-linear costs potentially arising at high intervention levels [31]. Thus, the terms Au_1^2 and Bu_2^2 describe the costs associated with intervention of tumor and estrogen cells respectively. Since we have shown that the system is bounded from chapter 3, now we need to determine the existence of the optimal control using the results in [49]. For our analysis we will assume that the two controls (u_1, u_2) are bounded and Lebesgue integrable. In particular, we seek an ideal control pair (u_1^*, u_2^*) such that

$$J(u_1^*, u_2^*) = \min_U J(u_1, u_2).$$

Theorem 4.1 *(Existence of an Optimal control)*
Given the objective function in (4.2), where U is the admissible set, there exists an optimal controls u_1^* and u_2^* such that

$$J(u_1^*, u_2^*) = \min_{u_1,u_2 \in U} J(u_1, u_2),$$

if the following holds:

- *The set of variables and controls of the state problem is non-empty.*
- *U is a closed convex.*
- *The Objective functional integrand is concave.*

Proof. Since the coefficients of the system (4.3) are bounded and the solutions are bounded on a finite time interval, we may use the result of [50] to determine the existence of the system's solution (4.3). Then the first condition is fulfilled. By definition the control set is closed convex, which gives the second condition. Now we need to prove the concavity of the integrand, note that we have Hessian matrix of J in u_1, u_2 is given by

$$H(u_1, u_2) = \begin{pmatrix} A & 0 \\ 0 & B \end{pmatrix},$$

then,

$$\det(H(u_1, u_2)) = AB \geq 0, \forall (u_1, u_2) \in U,$$

therefore, the objective functional integrand is concave. □

The above problem can now be solved either numerically by using total enumeration methods or linear programming techniques. This will be presented in chapter 5. Any solution to the above optimal control problem must also satisfy certain auxiliary conditions, which are discussed below. The necessary conditions that an optimal control pair must satisfy are derived from Pontryagin's Maximum Principle (PMP) [51]. There are various versions of PMP for problem statements of varying generality. The PMP states simply that the Hamiltonian ($\mathcal{H}$), must be minimized with respect to u_1 and u_2 over the set of all permissible controls U.

With the help of Pontryagin's Maximum Principle [51] (see A), we define the Hamiltonian for the problem of the system (4.2) and (4.3) as follows:

$$\mathcal{H}(t, N, T, I, E, u_1, u_2, \lambda_1, \lambda_2, \lambda_3, \lambda_4) = T + E + \frac{1}{2}Au_1^2 + \frac{1}{2}Bu_2^2 + \lambda_1\frac{dN}{dt} + \lambda_2\frac{dT}{dt} + \lambda_3\frac{dI}{dt} + \lambda_4\frac{dE}{dt}. \quad (4.5)$$

By applying the PMP to the model (4.3) and using the existence result proved above for the optimal control, we obtain the following theorem:

Theorem 4.2 *There exists an optimal control pair* (u_1^*, u_2^*) *with a corresponding solution* (N^*, T^*, I^*, E^*), *that minimizes* $J(u_1, u_2)$ *over* U. *Moreover, there exists adjoint functions,* $\lambda_1(t), \lambda_2(t), \lambda_3(t)$ *and* $\lambda_4(t)$, *such that*

$$\frac{d\lambda_i}{dt} = -\frac{\partial \mathcal{H}}{\partial x_i}, i \in \{1, 2, 3, 4\},$$

with $x_1 = N, x_2 = T, x_3 = I, x_4 = E$,

that is

$$\begin{aligned}
\frac{d\lambda_1}{dt} = -\frac{\partial \mathcal{H}}{\partial N} &= -\left(\lambda_1(\alpha_1 - 2\phi_1 N^* - \beta T^* - (1-u_2^*)\sigma_1 E^*) + \lambda_2(1-u_2^*)\sigma_1 E^*\right) \\
\frac{d\lambda_2}{dt} = -\frac{\partial \mathcal{H}}{\partial T} &= -\left(1 - \beta N^* \lambda_1 + \lambda_2((1-u_1^*)(1-u_2^*)\alpha_2 - 2\phi_2 T^* - \gamma_1 I^*) - \lambda_3\left(\frac{\rho\omega I^*}{(\omega + T^*)^2} - \gamma_2 I^*\right)\right) \\
\frac{d\lambda_3}{dt} = -\frac{\partial \mathcal{H}}{\partial I} &= -\left(-\lambda_2\gamma_1 T^* + \lambda_3\left(\frac{\rho T^*}{\omega + T^*} - \mu - \gamma_2 T^* - (1-u_2^*)\frac{\sigma_2 E^*}{\nu + E^*}\right)\right) \\
\frac{d\lambda_4}{dt} = -\frac{\partial \mathcal{H}}{\partial E} &= -\left(1 - \lambda_1(1-u_2^*)\sigma_1 N^* + \lambda_2(1-u_2^*)\sigma_1 N^* - \lambda_3(1-u_2^*)\frac{\sigma_1 \nu I^*}{(\nu + E^*)^2} - \lambda_4\delta\right),
\end{aligned} \tag{4.6}$$

with transversality conditions

$$\lambda_i(t_f) = 0, i \in \{1, 2, 3, 4\}.$$

The following characterization holds,

$$u_1^* = \begin{cases} 0 & \text{if } \frac{\partial \mathcal{H}}{\partial u_1} \leq 0, \\ \frac{\lambda_2 \alpha_2 T^*}{A} & \text{if } \frac{\partial \mathcal{H}}{\partial u_1} = 0, \\ u_{1\max} & \text{if } \frac{\partial \mathcal{H}}{\partial u_1} \geq 0, \end{cases}$$

and

$$u_2^* = \begin{cases} 0 & \text{if } \frac{\partial \mathcal{H}}{\partial u_2} \leq 0, \\ \frac{\sigma_1 N^* E^*(\lambda_2 - \lambda_1) + \lambda_2 \alpha_2 T^* + \Lambda\lambda_4}{B} + \frac{\lambda_3 \sigma_2 I^* E^*}{B(\nu + E^*)} & \text{if } \frac{\partial \mathcal{H}}{\partial u_2} = 0, \\ u_{2\max} & \text{if } \frac{\partial \mathcal{H}}{\partial u_2} \geq 0. \end{cases}$$

Thus the compact way of writing the optimal control is,

$$u_1^* = \min\left\{u_{1\max}, \max\left[0, \frac{\lambda_2 \alpha_2 T^*}{A}\right]\right\} \tag{4.7}$$

and

$$u_2^* = \min\left\{u_{2\max}, \max\left[0, \frac{\sigma_1 N^* E^*(\lambda_2 - \lambda_1) + \lambda_2\alpha_2 T^* + \Lambda\lambda_4}{B} + \frac{\lambda_3\sigma_2 I^* E^*}{B(\nu + E^*)}\right]\right\} \tag{4.8}$$

Proof. Let u_1^* and u_2^* be the given optimal control functions and N^*, T^*, I^* and E^* be the system's associated optimal control variables that minimize the objective functional. Then by Pontryagin's maximum principle [52], there exists adjoint variables $\lambda_1, \lambda_2, \lambda_3, \lambda_4$ which satisfy the equations below:

$$\begin{aligned}
\frac{d\lambda_1}{dt} = -\frac{\partial\mathcal{H}}{\partial N} &= -\left(\lambda_1(\alpha_1 - 2\phi_1 N^* - \beta T^* - (1-u_2^*)\sigma_1 E^*) + \lambda_2(1-u_2^*)\sigma_1 E^* + (1-u_2^*)\sigma_1\lambda_2 E^*\right)\\
\frac{d\lambda_2}{dt} = -\frac{\partial\mathcal{H}}{\partial T} &= -\left(1 - \beta N^*\lambda_1 + \lambda_2((1-u_1^*(1-u_2^*)\alpha_2 - 2\phi_2 T^* - \gamma_1 I^*) - \lambda_3(\frac{\rho\omega I^*}{(\omega+T^*)^2} - \gamma_2 I^*)\right)\\
\frac{d\lambda_3}{dt} = -\frac{\partial\mathcal{H}}{\partial I} &= -\left(-\lambda_2\gamma_1 T^* + \lambda_3(\frac{\rho T^*}{\omega+T^*} - \mu - \gamma_2 T^* - (1-u_2^*)\frac{\sigma_2 E^*}{\nu+E^*})\right)\\
\frac{d\lambda_4}{dt} = -\frac{\partial\mathcal{H}}{\partial E} &= -\left(1 - \lambda_1(1-u_2^*)\sigma_1 N^* + \lambda_2(1-u_2^*)\sigma_1 N^* - \lambda_3(1-u_2^*)\frac{\sigma_1\nu I^*}{(\nu+E^*)^2} - \lambda_4\delta\right),
\end{aligned} \tag{4.9}$$

with transversality conditions

$$\lambda_1(t_f) = \lambda_2(t_f) = \lambda_3(t_f) = \lambda_4(t_f) = 0,$$

evaluated at the optimal control pair and corresponding states, which results in the adjoint system (4.6) [53].

Note that u_1^* and u_2^* are candidate minimum solutions for the problem. By taking into account the optimality conditions,

$$\frac{\partial\mathcal{H}}{\partial u_1} = 0 \text{ at } u_1^* \text{ and } \frac{\partial\mathcal{H}}{\partial u_2} = 0 \text{ at } u_2^*$$

and solving for u_1^* and u_2^*, depending on the limits $0 \le u_1 \le u_{1max}$ and $0 \le u_2 \le u_{2max}$, then the characterizations in (4.7) and (4.8) can be derived as follows:

$$\begin{aligned}
0 &= \frac{\partial\mathcal{H}}{\partial u_1} = Au_1 - \alpha_2\lambda_2 T,\\
0 &= \frac{\partial\mathcal{H}}{\partial u_2} = Bu_2 + \sigma_1 NE(\lambda_1 - \lambda_2) - \frac{\sigma_2\lambda_3 IE}{\nu+E} - \Lambda\lambda_4.
\end{aligned}$$

The characterization of u_1^* and u_2^* are obtained as follows:

$$\begin{aligned}
u_1^* &= \frac{\lambda_2\alpha_2 T^*}{A},\\
u_2^* &= \frac{\sigma_1 N^* E^*(\lambda_2 - \lambda_1) + \lambda_2\alpha_2 T^* + \Lambda\lambda_4}{B} + \frac{\lambda_3\sigma_2 I^* E^*}{B(\nu+E^*)}.
\end{aligned}$$

The bounds $0 \leq u_1 \leq u_{1\max}$ and $0 \leq u_2 \leq u_{2\max}$, can now be imposed on the controls to obtain the following:

$$u_1^* = \min\left\{u_{1\max}, \max\left[0, \frac{\lambda_2\alpha_2 T^*}{A}\right]\right\} \tag{4.10}$$

$$u_2^* = \min\left\{u_{2\max}, \max\left[0, \frac{\sigma_1 N^* E^*(\lambda_2 - \lambda_1) + \lambda_2\alpha_2 T^* + \Lambda\lambda_4}{B} + \frac{\lambda_3\sigma_2 I^* E^*}{B(\nu + E^*)}\right]\right\}. \tag{4.11}$$

□

The optimality system comprises of the four state equations coupled with the corresponding four adjoint equations with the initial and transversality conditions together with the characterization of the optimal controls. Utilizing the characterization of the optimal controls above, we obtain the following set of equations:

$$\begin{aligned}
\frac{dN^*}{dt} &= (\alpha_1 - \phi_1 N^*)N^* - \beta N^* T^* - (1-u_2^*)\sigma_1 N^* E^*,\\
\frac{dT^*}{dt} &= ((1-u_1^*)(1-u_2^*)\alpha_2 - \phi_2 T^*)T^* + (1-u_2^*)\sigma_1 N^* E^* - \gamma_1 I^* T^*,\\
\frac{dI^*}{dt} &= s + \rho\frac{I^* T^*}{\omega + T^*} - \gamma_2 I^* T^* - \mu I^* - (1-u_2^*)\sigma_2\frac{I^* E^*}{\upsilon + E^*},\\
\frac{dE^*}{dt} &= (1-u_2^*)\Lambda - \delta E^*,\\
\frac{d\lambda_1^*}{dt} &= -\left(\lambda_1(\alpha_1 - 2\phi_1 N^* - \beta T^* - (1-u_2^*)\sigma_1 E^*) + \lambda_2(1-u_2^*)\sigma_1 E^*\right),\\
\frac{d\lambda_2^*}{dt} &= -\left(1 - \beta N^*\lambda_1 + \lambda_2((1-u_1^*)(1-u_2^*)\alpha_2 - 2\phi_2 T^* - \gamma_1 I^*) - \lambda_3\Big(\frac{\rho\omega I^*}{(\omega + T^*)^2} - \gamma_2 I^*\Big)\right),\\
\frac{d\lambda_3^*}{dt} &= -\left(-\lambda_2\gamma_1 T^* + \lambda_3\Big(\frac{\rho T^*}{\omega + T^*} - \mu - \gamma_2 T^* - (1-u_2^*)\frac{\sigma_2 E^*}{\nu + E^*}\Big)\right),\\
\frac{d\lambda_4^*}{dt} &= -\left(1 - \lambda_1(1-u_2^*)\sigma_1 N^* + \lambda_2(1-u_2^*)\sigma_1 N^* - \lambda_3(1-u_2^*)\frac{\sigma_1\nu I^*}{(\nu + E^*)^2} - \lambda_4\delta\right),
\end{aligned} \tag{4.12}$$

with $\lambda_1(t_f) = \lambda_2(t_f) = \lambda_3(t_f) = \lambda_4(t_f) = 0$ and $N(0) = N_0, T(0) = T_0, I(0) = I_0, E(0) = E_0$.

Chapter 5

Numerical Analysis

5.1 Introduction

In this chapter, we will perform sensitivity analysis on the basic reproduction number (R_0) in relation to the parameters and present numerical results for both the NTIE model and the corresponding OCP-NTIE model. Different optimal control strategies for the OCP-NTIE model will be discussed using estimated parameters.

5.2 Sensitivity analysis

Sensitivity analysis specifies the importance of each parameter to the model. Furthermore, sensitivity analysis is used to investigate the accuracy of model predictions for parameter values because errors in data collection and postulated parameter values can occur [53, 54]. Furthermore, it is used to determine which parameters have greater influence on R_0 than others.
In this section, we will perform a sensitivity analysis of the basic reproduction number using to identify which parameters have the most impact on the model. We are interested in learning more about how these parameters affect R_0 as their values vary. To find out which parameter in the model have high impact on R_0, we investigate the change in R_0 with respect to tumor growth parameters. From equation (3.43), the explicit expression of the basic reproduction number R_0 is

given by:

$$\begin{aligned} R_0 &= \frac{\beta\sigma_1\Lambda(1-k)^2\Big(\alpha_1\delta-(1-k)^2\sigma_1\Big)\Big(\mu(\nu\delta+(1-k)\Lambda)+(1-k)^2\sigma_2\Lambda\Big)}{\delta\Big(\alpha_1\delta\phi_1-\phi_1\sigma_1(1-k)^2\Lambda\Big)\Big((\nu\delta+(1-k)\Lambda)(s\gamma_1-\mu\alpha_2 r)-r\alpha_2(1-k)^2\sigma_2\Lambda\Big)}. \\ \text{where } r &= (1-d)(1-k) \end{aligned}$$

The normalized forward sensitivity index of a variable to a parameter is the ratio of the variable's relative change to the parameter's relative change. The sensitivity index is defined using partial derivatives if the variable is a differentiable function of the parameter [66]. The normalized forward sensitivity index of a variable u that depends differentiability on a parameter p is defined as [67]:

$$\Upsilon_u^p = \frac{\partial u}{\partial p}\times\frac{p}{u}$$

Since we have derived an explicit formula for R_0, using normalized forward sensitivity index, we obtain analytical expression for the sensitivity of R_0,

$$\frac{\partial R_0}{\partial p} = \frac{\partial R_0}{\partial p}\times\frac{p}{R_0}$$

To slow the growth of cancer cells, we must first understand the significance of the various factors that contribute to their development. The initial growth of cancer cells is determined by the reproduction number R_0. As a result, we investigate the sensitivity indices of the reproduction number R_0 in relation to the parameters in question. The following parameters are subjected to sensitivity analysis to determine their impact on basic reproduction number: constant rate of surgery (d), source of immune cells (s), tumor cell death rate due to immune response (γ_1), tumor formation rate (σ_1), and immune suppression rate due to excess estrogen (σ_2). We now investigate the change in R_0 with respect to (d) by computing:

$$\frac{\partial R_0}{\partial d} = -\frac{AB\alpha_2\Big(\mu(\nu\delta+(1-k)\Lambda)+(1-k)^2\sigma_2\Lambda\Big)}{CD^2}$$

where

$$\begin{aligned} A &= \beta\sigma_1\Lambda(1-k)^2\Big(\alpha_1\delta-(1-k)^2\sigma_1\Big), \\ B &= \mu(\nu\delta+(1-k)\Lambda)+(1-k)^2\sigma_2\Lambda, \\ C &= \delta\Big(\alpha_1\delta\phi_1-\phi_1\sigma_1(1-k)^2\Lambda\Big), \\ D &= (\nu\delta+(1-k)\Lambda)(s\gamma_1-\mu\alpha_2 r)-r\alpha_2(1-k)^2\sigma_2\Lambda. \end{aligned}$$

Since $0 \leq d < 1$ and all of the other parameters are considered to be positive, we obtain

$$\frac{\partial R_0}{\partial d} < 0.$$

This implies that the basic reproduction number R_0 in the cell population decreases with the rate of surgery performed on the tumor cells. This means that intervention of surgery to the infected cells, has a positive effect on the disease intervention and control because it decreases the number of cancer cells. An increase of surgery intervention, decreases the number of cancer cells produced. Now to investigate the effect of s and γ_1 on the basic reproduction number, we examine the change in R_0 with respect to s and γ_1 by computing:

$$\begin{aligned} \frac{\partial R_0}{\partial s} &= -\frac{\gamma_1(\nu\delta + (1-k)\Lambda)}{CD^2} < 0, \\ \frac{\partial R_0}{\partial \gamma_1} &= -\frac{s(\nu\delta + (1-k)\Lambda)}{CD^2} < 0. \end{aligned}$$

This implies that the number of secondary cases R_0 in the cell population will decrease with increasing the source of immune booster (s) and the number of tumor cells death rate due to immune response (γ_1). We now examine the effect of σ_1 on the basic reproduction number, by computing the change in R_0 with respect to σ_1:

$$\frac{\partial R_0}{\partial \sigma_1} = \frac{\beta\Lambda(1-k)^2(\alpha_1\delta - 2(1-k)^2\sigma_1)BC + AB\phi_1(1-k)^2\Lambda}{C^2D}.$$

Since all parameters are assumed to be positive, then we obtain:

$$\frac{\partial R_0}{\partial \sigma_1} > 0.$$

This implies that the number of secondary cases R_0 in the cell population increases with the tumor formation rate σ_1. Therefore, this parameter should be kept as low as possible. We now investigate the effect of σ_2 on R_0, we compute the change in R_0 with respect to σ_2:

$$\frac{\partial R_0}{\partial \sigma_2} = \frac{A((1-k)^2D\Lambda + \alpha_2 r(1-k)^2\Lambda B)}{CD^2} > 0.$$

This means that as the immune suppression rate increases, so does the number of secondary cases R_0 in the cell population. As a result, this parameter should be kept to a minimum value.

5.3 Model parameters and estimated initial conditions

In this section we summarize the parameter values and initial values of the $NTIE$ model. The parameter values and initial values were estimated using historical data. In numerical simulations, we will analyze the volume in a sphere to determine the number of cells that stretch across the diameter using Runge Kutta method. The mathematical formula of a volume of sphere is given by:

$$V = \frac{4}{3}\pi r^3,$$

where $r = \frac{d}{2}$ is the radius of the sphere, V is the volume [15]. We will derive all our initial values using the cell size of $0,01mm$. The initial values are $N(0) = 1$ cm^3 (10^{12} cells), $T(0) = 10^{-5}$ cm^3, $I(0) = \frac{s}{\mu} = 1.448$ cm^3 [15] and we have assumed the initial value of estrogen to be $E(0) = 0.02$ cm^3. A tumor of 1 cm^3 is assumed to contain 10^9 cells [55] and the clinical detection threshold for tumor is generally 10^7 cells [56], the initial volume of 10^{-5} is below clinical detection levels, implying that tumor can be eradicated. The initial tumor cells and estrogen cells are small, while immune and normal cells are at their healthy equilibrium points when surgery and hormone therapy are started. The parameters of the cost function are set to $A = 0.05$ and $B = 0.005$. These values ensure that the maximum control is equally weighted, and the maximum control input for both controls is 0.9. The maximum duration of observation is set at 100 days. All parameter values and sources, used in the numerical simulations are stated in the table below:

Table 5.1: Description of parameter values

Description	Parameter	Value	Units	Source
Per capita growth rate of normal cells	α_1	0.70	day^{-1}	[16]
Per capita growth rate of tumor cells	α_2	0.98	day^{-1}	[16]
Natural death of rate of normal cells	ϕ_1	0.3	day^{-1}	[17]
Natural death rate of tumor cells	ϕ_2	0.4	day^{-1}	[17]
Tumor formation rate by excess estrogen	σ_1	0.20	day^{-1}	[15]
Immune suppression due to excess estrogen	σ_2	0.002	day^{-1}	[16]
Rate of inhibition of normal cells	β	1	day^{-1}	[18]
Source of estrogen	Λ	0.5	day^{-1}	[18]
Tumor death rate due to immune response	γ_1	0.9	day^{-1}	[15]
Immune death rate due to tumor attack	γ_2	0.3	day^{-1}	[15]
Immune response rate	ρ	0.2710	day^{-1}	[57]
Immune threshold	ω	0.8620	day^{-1}	[57]
Natural death of immune cells	μ	0.29	day^{-1}	[16]
Decay factor of immune cells	ν	0.1	day^{-1}	[17]
Source of immune cells	s	0.4	day^{-1}	[16]
Natural death rate of estrogen	δ	0.97	day^{-1}	[17]
Constant rate of surgery	d	0-1	day^{-1}	[18]
Constant rate of hormone therapy	k	0-1	day^{-1}	[18]

5.4 Results and discussion

In this section, we use the Runge-Kutta method (RK4) to investigate the behavior of the NTIE and OCP-NTIE models. To solve the systems of state equations and adjoint equations, we ran numerical simulations in MATLAB using the forward-backward sweep method. The systems of state equations were solved forward in time simultaneously, and the systems of adjoint equations were solved backward in time simultaneously. We assume the step size $h = \frac{t_f}{M}$ where $t_f = 100$ and $M = 999$.

The graphical representations of the $NTIE$ model with and without controls are presented so that we can compare them and understand the effectiveness of using the control. Figure 5.1 shows

solutions to the model with no control measures.

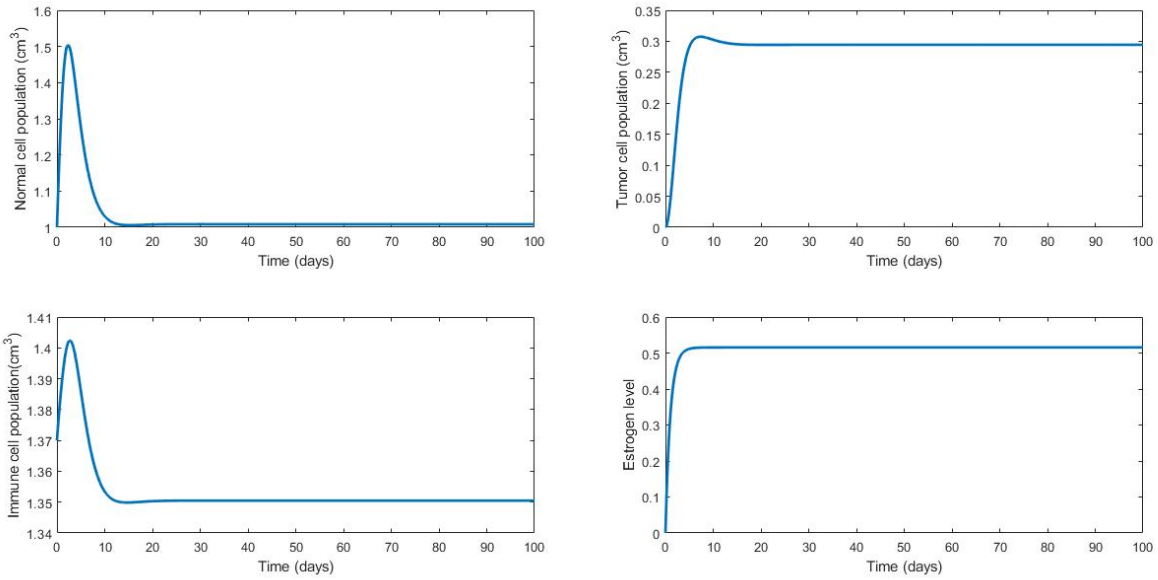

Figure 5.1: The Normal Tumor Immune and Estrogen (NTIE) model with no controls(days)

The numerical solution shows that in the presence of excess estrogen, tumor cell population grow as shown in the Figure 5.1, normal and immune cell population decrease, with normal cell population suffering the most. There is a suppression of normal and immune cell population as consequence of increase estrogen levels and the rapid growth of tumor cell population. This implies that introducing more estrogen into the body increases the rate of tumor formation, resulting in the development of breast cancer. The reason why tumor cell population are slightly decreasing, it is because the immune system identifies the threat caused by cancer cells and tries to fight it, but it is not potent enough to kill the tumor cells [58]. What we observed from the Figure above is that the tumor cell population are being delayed by the immune system and other internal factors; otherwise, if this suppression of immune system by tumor cells was greater than the suppression of tumor by immune system, the tumor cells might be able to invade other cells and gradually expand to other parts of the body [45]. The numerical solution shows that as estrogen levels rise, immune cell population decreases, weakening the immune system. Subsequently, the immune system will be unable to effectively compete with cancer cells and eventually fail to control the disease.

The $NTIE$ model in Figure 5.1 shows the undesirable results , because there is still a burden of breast cancer disease that needs to be treated. Now we apply the optimal control problem to in-

tervene in the problem by introducing the following intervention strategies to control breast cancer:

The three control strategies discussed further below are as follows:

- **Strategy 1**: Surgery (u_1) control on tumor cells.
- **Strategy 2**: Hormone therapy (u_2) control on excess estrogen and tumor cells.
- **Strategy 3**: Surgery(u_1) and hormone therapy(u_2) combined control on tumor cells growth and excess estrogen.

Strategy 1:

This strategy implements surgery (breast conserving) as the only control measure, thus the corresponding cost balancing factors are $A = 0.05$ and $B = 0$ for u_1 and u_2 respectively.

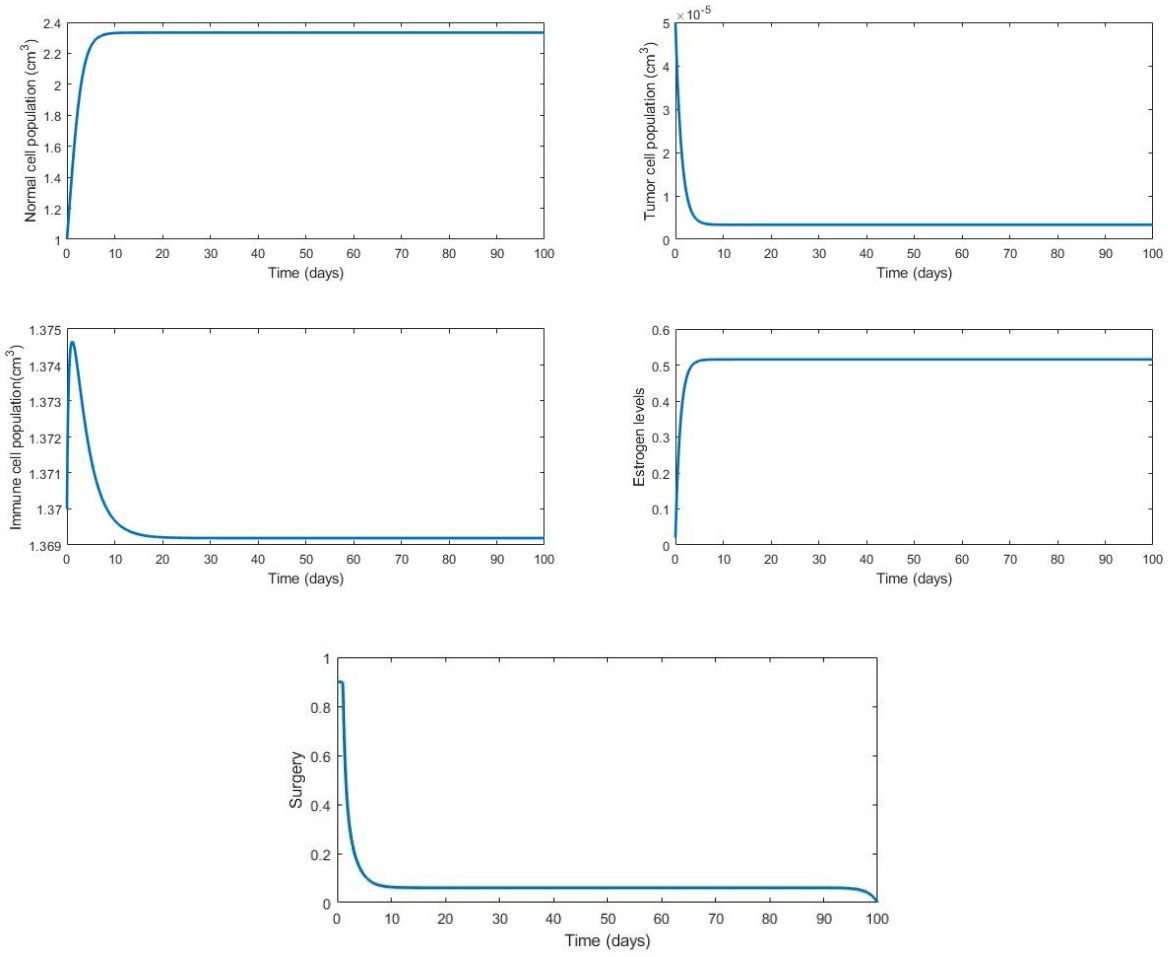

Figure 5.2: The optimal states and optimal control surgery(days)

In this strategy, we vary the value of one parameter σ_1, that was found to be more sensitive to the basic reproduction number. We reduce the tumor's ability to grow in order to monitor the behavior of tumor cells in Chapter 5. We apply surgical force to the initial variable $T(0) = 10^{-5}$. Figure 5.2 depicts the results of surgical simulations of tumor cell removal, and we can see that some tumor cells may have strayed beyond the surgical margin. Provided that tumor formation has been reduced, we can draw the conclusion that normal cells have reached an equilibrium, whereas immune cells are still affected by excess estrogen. The estrogen levels are still the same as in Figure 5.1 and these levels are not desirable because high levels of estrogen influence tumor cells to grow. The Figure also shows that after 90 days, the optimal control surgery decreases to

zero, which is primarily influenced by the adjoint system because the control is dependent on it. The results are depicted in Figure 5.3.

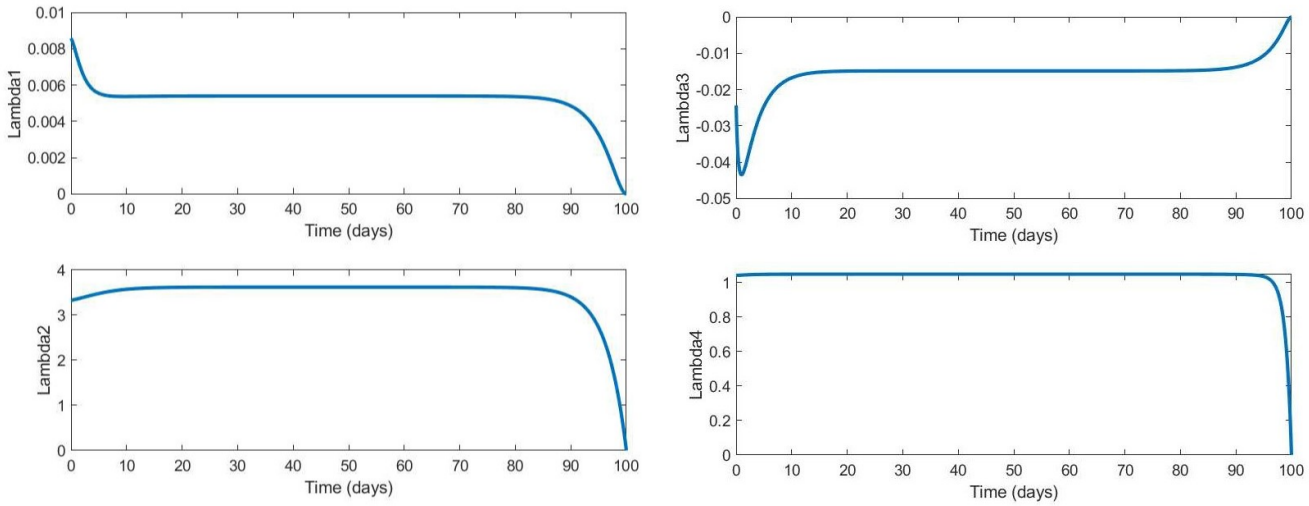

Figure 5.3: Adjoint system with optimal surgery(days)

Figure 5.2 shows that although surgery reduces the number of tumor cells, it does not eliminate all cancer cells because estrogen are activated and have a negative impact on normal and immune cells.

Strategy 2:

This strategy implements hormone therapy (tamoxifen) as the only control measure, thus the corresponding cost balancing factors are $A = 0$ and $B = 0.005$ for u_1 and u_2 respectively.

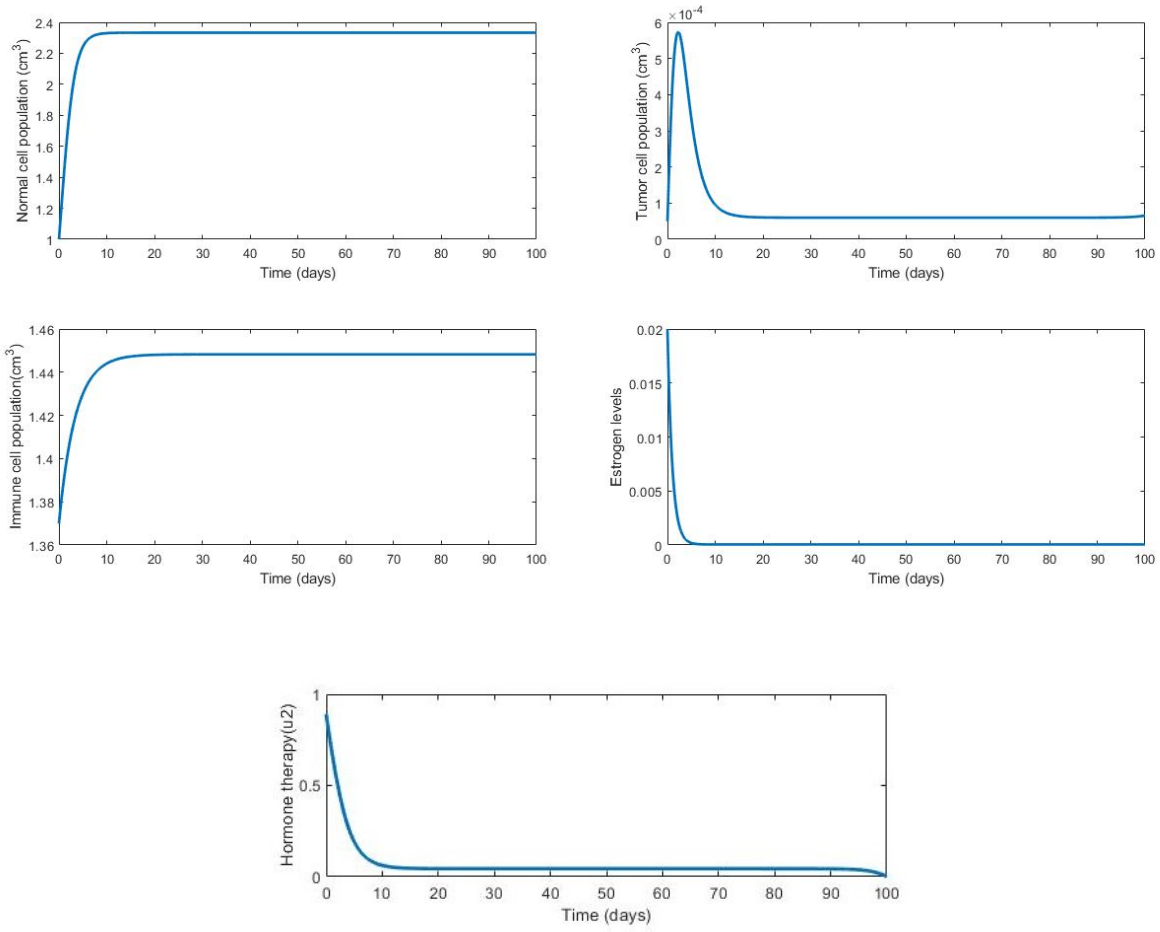

Figure 5.4: Optimal states and optimal hormone therapy(days

In this simulation we vary the two parameters σ_1 and Λ due to the fact that these parameters enable the estrogen hormone to develop cancer cells. and fix the other parameters. Figure 5.4 shows the numerical simulations of the state system with hormone therapy as the optimal control when $\sigma_1 = 0.002$ and $\Lambda = 0.005$. We note that, in the presence of hormone therapy (tamoxifen) reduces the activities of tumor cells, and we also note that using too much hormone therapy drug results in a rapid decrease of estrogen levels. The Figure 5.4 depicts an increase in immune and normal cells while a decrease in estrogen and tumor cells. The increase in normal cells is due to a decrease in estrogen intake (Λ), which results in less tumor formation (σ_1). The increase in immune cells is due to a reduction in estrogen consumption, which results in less suppression of immune cells by estrogen cells. We can see from the Figure 5.4 that the drug's strength was much

higher at the start of the treatment period, and there was a lag due to the singular control defined in equation 4.11. This means that the drug's dosage was initially high and gradually decreased to a constant intake. That is why there is a lag. We can conclude from this observation that optimal control is far more effective at reducing the number of tumor cells to near zero. The Figure 5.4 shows that the control reaches zero after 95 days. This is due to the control's reliance on the adjoint system, which eventually reaches zero after 100 days. The following graph depicts the adjoint system with hormone therapy:

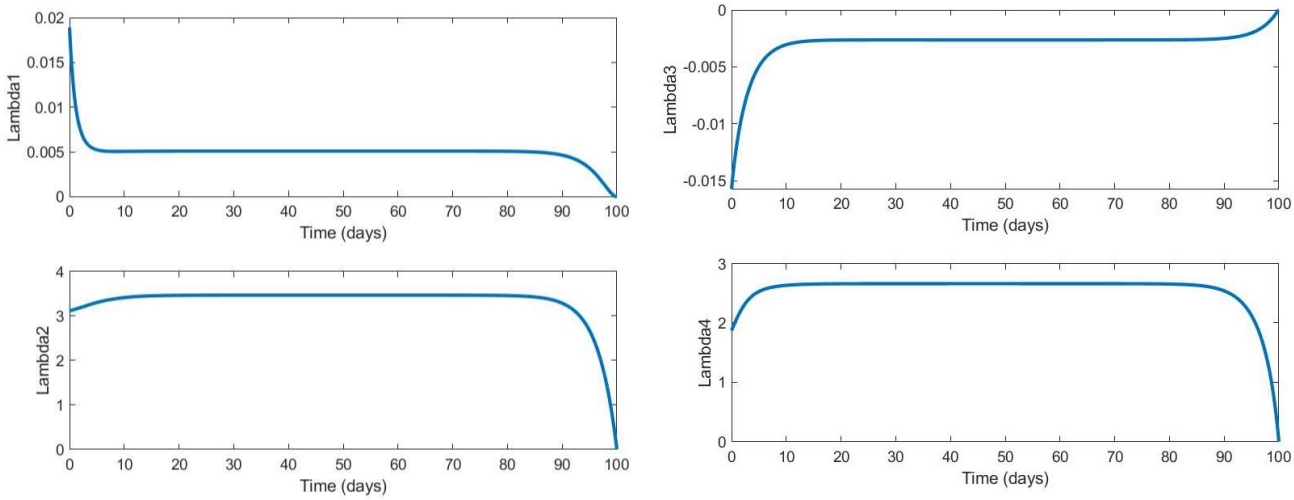

Figure 5.5: Optimal control (Hormone therapy)

Based on the optimal control diagram, we can conclude that we should give full effort at the beginning of the disease to reduce tumor cell spread. This means that hormone therapy is much more effective at the beginning of the disease than it is later on.

Strategy 3:

This strategy considers the implementation of both surgery (u_1) and hormone therapy (u_2) as control measures, with $A = 0.05$ and $B = 0.005$. In this strategy, hormone therapy is used as adjuvant therapy to help reduce the likelihood of cancer recurrence.

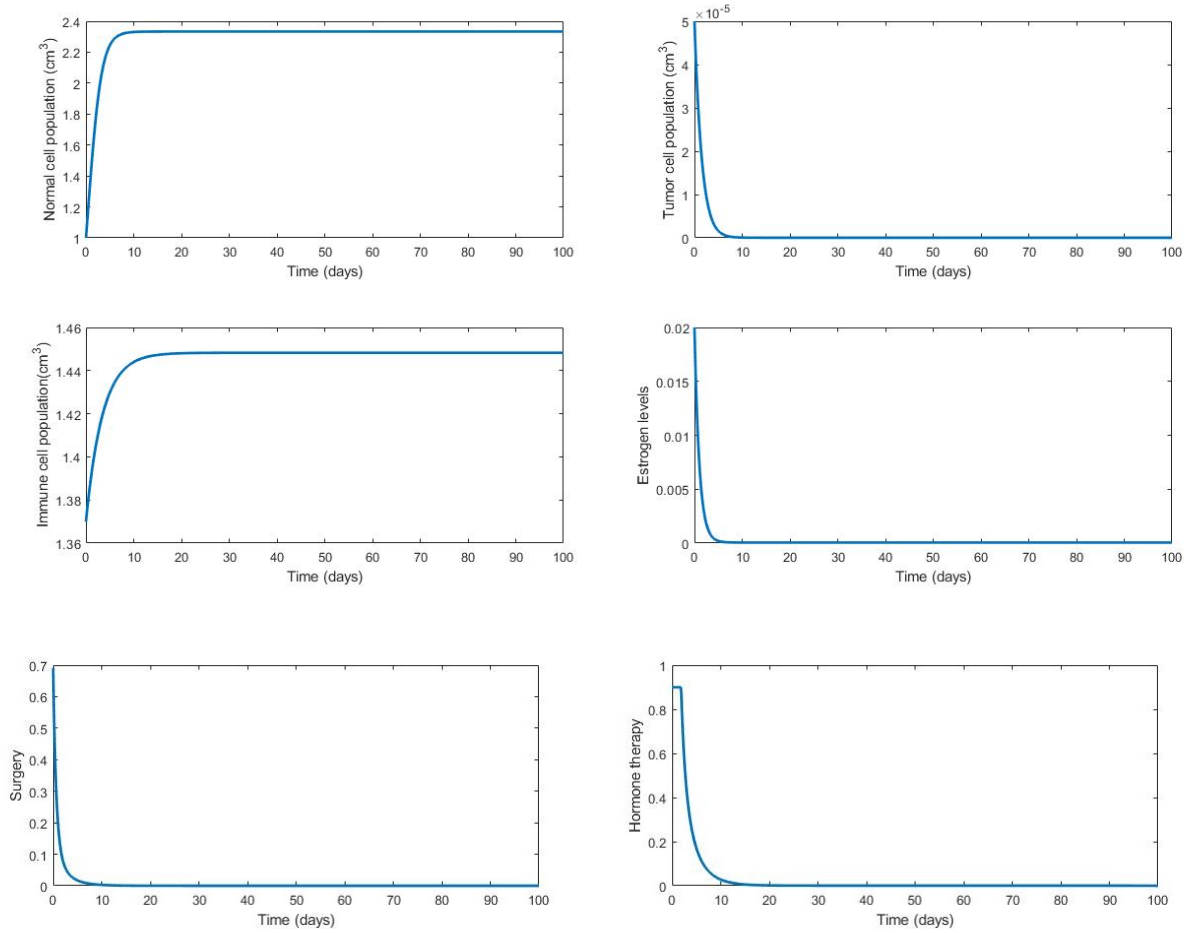

Figure 5.6: The optimal states and optimal controls (surgery (u_1) and hormone therapy (u_2))(days)

Figure 5.4 depicts the combination of two controls (surgery and hormone therapy), both of which have a significant impact on the increase of normal and immune cell populations. We notice that tumor cells can be eradicated after 10 days, which is faster compared to the results in Figure 5.2 and 5.4 when we used the controls alone. The rapid decrease in tumor cell population in the preceding Figure is caused by surgical intervention, and the remaining cancer cells after surgery are removed using hormone therapy.

The numerical results show that using the combination of hormone therapy and surgery is more

effective than using hormone therapy or surgery alone. The combination of surgery and hormone therapy resulted in significant tumor and estrogen cells eradication. The results depicted in Figure 5.4 resolved the problem depicted in Figure 5.1, indicating that breast cancer was successfully treated with the combination of surgery and hormone therapy.

Chapter 6

Discussions, conclusions and recommendations

6.1 Discussions

In this study, we developed a mathematical model that incorporated the dynamics of four cell populations, including normal cells, tumor cells, immune cells, and estrogen, with two optimal controls: surgery and hormone therapy. The associated ordinary differential equation's local and global stability was thoroughly examined, and the critical threshold basic reproduction number was determined. The tumor-free equilibrium (TFE) has been established as having local stability, and the system is only locally asymptotically stable if the reproductive number is less than unity ($R_0 < 1$). As a result, the development of breast cancer is unavoidable. This means that if the best treatments are used, the number of tumor cells in the body will be reduced to zero. We found out that the presence of excess estrogen increases the tumor formations depicted in Figure 5.1. This means that any extra estrogen introduced into the body through birth control increases the rate of tumor formation. The optimal control problem associated with the ordinary differential equation was developed and solved to find the adjoint system and characterization of optimal controls. We compared three control strategies that were implemented to reduce the number of tumor cells, estrogen levels, and the cost of treating breast cancer.In comparison to current clinical and research studies, reducing a tumor to undetectable levels in less than a week is biologically impossible. Several factors, including the type of cancer being treated and the character-

istics of the patient's cells, influence the length of cancer treatment. This makes predicting how long it will take to clear a tumor in body tissue difficult. A tumor can also be reduced to insignificant levels and then reappear [60]. Nonetheless, our findings suggest that surgery and hormone therapy have a good chance of reducing the tumor to undetectable levels in a short period of time (10 days).

The findings of this study are similar to those of Pranav *et al* [45], and Alharbi *et al* [54] in that they show that after using therapies, the tumor can be cleared after 10 days depending on the parameters chosen. These findings were presented by mathematical researchers despite the fact that they contradict the biological meaning, as medicine has demonstrated that cancer cells cannot be cleared in 10 days. The cancer cells must be removed over a period of months.

6.2 Conclusions

Numerical results demonstrated that surgery had a significant effect on tumor growth, and similar results were also observed for a hormone therapy approach, which clearly shows that hormone therapy can reduce estrogen levels. The results revealed that surgery is more effective compared to hormone therapy. Clearly, we observed that the combination of surgery and hormone therapy eradicates the tumor cells and excess estrogen. After a few days of treatment, the numerical results showed and confirmed that the optimal treatment strategies reduce the number of tumor cells and estrogen levels while increasing normal and immune cells to their healthy equilibrium. The combination therapy strategy surpassed the strategy of surgery or hormone therapy alone.

6.3 Recommendations

There are gaps in our study, because we were unable to capture valid data or laboratory data to predict the behavior of tumor cell population. We only used available data from previous papers, and we drew our conclusions based on the numerical solutions we obtained from this data. Considering the findings above, it is recommended that in order to reduce tumor cell population both controls should be implemented.

6.4 Extensions

The model presented in this study was made simple by assumptions that breast cancer is non-invasive. The model could be further extended to invasive breast cancer and incorporate different controls.

Chapter 7

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Appendix A

Relevant Definitions

Theorem A.1 ***Lyapunov stability theorem****: Let $\mathcal{E}$ be an open subset of $\mathbb{R}_4^+$ containing an equilibrium point $\mathcal{E}_0$ suppose that f is continuously differentiable and then there exists a continuous differentiable function, say $V(x)$, which satisfy the following conditions $V(\mathcal{E}_0) = 0$*

1. *$V(\mathcal{E}_0) = 0$*
2. *$V(x) > 0$, if $x \neq \mathcal{E}_0$ where $x \in \mathcal{E}$*

- *If $\dot{V} \leq 0$ $\forall x \in \mathcal{E}$, $\mathcal{E}_0$ is stable*
- *If $\dot{V} < 0$ $\forall x \in \mathcal{E}$, $\mathcal{E}_0$ is asymptotically stable*
- *If $\dot{V} > 0$ $\forall x \in \mathcal{E}$, $\mathcal{E}_0$ is unstable [55]*

Theorem A.2 *(Pontryagin's Maximum principle) (PMP) Consider the problem*

$$\min_{\mathbf{u}} \int_{t_0}^{t_f} \mathbf{f}(t, \mathbf{x}(t), \mathbf{u}(t))dt,$$

such that

$$\dot{\mathbf{x}}(t) = \mathbf{g}(t, \mathbf{x}(t), \mathbf{u}(t)),$$

$$\mathbf{x}(t_0) = \mathbf{x}_0 \text{ and } \mathbf{x}(t_f) = \text{ free}$$

If $\mathbf{u}^*(t)$ *and* $\mathbf{x}^*(t)$ *are optimal for the above problem then there exists a piecewise differentiable adjoint variable* $\lambda(t)$ *such that*

$$\mathcal{H}(t, \mathbf{x}^*(t), \mathbf{u}(t), \lambda(t)) \geq \mathcal{H}(t, \mathbf{x}^*(t), \mathbf{u}^*(t), \lambda(t))$$

for all controls u *at each time* t*, where the Hamiltonian* $\mathcal{H}$ *is*

$$\mathcal{H} = \mathbf{f}(t, \mathbf{x}(t), \mathbf{u}(t)) + \lambda(t)\mathbf{g}(t, \mathbf{x}(t), \mathbf{u}(t))$$

and

$$\begin{aligned} \dot{\lambda}(t) &= -\frac{\partial \mathcal{H}(t, \mathbf{x}^*(t), \mathbf{u}^*(t), \lambda(t))}{\partial \mathbf{x}} \\ \lambda(t_f) &= 0. \end{aligned}$$

[17]

There exist an optimal control $u^*(t)$ such that

$$J(u^*(t)) = \min_{u \in U} J(u(t)),$$

subject to the control system with initial conditions.

Definition A.1 Hessian matrix refers to a square matrix of second ordered partial derivatives of a scalar function [18].

Definition A.2 Tissue is a group of cells that have similar structure and that function together as a unit [4].

Definition A.3 Cells are basic building blocks of all living things [65].

Definition A.4 ([64]) A piecewise continous control $u(\cdot)$, defined on some time interval $t_0 \leq t \leq t_f$, with range in the control region U,

$$u(\cdot) \in U, \forall t \in [t_0, t_f], \text{is said to be an admissible control.}$$

A typical optimal control problem (OCP) requires a performance index or cost functional, $J[x(\cdot), u(\cdot)]$; which must be specified for evaluating the performance of a system quantitatively, a set of state variables, $x(\cdot) \in X$; and a set of control variables, $u(\cdot) \in U$. The main goal consists in finding a piecewise continuous control $u(t)$, $t_0 \leq t \leq t_f$, and the associated state variable $x(t)$, to maximize or minimize the given objective functional ([**?**]). An OC problem can be presented in many different, but equivalent ways, depending on the purpose or the software to be used.

Definition A.5 ([65]) (Basic OC Problem in Lagrange form). An OC problem is:

$$\min_u J[x(\cdot), u(\cdot)] = \int_{t_0}^{t_f} f(t, x(t), u(t))dt$$

s.t.

$$\dot{x}(t) = g(t, x(t), u(t))$$

$$x(t_0) = x_0$$

It is often assumed that f and g are continuously differentiable functions in all three arguments, the control(s) are piecewise continuous, and the associated state(s) are piecewise differentiable.