University of
Zululand

MATHEMATICAL MODELING FOR OPTIMAL CONTROL OF BREAST CANCER

by

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A thesis submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

in the

Department of Mathematical Sciences

Faculty of Sciences and Agriculture

University of Zululand, South Africa

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2019

DECLARATION

I, Segun Isaac OKE (Student No: 201629724), solemnly declare that the thesis entitled **"Mathematical modeling for optimal control of breast cancer "** submitted by the undersigned was carried out under the supervision of Dr. Maba Boniface Matadi and Prof. Sibusiso Southwell Xulu in the Department of Mathematical Sciences, University of Zululand. This study represents original work by the author and has not been submitted in any form to another university for any degree. The materials used are acknowledged in the text.

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DEDICATION

This research work is dedicated to: The Almighty God; my beloved wife, Basirat Abiola Oke; my cherished daughter, Deborah Anuoluwapo Oke; my parents, Mr. Moses Oyemomilara and Mrs. Sarah Oluwafunke Oke; and my parents-in-law, Mr. Abiodun and Mrs. Idowu Disu.

ACKNOWLEDGMENTS

"Except the Lord builds a house, they labour in vain that build it..." Do not despise these small beginnings for the Lord rejoices to see ..." Indeed, without the involvement of the Almighty God Omnipotent, Omniscient, Omnipresent, this work would not have been a success.

I would like to thank my supervisors, Dr M.B. Matadi and Professor S.S Xulu, for their tremendous support and guidance, which motivated me throughout the study. I appreciate their time, suggestions, ideas and constant encouragement. Many thanks go to Professor E.O. Ayoola, my MSc supervisor, Professor Y.A.S Aregbesola my B.Tech (Hons) supervisor and to all my teachers that taught me at all levels of my education for contributing to my career development as a research scientist. My gratitude goes to Dr Adebimpe Olukayode, Professor Okosun Kazeem O, Dr Joseph Malinzi, Usman Ahmed Danbaba, Mr M. Mukamuri and Professor Folashade Agusto for equipping me with the foundation knowledge on which this work is built. I am also indebted to Dr Adeniyi Michael and Dr Samson Olaniyi for sharing their knowledge at different times to enhance the quality of this project. I appreciate the friend that stick closer than a brother, Olukayode Oki, for setting the ball rolling. I further thank Dr Moses Ayoola and Dr Chinaza Uleanya for proofreading my drafts.

I also thank Dr. S.O. Salawu, Dr Hassan Anthony and Dr Adesanya Samuel for giving me a push along the way. Pastor Henock and the church family of RCCG, Christ Assembly, Eskhawini, South Africa, thank you all for the prayers and fellowship. To Pastor Fred Odekhian, Pastor Dare Adeogun and Dr Samuel Alori, of RCCG, Courts of

His Majesty, Lagos, Nigeria; distance was not a barrier for your support and I appreciate you. Dr Folorunso Osunsanmi, Dr Olaniyi Iyiola (California University of Pennsylvania, PA, USA), Dr Babatunji E. Oyinloye, Dr Stanley Ehiane, Dr Olumoye M.O., Dr Adeleke Olawale, Dr Matthew Adewole and Mr Matthew Ekum, thank you for checking up on me with words of encouragement and for your concern from time to time. I thank my uncles,I thank my uncles, Mr. I.G. Omolumo and Mr James Adeagbo, FCA, the Omotoyinbos and my siblings: Samuel and Adedoyin Oke, Gbenga and Felicia Adediran, Olanrewaju and Esther Obisesan and Racheal Oke; thank you all for holding forth. I also appreciate my siblings-in-law: Ajibola and Ajibola Disu, Ayobami and Oluwabunmi Disu, Yomi and Taiwo Ayinde, and Kehinde Disu for also holding forth each time I had to be away. I am indebted to Sylvie Djiomba Njankou, Linda Z. Chazuka and Evans Otieno Omondi, for sharing their ideas to enhance the quality of the work. I cannot but thank the following, for their various contributions to my research thesis: Yinka Ajifolokun, Alex Adekiya, Taiwo and Kehinde Aruleba and Aderonke Adesina may the Lord reward you all. A lot of gratitude to all the staff members and colleagues at the Department of Mathematical Science, University of Zululand, South Africa for making my stay in the department a pleasant and memorable one. Finally, I appreciate and acknowledge that this research was sponsored by National Research Foundation (NRF) South Africa. I am grateful for the financial support from University of Zululand Research Office.

PUBLICATIONS

The following articles are extracts from this thesis.

1. **Oke, S.I**., Matadi, M.B. and Xulu, S.S., 2018. Optimal Control Analysis of a Mathematical Model for Breast Cancer.*Mathematical and Computational Applications, 23(2), p.1-28. doi* : 10.3390/*mca*23020021

2. **Oke, S.I**., Matadi, M.B. and Xulu, S.S., 2017, August. Optimal Control of Breast Cancer: Investigating Estrogen as a Risk Factor. *In International Conference on Applied Mathematics, Modeling and Computational Science (pp. 451-463).D. M. Kilgour et al. (eds.), Springer, Cham. doi* : $10.1007/978-3-319-99719-341$

3. **Oke, S.I**., Matadi, M.B. and Xulu, S.S., 2018. Cost-Effectiveness Analysis of Optimal Control Strategies for Breast Cancer Treatment with Ketogenic-diet. *Far East Journal of Mathematical Sciences Volume 109 No. 2 pp 303-342 http* : *//dx.doi.org*/10.17654/*MS*109020303

Conferences and Symposiums

- " Cost-effectiveness analysis strategies for Breast Cancer". 2018 October Workshop on Modeling & Analysis in Life Science **(MALS) 2018** University of Pretoria, South Africa.

- "Optimal control analysis of a mathematical model for breast cancer". The 2018 Annual Meeting of the Society for Mathematical Biology & the Japanese Society for Mathematical Biology **SMB2018**. Sydney, Australia (July 8-12, 2018)

- "Optimal control of Breast Cancer:Investigating estrogen as a risk factor". The IV AMMCS Congress 2017: Applied Mathematics, Modelling and Computational Science **AMMCS Congress 2017**. Waterloo, Ontario Canada (August 20-25, 2017)

- "A Mathematical Analysis of Local Stability of Breast Cancer". **SANUM,2017**, Math. Dept., WITs, South Africa. (March 2017)

- "A Mathematical Analysis of Local Stability and Optimal Control Analysis of Breast Cancer". International Conference on Mathematical Methods and Models in Biosciences and a School for Young Scientists **BIOMATH 2017** (25 -30 June 2017), Skukuza Camp, Kruger Park, South Africa.

- "Mathematical Modeling of Breast Cancer: Investigating Estrogen as Risk factor and Hyperthermia Treatment". African Mathematical School, **(CIMPA) 2016** Landmark University, Nigeria

KEYWORDS

Epidemiology

Breast Cancer

Invasion reproduction number

Tumor-free equilibrium

Dead-equilibrium

Co-existing equilibrium

Bifurcation analysis

Stability analysis

Optimal control theory

State variables

Pontryagin's Maximum Principle

Optimality conditions

Adjoint variable or costate variable

Cost-effectiveness analysis

Ketogenic diet

Decrement of Tumor cells

ABSTRACT

Breast cancer, which often occurs in the inner lining of milk ducts, is the deadliest and most common form of invasive cancer among females according to a 2017 report of the World Health Organization. The purpose of this study was to develop a four compartmental mathematical model using a system of nonlinear Ordinary Differential Equations (ODEs) which investigates the impact of anti-cancer drugs, ketogenic-diets and immune boosters on the dynamics of breast cancer. The study focused on the dynamical interaction of normal and tumor cells as well as the invasion of tumor cells during the metastasis stage of breast cancer. The systems of ODEs were analytically solved for the equilibria. Using the next generation matrix method, a threshold quantity called *the treatment induced invasion reproduction number* (R_i^*) was computed. Center manifold theory was used to investigate the possibility of the bifurcation analysis of R_i^* being greater than unity. Using a suitable Lyapunov functions, the global stability of the tumor-free equilibrium was achieved in conjuction with LaSalle's invariance principle. Uncertainty and sensitivity analyses were performed on R_i^* using Latin Hypercube Sampling (LHS) and Partial Rank Correlation Coefficient (PRCC). R_i^* was used as the response function while investigating the most significant parameters (such as: α_1, α_2, μ_1, d, and ϕ_1) that affects disease progression and cell invasion. Optimal control theory was applied using the Pontryagins' Maximum Principle to investigate optimal strategies for controlling and eliminating tumor cells using time dependent controls such as $u_1(t)$ (anti-cancer drugs) and $u_2(t)$ (ketogenic diets). Numerical simulation results using a set of parameter values were provided to validate the analytical results. It was found that the tumor-free equilibrium points for

breast cancer was locally asymptotically stable when the associated invasion reproduction number was less than unity and that it was otherwise unstable. The tumor-free equilibrium was found to be globally asymptotically stable if $(R_i) < 1$. Sensitivity analysis showed that the natural death rate of normal cells has the most positive sensitivity index. However, increasing the death rate as a control measure is unreasonable biologically. The level of ketogenic diet rate was found to be most negatively sensitive to R_i. Therefore, the formulated model showed that reduction of the invasion reproduction number (R_i^*) below unity can be achieved by maintaining the level of ketogenic diet and by reducing tumor progression rate. It was shown from this study that the breast cancer model exhibited backward bifurcation with bifurcation parameter ϕ_1 which implies that the reduction R_i^* below unity alone is not sufficient to eradicate tumor cells from the body system while in the case of forward bifurcation, the reduction of R_i^* above unity is sufficient to eradicate tumor cells from the body system . The incremental cost-effectiveness analysis of control strategies adapted in treating breast cancer has shown that the integration of ketogenic diet and anti-cancer drugs as intervention strategy is the most cost-effective in fighting tumor cells.

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Chapter 1

Introduction

Cancer, though noted for its high mortality rate, can be treated. The focus of this study is to make use of a mathematical model and optimal control techniques to investigate the dynamics of breast cancer cells noting the impact of certain control measures on the proliferation of such cancerous cells. Of particular focus was the use of ketogenic diet and anti-cancer drugs in the formulation of the breast cancer mathematical model. In this chapter, we describe the background of the study, the questions guiding the research, research aim and objectives, what motivated the study and the mathematical preliminaries.

1.1 Background of the study.

Cancer generally develops progressively from multiple changes in the cell genetic structure. Cancers are usually classified according to the cells involved, the type of tissues from which they arise and the extent of the disease [91]. For example, *Carcinoma* originates from Epithelial cells, *Lymphoma* from lymphatic cells and *Ependymoma* from the *Ependyma* with a tissue of the central nervous system [140]. Some tumors such as benign tumors are, however, not cancerous and do not spread to different parts of the body.

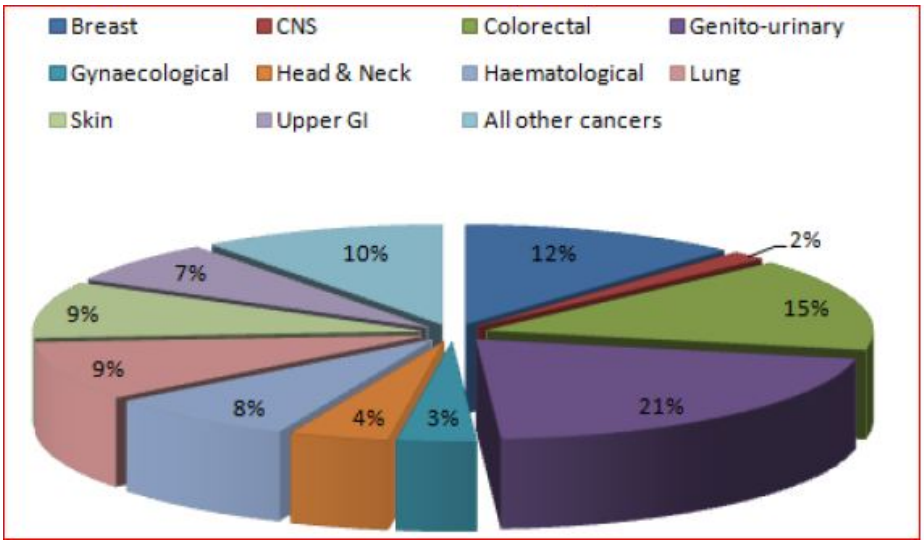

Figure 1.1: *The most common types of cancer. [Adapted and available online at www.keepurhealth.net] (Accessed April, 2018)*

Cancer is a leading cause of morbidity and mortality worldwide, yet a lot remains unknown about its mechanisms of establishment and destruction. Figure 1.1 shows the most common types of cancer. According to the World Health Organization (WHO) [140], approximately 14.1 million new cancer cases, excluding non-melanoma skin cancer, were diagnosed and 8.2 million cancer-related deaths were recorded (2017) [140]. The same report indicated that more than 60% of cancer cases occurred in Africa, Asia, Central and South America. Sub-Saharan Africa recorded the highest morbidity (25.5%) and mortality (25.2%) of breast cancer cases in women compared to the rest of the world. This research focuses on breast cancer, common among women as a result of imbalances of the estrogen hormone, which is responsible for tumor growths.

In South Africa, more than 10,000 people are diagnosed with cancer every year and the survival rate is very low according to the National Cancer Registry (NCR)[91] which also states that 1 out of 9 South African women is diagnosed with breast cancer. The occurrences of the new breast cancer cases worldwide is shown in Figure 1.2.

Figure 1.2: *The number of new breast cancer cases occurring worldwide [Adapted and available online at : webcache.googleusercontent.com/search?] (Accessed June, 2108)*

1.2 Research questions

The study set out to answer the following questions:

(i) What are the influences of the ketogenic diet, immune booster and anti-cancer drugs on the formulation of breast cancer mathematical model?

(ii) What are the equilibrium points of the model and how can the possible impact of the key parameters of the model be investigated?

(iii) What are the conditions for which the obtained equilibrium points are locally and globally asymptotically stable?

(iv) What are the effects of time dependent control variables on an optimal control model for breast cancer?

(v) What optimal control strategy will yield optimal results for the model using Pontryagin's Maximum Principle with the most cost-effective control measure(s)?

1.3 Research aim and objectives

1.3.1 Research aim

This study was designed to formulate a mathematical model, analyses and use optimal control theory with cost-effective techniques to investigate breast cancer treatment.

1.3.2 Research objectives

The aim of this study will be achieved through the following objectives which are to:

(i) Formulate a mathematical model of breast cancer by incorporating the ketogenic diet, immune booster and anti-cancer drugs into the existing model;

(ii) Determine the model equilibrium points and significance of the key parameters of the formulated model;

(iii) Investigate both local and global stabilities of tumor-free equilibrium points and co-existing equilibrium points of the formulated model;

(iv) Formulate an optimal control model for breast cancer using anti-cancer drugs and a ketogenic diet as control variables;

(v) analyse the optimal control for breast cancer model using Pontryagin's Maximum Principle and Cost-effectiveness Analysis

1.3.3 Motivation for the study

Cancer is one of the leading causes of death worldwide but it can be treated using surgery, chemotherapy, radiation, hormones, hyperthermia and immune therapy. It is projected that by 2030, the global burden would have grown to 21.7 million new cases, 13 million of which will result in death [140]. This has been attributed to many factors which include population growth, aging, genetics and family history, hormonal imbalances (estrogen and progesterone), environmental factors and unhealthy lifestyles [116]. According to a WHO report [141], there are four major types of cancer worldwide – lung, breast, prostate and colon cancer with breast cancer being the second leading cause of cancer related

mortality among women. Breast cancer has been attributed to several factors with high levels of hormonal imbalance as the major factor. It is therefore necessary to develop a mathematical model to examine cell dynamics during breast cancer treatment to study the impacts of the various forms of therapy (anti-cancer drugs and ketogenic diet) in terms of dynamical behaviour, optimal control and side effects. The goal is to determine suitable cost-effective strategies for tumor decrement and the minimisation of drug toxicity.

1.4 Mathematical preliminaries

The mathematical preliminaries used to carry out the findings in this thesis are hereby discussed: basic reproduction number, bifurcation analysis, optimal control method, the general optimal control problem, Pontryagin's maximum principle, necessary and sufficient conditions of the optimal control of breast cancer.

1.4.1 Basic reproduction number

The basic reproduction number, R_0, is defined as the average number of secondary infection generated by an infective individual during its course of disease in the case that all members of the population are susceptible [142]. In this study, invasion reproduction number, R_i, was adopted to represents average number of secondary cases caused by a typical invaded cells over an invasion period in a completely normal cells population. The invasion reproduction number helps in determining whether or not a disease (cancer) will spread through a population (normal cells). If $R_i < 1$, each cancerous cell produces, on average less than one new infected cell and the cancer therefore dies out of the population. When $R_i > 1$, each cancer cell produces more than one new cancerous cells, so that the disease persists in the population. The next generation technique which was studied by

Van den driessche and Watmough [132] is a general method for R_i in cases where one or more classes of infections are involved.

Let X_c be the set of all tumor-free state, that is

$X_c = \{x \geq 0 : x_i = 0, i = 1, 2, 3, ..., m\}$ where m is the number of tumor class in the population.

Let: $F_i(x)$ be the rate of appearance of new arrival in tumor compartment i

$\nu_i^+(x)$ be the rate of transfer of individual cells into compartment i by all other means

$\nu_i^-(x)$ be the rate of transfer of individuals out of compartment i by all other means and

P_0 is the tumor- free equilibrium.

The disease transmission model consists of non-negative initial conditions $x_i(0)$,

together with the following system of equations analogous to system.

$$x_i = F_i(x) - \nu_i(x), i = 1, 2, ..., n \tag{1.4.1}$$

where: $\nu_i = \nu_i^-(x)$ - $\nu_i^+(x)$ and n is the number of compartments in the population. If $\bar{x}$ is the tumor-free equilibrium point, then the derivatives of F and ν calculated at $\bar{x}$ are represented by $m \times m$ matrices F and ν respectively. That is

$F = \left[\frac{\partial F_i}{\partial x_i}\bar{x}\right]$ and $\nu = \left[\frac{\partial \nu_i}{\partial x_i}\bar{x}\right]$ with $1 \leq i \leq m$.

Thus, the basic reproduction number, R_i, is given by

$$R_i = \rho(F\nu^{-1}) \tag{1.4.2}$$

where ρ is the spectral radius of the product, $F\nu^{-1}$, that is spectral radius is also known as the dominant eigenvalue of $F\nu^{-1}$ known as the next generation matrix.

1.4.2 Bifurcation analysis

The mathematical examination of changes in the qualitative behaviour of a dynamical system as its parameter passes through a critical value called a bifurcation point which is also known as *Bifurcation Analysis*. These sudden changes in the solutions of the system are known as bifurcations and the parameter values responsible for these changes are called bifurcation parameters [9]. In mathematical epidemiology, transcritical bifurcation, an example of a local bifurcation, is used to analyse the changes in the stability of equilibria as a model parameter varies. A key parameter in this regard is the basic reproduction number R_0.

At $R_0 = 1$, the direction of the bifurcation (subcritical or supercritical) can be determined. A subcritical (backward) bifurcation occurs when a stable disease-free equilibrium coexists with an unstable endemic equilibrium at R_0 less than unity near the threshold $R_0 = 1$. However, the disease-free equilibrium loses its stability when R_0 is slightly greater than unity while a stable endemic equilibrium exists. Conversely, a supercritical (forward) bifurcation is said to occur only when a locally asymptotically stable positive equilibrium appears at R_0 slightly above unity. At this point, the disease-free equilibrium loses its stability near $R_0 = 1$. Castillo-Chavez and Song [25] have proposed a general center manifold theory to determine the existence of forward and backward bifurcations in epidemiological models. This theory can be used to establish the local asymptotic stability of the endemic equilibrium near the threshold parameter $R_0 = 1$, while a different approach can be seen in Chitnis *et al.* [28].

1.4.3 Optimal control method

Optimal control theory is a mathematical technique derived from the calculus of variation and is very useful in decision making regarding complex biological situations where the behaviour of a dynamical system is described by state variable(s) [75]. The assumption is that there is a way to control the state variable(s) x by acting upon it with a suitable control. Thus the dynamics of the system (state x) depends on the control u [95-98]. The ultimate goal is to adjust the control u to minimize or maximize a given objective functional, $J(u(t), x(t), t)$ that attains the desired goal and the required cost to achieve it [41]. The optimal solution is then obtained when the most desired goal is achieved at the least cost. The functional depends on the control and state variables. There are number of different methods for calculating the optimal control for a specific model [95-98]. Pontryagin's Maximum Principle [112], for example, allows the calculation of the optimal control for an ordinary differential equations model system with given constraints. However, other powerful optimal control techniques have been derived for partial differential equations and difference equations [112].

1.4.3.1 Importance of optimal control theory

Optimal control can be used for the following:

(i) Stabilization: It helps to implement controls to force stability;

(ii) Controllability: Applying controls to steer a system from one position to another,

(iii) Observability: It aids the system to deduce information from control inputs and to observe output.

1.4.3.2 The general optimal control problem

We consider optimal control problems of the form

$$\min_{u} \left\{ \phi(t_f, x(t_f) + \int_0^{t_f} g_0(t, x(t), u(t))dt \right\}$$

where

$$f(x(t)) = [x_1(t), x_2(t), ..., x_{n_s}(t)]^T \in R^n$$

is the state vector and

$$f(u(t)) = [u_1(t), u_2(t), ..., u_{n_c}(t)]^T \in R^m$$

is the control vector.

The state and control variables are governed by the dynamics described by a set of first order ordinary differential equations:

$$\frac{dx}{dt} = f(t, \mathbf{x}(t), \mathbf{u}(t)); \; x_0 = x(0), 0 \leq t \leq t_f. \tag{1.4.3}$$

The functions:

$$f(h_0) : T \times R^n \times R^m \to R^n$$

$$f(g_0) : T \times R^n \times R^m \to R^n$$

are continuously differentiable with respect to each component of $\mathbf{x}$ and $\mathbf{u}$, and piece-wise continuous with respect to t

1.4.3.3 Pontryagin's Maximum Principle

This principle converts the maximisation or minimisation of the objective functional, J, coupled with the state variable into maximising or minimising pointwise, the Hamiltonian, with respect to the control. In this thesis, an optimal control problem is formulated

with the goal of minimizing the tumor cells and estrogen level. We incorporate into the model time dependent control measures for preventive interventions such as anti-cancer drugs and ketogenic diets. Then, we applied optimal control method using Pontryagin's Maximum Principle to determine the necessary and sufficient conditions for the optimal control of the breast cancer. This approach may lead to therapeutic strategy that is relevant to clinical studies.

Theorem 1.4.1.

If $u^*(t)$ and $x^*(t)$ are optimal for problem (1.4.3), then there exists a piecewise differential adjoint variable $\theta(t)$ such that

$$H(t, x^*(t), u(t), \theta(t)) \leq H(t, x^*(t), u^*(t), \theta(t)) \tag{1.4.4}$$

for all controls u at each time t, where the Hamiltonian H is

$$H = f(t, x(t), u(t)) + \theta(t) g(t, x(t), u(t)) \tag{1.4.5}$$

and

$$\frac{\lambda(t)}{dt} = -\frac{\partial H(t, x^*(t), u^*(t), \theta(t))}{\partial x}, \theta(t_f) = 0. \tag{1.4.6}$$

1.4.3.4 Necessary conditions

If $u^*(t)$ and $x^*(t)$ are optimal, then the following conditions hold:

$$\begin{aligned} &\frac{\theta(t)}{dt} = -\frac{\partial H(t, x^*(t), u^*(t), \theta(t))}{\partial x}, \\ &\theta(t_f) = 0, \\ &\frac{\partial H(t, x^*(t), u^*(t), \theta(t))}{\partial u} = 0. \end{aligned} \tag{1.4.7}$$

1.4.3.5 Sufficient conditions

If $u^*(t)$, $x^*(t)$ and $\theta(t_f)$ satisfy the following conditions

$$\begin{aligned} &\frac{\theta(t)}{dt} = -\frac{\partial H(t, x^*(t), u^*(t), \theta(t))}{\partial x}, \\ &\theta(t_f) = 0, \\ &\frac{\partial H(t, x^*(t), u^*(t), \theta(t))}{\partial u} = 0. \end{aligned} \tag{1.4.8}$$

Then $u^*(t)$ and $x^*(t)$ are optimal where $\theta(t)$ is the shadow price or co-state variable. This denotes the increase of the objective function due to a marginal increase of the state variable. At any time the decision maker can use the control variable to generate direct contributions to the objective function (represented by the term $f(t, x(t), u(t))$ in the Hamiltonian, or it can use the control variable to change the value of the state variable in order to generate contributions to the objective function in the future. These indirect contributions are measured by the term $\theta(t)g(t, x(t), u(t))$ in the Hamiltonian [4-6,13,61,95-99,112].

1.4.4 Structure of the thesis

The thesis is organized as follows: In Chapter 1, we outline the overview of the study, background to the study, research questions, aim and objectives, rationale for the study as well as research methodology. Chapter 2 is devoted to a literature review on mathematical models of cancer growth and progression, treatment responses with application of optimal control methods in mathematical biology, and application of ketogenic diet to cancer disease. In Chapter 3, we develop and analyse deterministic models with anti-cancer treatment drugs, ketogenic diet and immune booster. The existence and stabilities of equilibria without tumor (tumor-free equilibrium), dead equilibria, co-existing equilibria points, global stability using Lyapunov function (at tumor-free equilibrium), bifurcation

analysis, sensitivity analysis and numerical simulations are also presented. In Chapter 4, we incorporate into the breast cancer model, two control variables such as anti-cancer drugs and ketogenic diets. We apply optimal control methods to determine the most cost effective strategy from the combination of anti-cancer drugs only, ketogenic diet alone, as well as anti-cancer drugs with ketogenic diet. Furthermore, we find optimal conditions for the elimination of tumor cells rather than control. However, when elimination is not possible, we find the necessary conditions for the optimal control of tumor cells' metastasis. In Chapter 5, we provide a conclusion and summary of the entire study while outlining possible areas for further research.

Chapter 2

Literature Review

2.1 Introduction

The occurrence of cancer may require the build-up of multiple mutations which allow cells to breakout from regulatory networks that ensure cooperation, a process termed multi-stage tumorigenesis [94, 102]. Usually, the death of the organism is not as a result of a single or primary cancer. This is because cancer cells have the ability to travel within the blood supply mechanism to distant sites leading to metastasis which is growth in different organs. It is this metastatic growth that leads to the death of the organism [116]. In this section, we review existing literature on the formation and progression of cancer cells, ketogenic diet, tumor growth models, treatment response models and breast cancer models in the treatment of medical ailments.

The literature search was performed using the following databases: PubMed, MEDLINE, Scopus and ScienceDirect; from inception to 2018. The search strategy consisted of four separate components, each containing key words related to "mathematical modeling", "breast cancer", " ketogenic diet", and "optimal control theory". The key words in each component were linked using Boolean function "AND" in the final search.

However, the search was limited to original articles, clinical studies, epidemiological studies and mathematical modeling. Studies in languages other than English language were excluded. The titles and abstracts of retrieved studies were screened to select the relevant articles.

2.2 Cancer and its managements

2.2.1 The genesis of cancer growth and progression

Tumor cells undergo proliferation like normal cells until they out-grow and crowd out the normal cells (see Figure 2.1). This irregular division and increase is facilitated by some genes that are either effective or ineffective [71] as well as by the mutation and epimutation of genetic material at the molecular level. Sbeity and Younes [116] have explained that tumor growth process involves several degrees of change within the cells of the cancer colony leading to rapid growth. The off-springs inside mutating cells then fill the colony. This affects the cells' manner of growth and digestive enzymes. Tumor growth also has the capacity to enlarge blood vessels and blood supply as well as facilitate the supply of nutrients to cancer cells [116, 84].

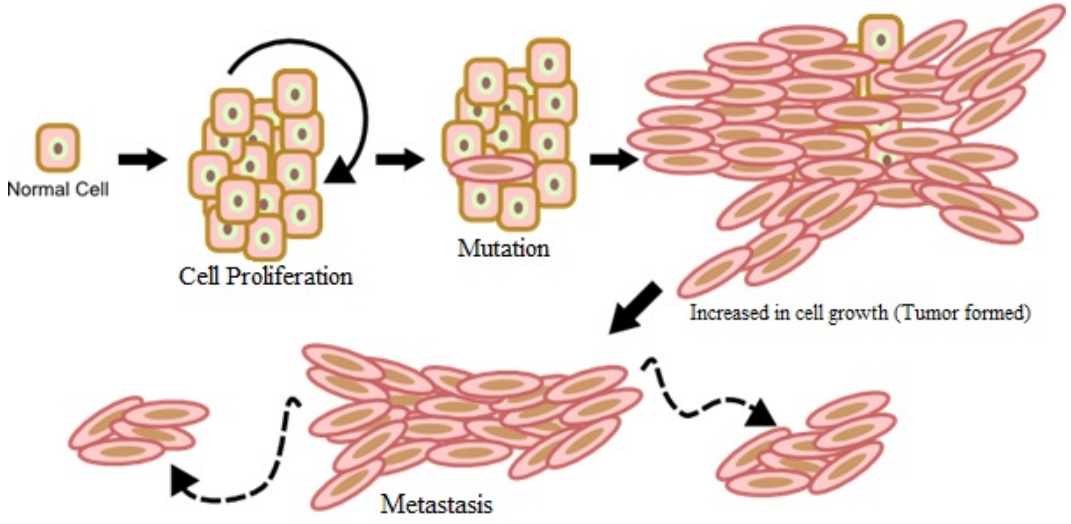

Figure 2.1: *The genesis of cancer formation from a single mutated cell and progression [84].*

Estrogen and Progestins are known to be involved in breast cell proliferation and the progressive stages of Hormone-Responsive Therapy (HRT). Postmenopausal women are prone to breast cancer when exposed to endogenous steriod hormones such as estrogen [42]. In fact, using HRT for 5 years is known to predispose a postmenopausal woman to breast cancer and also increases breast density [21]. The combination of estrogen replacement therapy (ERT) and progestin increases the chances of acquiring breast cancer than estrogen alone [115,117]. However, long time use of HRT brings about reduced breast cancer death and enhance survival [19,51,139].

2.2.2 Ketogenic Diet (KD)

In the early 1920s, Otto Warburg noticed that most cancer cells, regardless of oxygen availability and functional mitochondria, capture and metabolise large amounts of glu-

cose and convert it to lactate rather than fully oxidizing it to carbon(iv)oxide like healthy respiring cells [65, 135, 136]. This process , called the Warburg effect, is associated with fuel oxidation such that dietary manipulations become hypothesised as important ways to prevent and treat cancer. Thus, the ketogenic diet has emerged as a potential metabolic therapy with the purpose of achieving the above-mentioned metabolic vulnerability of cancer cells; that is, excessive reliance on glycolysis [64]. Even though an assertion of the influence of ketogenic diet as an anti-cancer agent is limited, a ketogenic diet approach has been widely studied for the treatment of epileptic seizures [47]. In general, a ketogenic diet (KD) is characterised by high-fat, moderate-to-low protein and very-low carbohydrate content. The conventional fat to carbohydrate and protein ratio of this diet is $4:1$ and $3:1$ respectively, which gives a macronutrient distribution of approximately 90% fat, 2% carbohydrate and 8% protein [8]. However, its therapeutic mechanisms may be beyond the concern in clinical settings. Its effects have been monitored in different circumstances such as epilepsy and other neurologic diseases [123], obesity, diabetes, polycystic ovary syndrome cancer, respiratory disease and cardiovascular disease [8, 20, 59, 79, 105, 106].

In light of the potential influence of a KD on breast cancer prognosis or treatment and the lack of focus on diet, Oliveira *et al.* [94] support its use in cancer therapy study either as independent treatment or in conjunction with other therapies due to its nutritional advantages. Schroeder *et al.* [118] demonstrate that there is a decrease in lactate levels in tumor tissue when compared with tumor-free mucosa after five days following a KD. High lactate levels in tumor cells are related to negative prognoses in patients with head and neck squamous cell carcinoma. This finding highlights on the one hand, how nutrition can influence cancer cell metabolism, and on the other hand, that KD may be a promising therapeutic dietary approach for this cancer type. However, there are limitations on their study which include lack of optimal control level, lack of information regarding diet

composition, level of ketosis and effect on disease progression.

Furthermore, there is limited work done on clinical trials and direct observations on the use of KD as a potential therapeutic agent in patients with breast cancer. Moreover, O'Flanagan *et al.* [92] worked on calorie restriction (CR), focusing on the preclinical studies of CR mimetic drugs and other dietary interventions (such as the ketogenic diet) on non-obese patients and rodents. It was observed that there are promising improvements in the efficacy of anti-cancer therapies and also reduced side effects of cytotoxic treatments. It was also established by O'Flanagan *et al.* [92] that calorie restriction is a good anti-tumor agent with the potential to reduce systemic inflammation and growth factor signalling, as well as improve metabolic markers. In this connection, Schwartz *et al.* [119] showed that diet is well permitted in cancer patients either as monotherapy or adjuvant. The use of diet as a monotherapy is promising in that it is known to halt the growth rate of cancerous cells. Toth and Clemens [129] further explained that, in some situations, a ketogenic diet alone may be adequate for cancer management. However, some preclinical studies have shown better outcomes for low-carbohydrate ketogenic diets in decreasing tumor growth in breast cancer and gastric cancer models [24, 40, 56, 101, 124]. In addition, Erickson *et al* [40] advised that before recommending the use of a ketogeic diet for oncology patients, it is essential to understand the different macronutrient compounds of the main form of the KD.

However, Arends*et al.* [14] argued that if long-term application of the KD has been correlated with calcium deficiency and the metabolic state of acidosis can aggravate bone loss in the presence of osteoporosis or osteopenia which could be essential when recommending its use among patients with higher risks of osteoporosis. It may therefore not be a suitable option for a patient with a history of renal tubular acidosis or nephrolithiasis and can also increase the incidence of kidney stone formation (Neuropadiatrie & S1-Leitline)

[66, 67]. Furthermore, Hyde *et al.* [57] have explored the fundamental principle in Figure 2.2 for nutritional ketosis as a pleiotropic treatment modality relevant to breast cancer and the potential for keto-adaptation to serve as an adjunct or independent therapy in breast cancer. However, Seyfried *et al.* [120] claimed that restricted KD, calorie restriction and water-only fasting reduce circulating glucose and insulin levels, although it promotes ketone bodies' circulation.

Thomson *et al.* [130] investigated placebo-controlled trial of diidolylmethane (DIM) for breast cancer biomarker dynamics in patients treated with Tamoxifene and concluded that DIM increases the level of Sex Hormone Binding Globulin (SHBG) and ratio of 2-*hydroxyestrone* $(2-OHE1)$ to 16α-*hydroestrone* which are known to be anti-cancerous and pro-cancerous respectively. However, DIM was known to decrease endoxifen (a metabolite of tamoxifen metabolism) but has no effect on breast density.

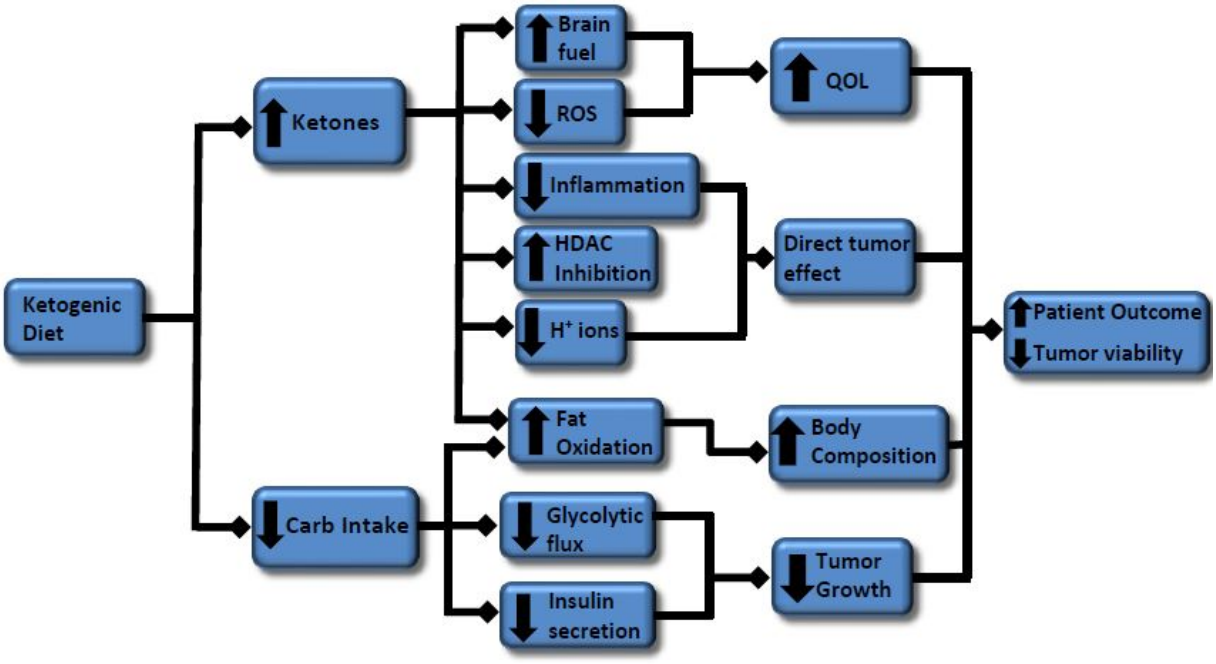

Figure 2.2: *Mechanism through which ketogenic diet affected tumor and patient outcomes [57]*

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2.3 Mathematical modeling reviews

This underlines the interest of this study in the use of mathematical models to control breast cancer. Since they are capable of providing insight into different phenomena, mathematical models are extremely useful in proving theoretical frameworks across various disciplines. Several mathematical models have been used to explore the genetical (obesity) and environmental (alcohol, smoking, etc) dimensions of breast cancer [95]. Furthermore, different attempts have been made to propose useful mathematical models for the dynamics of breast cancer. Some of these include Matzaivos *et al.,* [82] as well as Davies *et al.,* [30]. However, only a few studies have attempted to propose a mathematical model that examines the hormonal risk factors of the disease (Mufudza *et al.,* [87]; Michelle [85]). Previous studies [30, 82, 85, 87], have also not considered ketogenic diet as well as the use of optimal control theory as likely cost effective strategies for the treatment of breast cancer. This study therefore seeks to investigate the dynamical behaviour of breast cancer models with anti- cancer drug therapy, an immune booster and a ketogenic diet. The use of anti-cancer drugs, immune boosters and a ketogenic diet as constant parameters will enhance positive results by reducing cancer cells in the body and enhancing survival rates [118, 129]. Numerous treatment choices exist for cancer with chemotherapy and surgery being the most widely used. While chemotherapy is often the main treatment method preferred, it is conceivable that the patient will likewise get different medications. Synergistic impacts have additionally been overused on accounts of various medications (e.g *5-Fluorouracil* and Tamoxifen in breast cancer) with blended treatments to enhance efficacy and lessen resistance to medications [32, 38].

Mathematical oncology is emerging as a foundational discipline for modern cancer treatment innovations. Kuang *et al.,* [68] explained that mathematical models are for-

mulated to provide tools for both theory and practice, for patient-specific drugs and customised cancer treatment. There is no doubt that mathematical models, in mathematical oncology research, are approved as vital tools that can shed more light on cancer treatment. The present study used optimal control techniques to analyse minimisation of treatment cost. The researcher will model the impacts of therapy in the form of drug-specific models, which address the efficacy of the anti-cancer drugs and ketogenic diet. This research constructs the local sensitivity analysis index with uncertainty analysis for the model parameters, in order to determine parameters that are important for cancer cells invasion. The study also examined and compared the cost-effectiveness of these interventions to determine the optimal control strategy for eradication or control of the disease.

The importance of mathematical models and their application to the investigation of cancer cannot be over-emphasized. Mathematical models have thus been increasingly used in different fields including in the study of tumor progression and medication target forecasting [108]. Cancer biology models range from general models (e.g tumor growth, angiogenesis), to specific models (e.g behaviour in response to specific stimuli). These are discussed in the sections to follow.

2.3.1 Tumor growth models

According to Patel and Nagl [108], the total increase in the mass of an organism is referred to as growth. Tumor growth can be studied in terms of exponential growth, logistic growth and Gompertz growth law for example, malignant tumor [50]. The development of the tumor core has been modeled in a continuous setting using differential equations with explicit spatial dependence. Adam [3] used an ordinary differential equations to model a phenomenon which shows the mass conservation of tumor cells, coupled with reaction-

diffusion equations reflecting the distribution of nutrients within the tumor. Cruywagen and his coworker [29] used Jansson-Revesz equations to model tumor growth in colon cancer. This resulted in competitive effects between tumor cells and normal cells. These equations are mainly the classical Lotka-Volterra equations of logistic growth with an inclusive term to account for the conversion of one specie into the other. Also, to account for passive cellular motion, Cruywagen and Coworker included a diffusive term to each equation.

Wasserman *et al* [137] used a finite element analysis technique to describe the macroscopic behavior of tumor growth based on stresses imposed by various factors. This approach is similar to that of Chaplain and Sleeman [27] who used nonlinear elasticity theory to model a tumor, arguing that the growth of a tumor is governed by a strain-energy function. According to Ward and King [134], nonlinear partial differential equations can be used to generate profiles for an avascular tumor based on nutrient distribution. Byrne and Chaplain [23] proposed a mathematical model which differentiates necrosis from apoptosis using analytical and numerical techniques. They argue that as tumors develop apoptosis and necrosis experience changes.

Anderson*et al.* [12] derived a discrete model of cancer cell invasion for tumor growth from the continuum partial differential equations model. The simulation results of this model reinforced the suggestion that individual cancer cells can metastasis above a visible margin of tumor cells. Furthermore, the study is considered as the first to examine the issue of stochastic events and probability in tumor growth. It revealed that individual cancer cells possess the ability to penetrate normal tissues at a greater depth than would be predicted by a deterministic ODEs model.

Kansal *et al.*[60] developed a simulated brain tumor growth dynamics using a three-dimensional cellular automaton and simulating Gompertzian growth for a tumor growing

over nearly three orders of magnitude in radius. The model predicts the composition and dynamics of tumor growth at selected points using random processes of probability. Recently, Haeno *et al.* [52] adopted a stochastic process to model tumor growth, death, mutation and dissemination events parameterised using pancreatic cancer patient data. It was shown in their finding that therapies which efficiently reduce the growth rate of cancer cells earlier in the course of treatment appear to be superior to upfront tumor resection. This model functions on the probability of metastasis formation before tumor diagnosis as well as the number and size distribution of cancerous cells.

2.3.2 Angiogenesis models

Angiogenesis is a process of developing new blood vessels which are critically important during the normal development of the embryo and foetus. Early cancer growth is known as the avascular stage of growth with newly formed tumors being dependent on nutrient supply by diffusion from the surrounding tissues. However, according to Michor *et al* [86], tumor cells are unable to get sufficient nutrients for continued exponential growth before the development of blood supply. In support of this, Owen *et al* [102] explained that the development of new blood vessels is necessary to guarantee the steady supply of nutrients to the tumor which enhances its limitless growth. Anderson and Chaplain [11] used a hybrid approach which focused on three important variables to design a tumor induced angiogenesis model with the capability to follow the motion of endothelial cells (ECs) at the capillary tips and to control vital activities like proliferation, anastomosis and branching. The variables include EC density, proangiogenetic proteins (PAP) and fibronectin concentrations (FC).

Other scholars such as McDougall *et al* [83] have developed hybrid models relating to offsprings resulting from the breeding of two genetically distinct individuals. These

will usually result in high degrees of heterozygosity (cells or organisms) which focus on vascular adaptation and angiogenesis without considering tumor development. Similarly, Bartha and Rieger [17], Gevertz with Torquato [48], have developed mathematical models of angiogenesis in which individual vessels form a network that delivers nutrients and drugs to tissues. Owen and Coworker [103] examined angiogenesis and vascular modeling in normal and cancer cells. In their work, a multiscale model of vascular tissue growth which combines blood flow, angiogenesis, vascular modeling, subcellular and tissue scale dynamics of multiple cell populations was developed. The mathematical analysis based on their work shows that vessel removal is due to low wall shear stress, and is highly sensitive to pressure drop across a vascular network, while the degree of elimination of tumor increases as the pressure decreases. They pointed out that low tissue oxygen levels change the internal dynamics of healthy cells, causing them to produce vascular endothelia growth factor (VEGF) which promotes angiogenic sprouting. Subsequently, the level of blood oxygenation regulates the extent of angiogenesis with higher oxygenation leading to fewer vessels.

2.3.3 Treatment response models

Cancer treatment is aimed at eliminating or reducing cancerous cells from the body. However, the high toxicity of anti-cancer drugs used during chemotherapy damages healthy cells in the body as the drugs circulate in the bloodstream. Using a lattice Boltzmann approach, Bellomo *et al.* [18] developed a theoretical framework which deals with the relationship between the immune system and discrete cells population. This approach employs the single scale computational techniques known from fluid dynamics to study cancerous cells. They argue that for a cautious application of this statistical physics approach to tumors due to the fact that the behaviour of tumors is changes or alters in

intercellular and intracellular biochemical signalling networks. Owen *et al.* [103] modelled the application of macrophages in drug delivery to hypoxic (i.e subnormal concentration of oxygen in arterial blood) tumors. The model was designed on the basis of a growing avascular tumor spheroids that is filled by tumor cells, extracellular components, macrophages and tumor metastasis.

Similarly, Ledzewicz and Schattler [74] worked on anti-angiogenic therapy as a therapeutic technique of cancer therapy to prevent the development of tumors through blood supply. They used geometric analyses of optimal control theory to validate and analyse how to plan specific amounts of angiogenic inhibitors in order to achieve optimal reduction of cancerous cells. Baish *et al.* [16] also developed a mathematical model using fluorescent vascular images (fluorescence imaging is generally employed in the measuring of the functional and structural specifications) that cannot be easily imaged using endogenous sources of contrast. The application of fluorescent vascular imaging includes molecular imaging, cancer imaging and the functional imaging of hemodynamic properties. Furthermore, Davies*et al* [30] used partial differential equations to formulate a mathematical model that determines the effect of the architectural and physiological irregularities of tumor vasculature on the delivery of therapeutic agents and nutrients.

The application of optimal control to several disease conditions started in the mid-1970s, and ever since, it has been the subject of much research. In Bahrami and Kim [15], engineering optimal control theory is employed to determine the drug regimen for reducing an experimental tumor cell population. Studies by Swan [126-128] are crucial for the fundamental comprehension of the early mathematical modeling methods of chemotherapy treatment planning problem. Kimmel and Swierniak [62] confirmed that the two main problems facing successful chemotherapy of cancer are cell-cycle-phase treatment dependence and the development of resistance of tumor to cytotoxic agents. The obstacles can

be tackled by using optimal control theory to model cell dynamics.

Recent studies that discuss the application of optimal control theory to solve diverse epidemiological problems include Ledzewicz and Schattler [74], Agusto [4], Ding *et al.* [36], Ding *et al.* [37] and Nana-Kyere *et al.* [89]. The Taguchi Immune Algorithm (TIA) was proposed by Tsai *et al.* [131] for improving multi-dose drug schedules, treatment times and drug toxicities in cancer chemotherapy. The aim was to maximize the efficiency of a drug schedule for a given time of chemotherapy. The use of TIA is combined with Artificial Immune Algorithm (AIA) for exploring the optimal feasible region in macro-space. However, the experimental simulation results show that the application of the TIA is more effective in providing solution to multi-dose drug timing for chemotherapy problems. The simulations also show that cumulative drug toxicity is an important factor in the reduction of tumor cells.

Tamoxifene and Raloxifene are types of Selective Estrogen Receptor Modulators (SERMs) that serve as an alternative to HRT with fewer side effects compared to ERT [53]. They were originally designed to prevent breast cancer and osteoporosis but in-vitro studies have shown that Tamoxifene has selective estrogen properties in sites such as bone and anti-estrogenic potentials in the mammary tissues [133]. In post-menopausal women, Tamoxifene raises the chances of endomentrial cancer, reduces the level of circulating cholesterol and maintains bone density [39]. In addition, long term use of Tamoxifene in ER-positive breast cancer patients lowers the risk of death and the occurrence of contralateral breast cancer [107]. For its part, Raloxifene is excreted quickly and has low bioavailability unlike Tamoxifene which accumulates [70]. However, Raloxifene is still at the clinical trial stage and is thus not a substitute for Tamoxifene [122].

Chemotherapy, as a conventional treatment, has become a part of therapy regimen for most tumor patients and aims at shrinking primary tumors, slowing their growth, and

killing tumor cells that may have metastasized to other parts of the body from the original, primary tumor. However, one of the defects of chemotherapy is that it also kills normal cells and has serious side effects. Recently, clinical evidence has shown that combined conventional treatment (such as chemotherapy and radiotherapy) with ketogenic diet is more efficient in inhibiting tumor growth and elongating the survival times of patients [119,129].

Pang *et al.* [104] investigated the implementation of immunotherapy and chemotherapy over a certain period to reduce the number of tumor cells while minimising the total cost of the implementation of the two therapeutic strategies. They developed a model for combined immunotherapy and chemotherapy and considered the infusion dose of immune cells and the increment of drug concentration caused by chemotherapy as control variables. They further attempted to explore the existence of an optimally combined immunotherapy and chemotherapy strategy and applied numerical simulations find out which strategy is the most cost-effective. Similarly, De Pillis and Radunskaya [31] applied optimal control to design a therapeutic regimen with immunotherapy or chemotherapy. Castiglione and Piccoli [26] considered dendritic cell transfection immunotherapy to describe the immune-cancer interaction and characterised the optimal infusion dose of dendritic cells. In the same vein, Bratus *et al.* [22] applied an optimal control method to obtain a chemotherapy regimen which makes tumor cells clear-out over time.

2.3.4 Breast cancer models

Mufudza *et al.* [87], considered a Lotka-Volterra type system of four ordinary differential equations to describe the interactions among healthy, tumor and immune cells, as well as excess estrogen levels in breast cancer dynamics that is responsible for tumor growth. The authors were able to establish equilibrium points, as well as conditions for local and

global stabilities of the models with and without excess estrogen. Abernathy *et al.* [1], extended on model in [87] by including the cancer stem cell hypothesis, limited rates of estrogen-induced proliferation and mutation, and estrogen absorption rates for each of their cell populations. In their study, the authors in [1] were able to divide the model into basic competition submodel and immune-free submodel. They analysed the stability of both basic competition submodel and immune-free submodel to show better understanding of the dynamics among cell population of the role of estrogen. The authors in [1], determined the global attractivity of cancer persistence in each case. The full model was analysed and conditions for a globally attractive cure state was established. Michelle [85], developed a mathematical model of cancer network, which described the growth of an estrogen-receptive cancer linear network. In their study, cancer stem cells, tumor cells, healthy cells and estrogen level formed their compartmental model. The authors established the equilibrium points, sensitivity analysis, as well as the conditions for local stability for each equilibrium point. In addition, Gregory *et al.* [50], designed a mathematical model to describe and quantify the mechanisms and dynamics of tumor growth, cell-kill and resistance as they affect the period of benefits after cancer development. The authors in [50] explored the treatment efficacy that may be related to primary tumor characteristics, with the potential to guide future trial design and appropriate selection of therapy. Log-normal distribution of both resistant disease and tumor doubling times generates disease-free survival (DFS) or invasive DFS was assumed.

From the literature, it is clear that epidemiological models have been used to discuss the dynamics of breast cancer and tumor cells elimination. However, only a few mathematical models that investigating estrogen as a risk factor for breast cancer are available from existing literature. In addition, to the best of the knowledge of this author, as at the time of this write-up, there is no existing mathematical biology study that incorporates

ketogenic-diet with anti-cancer drug in the treatment of breast cancer. Based on the problem we have described so far, our objective is to formulate a mathematical model that can specifically investigate the dynamics of the breast cancer in different regions, with special interest in its treatment and control strategies. We will employ relevant techniques to analyse the model with the aim of decreasing or eradicating tumor cells from the body system. The next chapter discusses the formulation of the mathematical model.

Chapter 3

Model Formulation and Analysis

3.1 Introduction

In this chapter, a mathematical model for breast cancer is presented. The model does not only describe tumor growth and anti-cancer drug dynamics, it also captures the influence of nutritional diet (the ketogenic diet) on tumor cells. The cell population is divided into four compartments, namely normal cells compartment $N(t)$, tumor cells compartment $T(t)$, immune response compartment $M(t)$, and estrogen compartment $E(t)$. The normal cells compartment refers to healthy cells that have not been invaded by the cancer but that are at risk of invasion. The tumor cells compartment refers to cancer-invaded cells while the immune response compartment refers to natural killer cells, NK and CD^+ T-cells. The estrogen compartment $E(t)$, refers to levels of estrogen which result in hormonal imbalances that lead to hormone-receptor-positive breast cancer. The major section of this chapter consists of the analysis of the model. The next generation matrix method by *Van Driessche and Watmough [132]* will be used to calculate the treatment induced invasion reproduction number, R_i^*, of the formulated model. A suitable Lyapunov function is constructed to investigate the global asymptotic stability of the treatment tumor-free

equilibrium (TTFE). Subsequently, the uncertainty and sensitivity analysis are done to determine the most sensitive parameters of the model. can be determined. The possibility of the occurrence of bifurcation where both equilibria co-exist as the invasion reproduction number crosses unity is then analysed using the center manifold theory.

3.1.1 Model formulation

Mufudza et al. [87] considered the following model on breast cancer with estrogen:

$$\begin{aligned}
\frac{dH}{dt} &= H\left(\alpha_1 - \beta_1 H - \delta_1 T\right) - \sigma_1 HE \\
\frac{dT}{dt} &= T\left(\alpha_3 - \beta_2 T\right) - \gamma_2 IT + \sigma_2 HE \\
\frac{dI}{dt} &= s + \frac{\rho IT}{\omega + T} - \gamma_3 IT - \mu I - \frac{\sigma_3 IE}{\nu + E} \\
\frac{dE}{dt} &= \pi - \theta E
\end{aligned}$$

where: H(t) = Normal cells class, T(t) = Tumor cells class, I(t) = Immune cells class, E(t) = Estrogen class.

The breast cancer model presented in this work was built on that of Mufudza et al. [87] by incorporating anti-cancer drug, ketogenic-diet and immune booster.Following scientific evidence, our model formulation was driven by Allen et al. [8]; it was established in their study that parameter d (ketogenic-diet) is the conventional fat to carbohydrate and protein ratio of 4:1 and 3:1 respectively, which means macro-nutrient distribution of approximately 90% fat, 2% carbohydrate and 8% protein.

Therefore, for the purpose of this study, the normal cells $N(t)$ compartment is based on modified logistic growth with the carrying capacity set to one in relation to the size N and the general growth rate for parameters broken into two, namely α_1 and μ_1 where α_1 is exponential growth rate for N while μ_1 is the depletion rate due to competitive factors. They compete for space and resources such as nutrients and oxygen supplied by

blood vessels to tumor cells $T(t)$. Thus, the growth rate of normal cells population, $N(t)$ maybe negatively affected by a factor $\phi_1 NT$, where ϕ_1 represent the probabilistic rate of normal cells mutation into tumor cells [7,121], while damaged normal cells will now form the compartment of tumor cells . The final term describes gene transactivation that can be a contributing growth factor responsible for the estrogen stimulated by breast cancer, which can result in damage of *deoxyribonucleic acid* (DNA). There will be a reduction in the population of normal cells being transformed into tumor cells by $\lambda_1 NE$ where λ_1 represents tumor formation rate resulting from DNA mutation caused by the presence of excess estrogen [1, 87]. The effectiveness of anti-cancer drugs (Tamoxifen) is represented by k, where $0 \leq k \leq 1$. Tamoxifen is a selective estrogen receptor modulator (SERM) used in the treatment and prevention of estrogen receptor-positive ($ER+$) breast cancers. The primary action of tamoxifen is competition with estradiol for binding ER in breast tissue. The efficacy of tamoxifen is well established [130, 133]. The equation for tumor cells is similar:

$$\frac{dN}{dt} = \overbrace{N\alpha_1}^{normal\ cells\ growth} - \overbrace{\mu_1 N^2}^{natural\ death} - \overbrace{\phi_1 NT}^{mutation\ into\ tumor} - \overbrace{(1-k)\,\lambda_1 NE}^{transition\ to\ tumor} \tag{3.1.1}$$

The tumor cells compartment can be denoted by $T(t)$ in the form an abnormal mass of tissue. Cancer names usually reflect the kind of tissue (where there is alteration of DNA) that they arise form such as breast cancer,cervical cancer and skill cancer. The 145 identified primary breast tumors reflect 51 cancer cell lines which are classified into two main strands-one with estrogen receptors ($ESR1 + ve$) known as the luminal, and the other without which are basal-like [1, 50]. The first term of the tumor compartment is a logistic growth term for tumor cells which depends on the rate of the parameter α_2 (tumor cells growth rate), d is constant rate of ketogenic diet while μ_2 depletion rate due

to competition . However, $\phi_1 NT$ is a construct that captures the erratic nature of cancer mutation in which tumor cell numbers could increase higher than normal cells. This could produce an advantageous effects on tumor cells over normal cells, since the production of normal cells could cease while tumor cells production progresses over abnormally longtime intervals [7,121]. Although, if $d = 0$, the tumor cells growth rate will be reduced, any DNA mutation caused by excess estrogen continue to repopulate tumor cells by a factor of $\lambda_1 NE$. The induced death rate μ_5 is as a result of tumors being starved of nutrients, glucose and other resources by the body system during nutrition altered by a ketogenic diet. We assume that γ_2 is the rate at which tumor cells are removed as a result of immune responses.

$$\frac{dT}{dt} = \overbrace{T\alpha_2 d}^{\text{ketogenic diet inhibit tumor cells growth}} - \overbrace{\mu_2 T^2}^{\text{natural death}} - \overbrace{\gamma_2 MT}^{\text{immune inhibition}} - \overbrace{\mu_5 T}^{\text{tumor death due to ketogenic}} + \overbrace{\phi_1 NT}^{\text{tumor mutants}} + \overbrace{(1-k)\,\lambda_1 NE}^{\text{arrival in tumor}} \tag{3.1.2}$$

The immune cells compartment is represented by $M(t)$ which comprises of Natural Killer cells (NK) and $CD8^+$T-cells. The growth of immune response cells may be stimulated by the presence of the tumor and they can destroy tumor cells through a kinetics process. We also assume that the presence of a detectable tumor in a body system does not necessarily imply that the tumor has completely escaped active immunosurveillance. However, if a tumor is immunogenic, it is possible that the immune response may not be sufficient on its own to completely combat the rapid growth of tumor cells and the eventual development of a tumor [26, 82, 139]. As is the case in Mufudza et al. [87], a similar equation was used to model the immune response dynamic by introducing immune booster (ketone bodies) and anti-cancer drug efficacy. The immune response is represented by the following equation:

$$\frac{dM}{dt} = \overbrace{s\beta}^{immune\ source} + \overbrace{\frac{\rho MT}{\omega + T}}^{immune\ growth} - \overbrace{\gamma_3 MT - \mu_3 M}^{death\ of\ immunecells\ due\ to\ interaction\ with\ tumor} - \overbrace{\left((1-k)\frac{\lambda_3 ME}{g+E}\right)}^{decay\ factor\ due\ to\ anticacer\ drug\ efficacy} \tag{3.1.3}$$

The constant source parameter s denotes the source rate of immune response fully infused daily into the body and we introduced immune booster β (supplement such as ketone bodies) to assist immune response whenever tumor cells overpower immune cells. This is done to activate immune response and fight the cancer cells. The next term is a nonlinear growth term for immune response where ρ is the rate of immune response and ω is the immune cell threshold [31]. We use γ_3 to denote the rate at which immune response is activated upon interacting with tumor cells while μ_3 represents the natural death rate as a result of immune cells due necrosis. The final term explains the limited rate at which estrogen suppresses immune cells activation where λ_3 is the rate of immune suppression and g is the estrogen threshold [87].

Finally, we use $E(t)$ to denote estrogen, a female steroid hormone produced in lesser amounts by ovaries, the adrenal cortex, plancenta and male testes. Estrogen helps to control and guide sexual development, including the physical changes associated with puberty [19, 51]. However, increases in estrogen levels can lead to the growth of tumor cells. It also serves as a mitogen by triggering cell division in breast tissue [71]. Estrogen acts as a carcinogen by directly damaging DNA, making healthy epithelial cells to have a higher likelihood of malignant conversion [19,30,51,71]:

$$\frac{dE}{dt} = \overbrace{\epsilon}^{estrogen\ source} - \overbrace{\mu_4 E}^{estrogen\ natural\ death} \tag{3.1.4}$$

The constant replenishment of excess estrogen is denoted by ϵ. However, beyond the production by the ovaries, excess estrogen is released into the system as a result of the

use of oral contraceptive, and during hormone and estrogen replacement therapy. We therefore assumed a constant source, ϵ of $17-\beta$ *estradiol*, the primary biologically most active estrogen which is all the estrogen in the system at any particular time. The majority of cancer cells are assumed to be estrogen-receptor positive. We also assume that only a small proportion of epithelial cells are estrogen-receptor positive which can only be blocked. μ_4 is the rate at which estrogen is being washed out from the body system. Thus, the following ordinary differential equations is considered to be the breast cancer model for the study:

$$\begin{aligned}
\frac{dN}{dt} &= N\left(\alpha_1 - \mu_1 N - \phi_1 T\right) - \left(1-k\right)\lambda_1 NE \\
\frac{dT}{dt} &= T\left(\alpha_2 d - \mu_2 T\right) - \gamma_2 MT - \mu_5 T + \phi_1 NT + \left(1-k\right)\lambda_1 NE \\
\frac{dM}{dt} &= s\beta + \frac{\rho MT}{\omega + T} - \gamma_3 MT - \mu_3 M - \left(1-k\right)\frac{\lambda_3 ME}{g+E} \\
\frac{dE}{dt} &= \epsilon - \mu_4 E
\end{aligned} \tag{3.1.5}$$

It is important to state that the model presented in (3.1.5) is unique, in that, it provides more treatment options (anti-cancer drug and ketogenic-diet), and immune booster compared to the models in [1, 50, 85, 87]. In addition, the optimal control theory and cost-effectiveness analysis of our model in (3.1.5) were considered.

3.2 Model analysis

3.2.1 Positivity of solutions and boundedness

The system of equations (3.1.5) has an initial condition by

$N(0) = N_0 \geq 0,\ T(0) = T_0 \geq 0,\ M(0) = M_0 \geq 0,$ and $E(0) = E_0 \geq 0$

Since our model is to investigate cellular populations, all the variables and parameters of the model are non-negative. The system of equations (3.1.5) will be studied in the following region : $\Delta = \{(N, T, M, E) \in \Re^4_+\}$

The following theorem assures that the system of equations (3.1.5) is well-posed such that solutions with non-negative initial conditions remain non-negative for all $0 < t < \infty$ and therefore is biologically meaningful [6, 55, 80, 81]. Hence , we have the following result:

Theorem 3.2.1. : *The region $\Delta \subset \Re^4_+$ is positively invariant with respect to the system of equations(3.1.5) and non-negative solution exists for all time $0 < t < \infty$*

Proof: Let $\Delta = \Delta_c \subset \Re^4_+$ with $\Delta = \{(N, T, M, E) \in \Re^4_+ : N \leq \frac{\alpha_1}{\mu_1},$

$T(t) \leq \frac{\mu_1(\alpha_2 d - \mu_5) + \phi_1\alpha_2}{\mu_1\mu_2},\ \ M(t) \leq \frac{1}{s\beta(\omega+T)}\left(\gamma_3 T(\omega + T) + \mu_3(\omega + T) - \rho T\right),\ \ E(t) \leq \frac{\mu_4}{\epsilon}\}$

Then the solutions (N(t),T(t),M(t),E(t)) of system (3.1.5) are therefore positive $\forall\, t \geq 0$.

It is obvious from the first compartment of system (3.1.5) that in the absence of tumor,

$$\frac{dN}{dt} \leq N(t)\alpha_1 - \mu_1 N^2(t)$$

Solving with the Bernoulli method and taking $N(0) = N_0$,

we have,

$$N(t) \leq \frac{\alpha_1}{\mu_1 + k\alpha_1 e^{-\alpha_1 t}}$$

with

$$k = \frac{\alpha_1 - N_0\mu_1}{N_0\alpha_1}$$

$$N_0 = \frac{\alpha_1}{\mu_1 + k\alpha_1}$$

Then,

$$N(t) \leq \frac{\alpha_1}{\mu_1 + \left(\frac{\alpha_1 - N_0\mu_1}{N_0}\right) e^{-}\alpha_1 t}$$

$$N(t) \leq \frac{\alpha_1}{\mu_1} \quad as \quad t \to \infty$$

Therefore, $N(t) > 0, \forall\ t > 0$ since $\alpha_1,\ \mu_1$ are nonnegative.

Consequently,

$$T(t) \leq \frac{\mu_1(\alpha_2 d - \mu_5) + \phi_1\alpha_2}{\mu_1\mu_2} \quad as \quad t \to \infty,$$

Therefore, $T(t) > 0, \forall\ t > 0$ since $\alpha_2 d > \mu_5$ are nonnegative.

It can be shown by similar reasoning that

$$M(t) \leq \frac{1}{s\beta(\omega + T)} \left(\gamma_3 T(\omega + T) + \mu_3(\omega + T) - \rho T\right)$$

Therefore, $M(t) > 0, \forall\ t > 0$ since $\gamma_3 T(\omega + T) + \mu_3(\omega + T) > \rho T$ are nonnegative.

$M(t) > 0, \quad M(t) > 0, \quad and \quad E(t) > 0 \quad \forall t > 0$ if and only if $(1 - k) \geq 0$.

Lastly,

$$E(t) \leq \frac{\mu_4}{\epsilon} \quad as \quad t \to \infty$$

$E(t) > 0 \quad \forall t > 0$. This complete the proof.

3.3 Equilibrium points

The equilibrium points of the system (3.1.5) are determined by solving the resulting equation obtained by equating the derivatives of the system (3.1.5) to zero and setting

$N = N^*, T = T^*, M = M^*, E = E^*$

Thus,

$$N^*\left(\alpha_1 - \mu_1 N^* - \phi_1 T^*\right) - (1-k)\left(\lambda_1 N^* E^*\right) = 0 \tag{3.3.6}$$

$$T^*\left(\alpha_2 d - \mu_2 T^*\right) - \gamma_2 M^* T^* - \mu_5 T^* + \phi_1 N^* T^* + (1-k)\left(\lambda_1 N^* E^*\right) = 0 \tag{3.3.7}$$

$$s\beta + \frac{\rho M^* T^*}{\omega + T^*} - \gamma_3 M^* T^* - \mu_3 M^* - \left((1-k)\frac{\lambda_3 M^* E^*}{g + E^*}\right) = 0 \tag{3.3.8}$$

$$\epsilon - \mu_4 E^* = 0 \tag{3.3.9}$$

At equilibrium points, we have equation (3.3.9)

$$E^* = \frac{\epsilon}{\mu_4}$$

substitute E^* into equation (3.3.6), we have

$$N^* = 0, \quad \text{or} \quad (\alpha_1 - \mu_1 N^* - \phi_1 T^*) - (1-k)\left(\lambda_1 E^*\right) = 0$$

$$N^* = \frac{\alpha_1 - \phi_1 T^* - (1-k)\lambda_1 E^*}{\mu_1}$$

$$N^* = \frac{\alpha_1 - (1-k)\lambda_1 \epsilon}{\mu_1 \mu_4}$$

Therefore,

$N^* = 0 \quad \text{or} \quad N^* = \frac{\alpha_1 - (1-k)\lambda_1 \epsilon}{\mu_1 \mu_4}$

substitute, $N^* = 0, \quad E^* = \frac{\epsilon}{\mu_4}$ into (3.3.7), we have

$T^* = 0 \quad \text{or} \quad \frac{d\alpha_2 - \gamma_2 M^* - \mu_5}{\mu_2}$

substitute, $N^* = 0, \quad T^* = 0 \quad$ and $E^* = \frac{\epsilon}{\mu_4}$ into equation (3.3.8), we have

$$s\beta = M^*\left(\frac{\mu_3(g + E^*) + (1-k)\lambda_3 M^* E^*}{(g + E^*)}\right)$$

where,

$$M^* = \left(\frac{s\beta(g\mu_4 + \epsilon)}{\mu_3(g\mu_4 + \epsilon) + \lambda_3(1-k)}\right)$$

Therefore,

$$P_0 = (N_1^*, T_0^*, M^*, E^*) = \left(\frac{\alpha_1\mu_4 - (1-k)\lambda_1\epsilon}{\mu_1\mu_4}, 0, \frac{s\beta(g\mu_4+\epsilon)}{\mu_3(g\mu_4+\epsilon) + \lambda_3\epsilon(1-k)}, \frac{\epsilon}{\mu_4} \right)$$

Tumor-Free Equilibrium (TFE) occurs when the tumor cells can no longer proliferate and are terminated from the population due to competition with tumor suppressing proteins $P53$, immune response, normal cells and driven by effective anti-cancer drugs.

Solving equations (3.3.6), (3.3.7), (3.3.8),and (3.3.9) simultaneously give rise to the polynomial

$$b_0(M^*)^3 + b_1(M^*)^2 + b_2M^* + b_3 = 0 \tag{3.3.10}$$

where;

$$b_0 = \gamma_2^3(g\mu_4 + \epsilon)$$

$$b_1 = (2\gamma_2^2\mu_5 - 2\gamma_2^2\alpha_2 d - \gamma_2^2\omega\mu_2)(g\mu_4 + \epsilon)$$

$$b_2 = (\gamma_2\alpha_2 d\omega\mu_2 - 2\gamma_2\alpha_2 d\mu_5 - \gamma_2\alpha_2^2 d^2 - \gamma_2\mu_2\mu_5 + \gamma_2\mu_5^2 - \gamma_2\mu_2 - s\beta\mu_2\gamma_2)(g\mu_4 + \epsilon)$$

$$b_3 = (s\beta\mu_2^2\omega + s\beta\mu_2\alpha_2^2 d - s\beta\mu_2\mu_5 + \alpha_2\mu_2 d - \mu_2\mu_5)(g\mu_4 + \epsilon)$$

$$\left\{\left\{M_1^* = \frac{\sqrt[3]{-2b_1^3+9b_0b_2b_1-27b_0^2b_3+\sqrt{4\left(3b_0b_2-b_1^2\right)^3+\left(-2b_1^3+9b_0b_2b_1-27b_0^2b_3\right)^2}}}{3\sqrt[3]{2}b_0}\right\}\right\}$$

$$-\left\{\left\{\frac{b_1}{3b_0}-\frac{\sqrt[3]{2}\left(3b_0b_2-b_1^2\right)}{3b_0\sqrt[3]{-2b_1^3+9b_0b_2b_1-27b_0^2b_3+\sqrt{4\left(3b_0b_2-b_1^2\right)^3+\left(-2b_1^3+9b_0b_2b_1-27b_0^2b_3\right)^2}}}\right\}\right\},$$

$$\left\{M_2^* = -\frac{\left(1-i\sqrt{3}\right)\sqrt[3]{-2b_1^3+9b_0b_2b_1-27b_0^2b_3+\sqrt{4\left(3b_0b_2-b_1^2\right)^3+\left(-2b_1^3+9b_0b_2b_1-27b_0^2b_3\right)^2}}}{6\sqrt[3]{2}b_0}\right\}$$

$$-\left\{\frac{b_1}{3b_0}+\frac{\left(1+i\sqrt{3}\right)\left(3b_0b_2-b_1^2\right)}{3\ 2^{2/3}b_0\sqrt[3]{-2b_1^3+9b_0b_2b_1-27b_0^2b_3+\sqrt{4\left(3b_0b_2-b_1^2\right)^3+\left(-2b_1^3+9b_0b_2b_1-27b_0^2b_3\right)^2}}}\right\},$$

$$\left\{M_3^* = -\frac{\left(1+i\sqrt{3}\right)\sqrt[3]{-2b_1^3+9b_0b_2b_1-27b_0^2b_3+\sqrt{4\left(3b_0b_2-b_1^2\right)^3+\left(-2b_1^3+9b_0b_2b_1-27b_0^2b_3\right)^2}}}{6\sqrt[3]{2}b_0}\right\}$$

$$-\left\{\frac{b_1}{3b_0}+\frac{\left(1-i\sqrt{3}\right)\left(3b_0b_2-b_1^2\right)}{3\ 2^{2/3}b_0\sqrt[3]{-2b_1^3+9b_0b_2b_1-27b_0^2b_3+\sqrt{4\left(3b_0b_2-b_1^2\right)^3+\left(-2b_1^3+9b_0b_2b_1-27b_0^2b_3\right)^2}}}\right\}$$

Using our parameter values as presented in Table (3.1) $M_1^* > 0$ and positive real root.

$$\left\{\left\{M_1^* = \frac{\sqrt[3]{-2b_1^3+9b_0b_2b_1-27b_0^2b_3+\sqrt{4\left(3b_0b_2-b_1^2\right)^3+\left(-2b_1^3+9b_0b_2b_1-27b_0^2b_3\right)^2}}}{3\sqrt[3]{2}b_0}\right\}\right\}$$

$$-\left\{\left\{\frac{b_1}{3b_0}-\frac{\sqrt[3]{2}\left(3b_0b_2-b_1^2\right)}{3b_0\sqrt[3]{-2b_1^3+9b_0b_2b_1-27b_0^2b_3+\sqrt{4\left(3b_0b_2-b_1^2\right)^3+\left(-2b_1^3+9b_0b_2b_1-27b_0^2b_3\right)^2}}}\right\}\right\}$$

However, M_2^* and M_3^* are complex roots and not admissible.

Also, we have different types of dead equilibrium points that emerges.

Type 1-dead equilibrium points:

$$P_{d1} = (N_0^*, T_0^*, M^*, E^*) = \left(0, 0, \frac{s\beta(g\mu_4+\epsilon)}{\mu_3(g\mu_4+\epsilon)+\lambda_3\epsilon(1-k)}, \frac{\epsilon}{\mu_4}\right)$$

The presence of Type 1-dead equilibrium is as a results of both tumor cells and normal cells population being dead. This maybe due to breast tissue removal through death or mastectomy surgery.

Type 2-dead equilibrium points happen when normal cells are overpowered by tumor cells at different time, is the situation that results in the lost of normal cells. However, this assumption means that the population of normal cells can no longer be recovered due to the damage or death caused by tumor cells.

$$P_{d2} = (N_0^*, T_1^*, M_1^*, E^*) = \left(0, \frac{\alpha_2 d - \mu_5 - \gamma_2 M_1^*}{\mu_2}, M_1^*, \frac{\epsilon}{\mu_4}\right)$$

And, the following are the co-existing equilibrium point:

$$\xi_1^* = (N_1^*, T_1^*, M_1^*, E^*) = \left(\frac{\alpha_1\mu_4 - \phi_1\mu_4 T_1^* - (1-k)\lambda_1\epsilon}{\mu_1\mu_4}, \frac{\alpha_2 d - \mu_5 - \gamma_2 M_1^*}{\mu_2}, M_1^*, \frac{\epsilon}{\mu_4}\right)$$

Co-existing equilibrium points occur when the population of all the cells survive in the competition for the nutrients, thereby resulting in progression of all cells population.

3.4 The invasion reproduction number

Invasion reproduction number, R_i, was adopted to represents average number of secondary cases caused by a typical invaded cells over an invasion period in a completely normal cells population. Invasion reproduction number helps in determining whether or not a disease (cancer) will spread through a population (normal cells).

3.4.1 Analysis of invasion reproduction number

The breast cancer model (3.1.5) has a TFE, which determined through the modification of the right-hand sides of the model's equations to zero:

$$P_0 = (N_1^*, T_0^*, M^*, E^*) = \left(\frac{\alpha_1\mu_4 - (1-k)\lambda_1\epsilon}{\mu_1\mu_4}, 0, \frac{s\beta(g\mu_4 + \epsilon)}{\mu_3(g\mu_4 + \epsilon) + \lambda_3\epsilon(1-k)}, \frac{\epsilon}{\mu_4}\right)$$

The linear stability of P_0 can be established using the next generation operator of the system (3.1.5). We take T as our infected compartment, then using the notation in [132],

the Jacobian matrices F and V for the new tumor cell invasion terms and the remaining transfer terms are respectively given by,

$$F = \begin{pmatrix} \phi_1 N^* & 0 \\ 0 & 0 \end{pmatrix}$$

and

$$V = \begin{pmatrix} \gamma_2 M^* + \mu_2 - \alpha_2 d & 0 \\ \frac{\gamma_3 M^* \omega - \rho M^*}{\rho} & \frac{\mu_3(g+E^*)+(1-k)\lambda_3 E^*}{g+E^*} \end{pmatrix}$$

where

$$N^* = \frac{\alpha_1\mu_4 - (1-k)\lambda_1\epsilon}{\mu_1\mu_4}, \quad M^* = \frac{s\beta(g\mu_4+\epsilon)}{\mu_3(g\mu_4+\epsilon)+\lambda_3\epsilon(1-k)}, \quad E^* = \frac{\epsilon}{\mu_4}$$

It follows that the invasion reproduction number of the breast cancer system (3.1.5), denoted by R_i, is given by $R_i = \rho(FV^{-1})$,and according to Theorem 2 in [132], the following result is established. The dominant eigenvalue is thus the invasion reproduction number for breast cancer denoted by R_i:

$$R_i = \frac{(\phi_1\alpha_1\mu_3 - \phi_1\lambda_1\epsilon(1-k))(\mu_3(g\mu_4+\epsilon)+\lambda_3\epsilon(1-k))}{\mu_1\mu_4(\gamma_2 s\beta(g\mu_4+\epsilon)+(\mu_2-\alpha_2 d)(\mu_3(g\mu_4+\epsilon)+\lambda_3\epsilon(1-k)))} \tag{3.4.11}$$

3.4.2 Local stability of equilibrium points

The tumor-free equilibrium of the model (3.1.5) exists and is given by

$$P_0 = (N_1^*, T_0^*, M^*, E^*) = \left(\frac{\alpha_1\mu_4 - (1-k)\lambda_1\epsilon}{\mu_1\mu_4}, 0, \frac{s\beta(g\mu_4+\epsilon)}{\mu_3(g\mu_4+\epsilon)+\lambda_3\epsilon(1-k)}, \frac{\epsilon}{\mu_4}\right)$$

We can consider a point as tumor-free equilibrium when only tumor cells has died-off as a result of administration of anti-cancer drug (Tamoxifene), ketogenic diet and immune

booster. It is reasonable to set $k = 1$ since there no tumor in the body system. We assumed that the anti-cancer drug is very effective at Treatment Tumor-Free Equilibrium (TTFE). Therefore, we have *treatment induced invasion reproduction number* R_i^*

$$P_0^* = (N_1^*, T_0^*, M^*, E^*) = \left(\frac{\alpha_1}{\mu_1}, 0, \frac{s\beta}{\mu_3}, \frac{\epsilon}{\mu_4}\right)$$

and,

$$R_i^* = \frac{\phi_1 \alpha_1 \mu_3}{\mu_1 \left(\gamma_2 s\beta + \mu_3(\mu_5 - \alpha_2 d)\right)}, \quad at \quad k = 1$$

In this section, we mainly analysed the stability behaviours of system (3.1.5) by means of eigenvalues. We apply the Hartman Grobman Theorem which states that in the neighbourhood of a hyperbolic equilibrium point, a nonlinear dynamical system is topologically equivalent to its linearisation [109].

Theorem 3.4.1. : *The treatment tumor-free equilibrium point of the breast cancer model (3.1.5), given by P_0, is locally asymptotically stable (LAS) if $R_i^* < 1$ otherwise unstable.*

Proof: Linearising system (3.1.5) around Treatment Tumor-free equilibrium (TTFE) P_0^*, we obtained the following Jacobian matrix $J(P_0^*)$.

$$J(P_0^*) = \begin{pmatrix} \alpha_1 - 2\mu_1 N^* & -\phi_1 N^* & 0 & 0 \\ 0 & (\alpha_2 d - \gamma_2 M^* - \mu_5 + \phi_1 N^* & 0 & 0 \\ 0 & \frac{\rho M^*}{\omega} - \gamma_3 M^* & -\mu_3 & 0 \\ 0 & 0 & 0 & -\mu_4 \end{pmatrix}$$

$$J(P_0^*) = \begin{pmatrix} \psi_0 & \psi_1 & 0 & 0 \\ 0 & \psi_2 & 0 & 0 \\ 0 & \psi_3 & -\mu_3 & 0 \\ 0 & 0 & 0 & -\mu_4 \end{pmatrix}$$

$$|J(P_0^*)| = \begin{vmatrix} \psi_0 - \delta & \psi_1 & 0 & 0 \\ 0 & \psi_2 - \delta & 0 & 0 \\ 0 & \psi_3 & -\mu_3 - \delta & 0 \\ 0 & 0 & 0 & -\mu_4 - \delta \end{vmatrix} = 0$$

Then the characteristic equation at P_0^* of the linearised system of the model (3.1.5) is given below.

Obviously , there exists two negative characteristic roots

$\delta_1 = -\mu_4, \quad \delta_2 = -\mu_3$

However, we only need to consider

$$\delta^2 - (\psi_0 + \psi_2)\delta + \psi_0\psi_2 = 0$$

But, $\psi_0 = -\alpha_1$ and

$$\psi_2 = \frac{\mu_1[\alpha_2\mu_3 d - (\gamma_2 s\beta + \mu_3\mu_5)] + \phi_1\alpha_1\mu_3}{\mu_1\mu_3}$$

$$\psi_2 = \frac{\mu_1[\mu_3(\alpha_2 d - \mu_5) - \gamma_2 s\beta] + \phi_1\alpha_1\mu_3)]}{\mu_1\mu_3}$$

$$= \mu_1 \left(\frac{\mu_3(\alpha_2 d - \mu_5) - \gamma_2 s\beta}{\mu_1\mu_3} \right) \left[1 + \frac{\phi_1\alpha_1\mu_3}{\mu_1[\mu_3(\alpha_2 d - \mu_5) - \gamma_2 s\beta]} \right]$$

$$= - \left(\frac{\gamma_2 s\beta + \mu_3(\alpha_2 d - \mu_5)}{\mu_3} \right) \left[1 - \frac{\phi_1\alpha_1\mu_3}{\mu_1[\mu_3(\alpha_2 d - \mu_5) - \gamma_2 s\beta]} \right]$$

$$\psi_2 = -\left(\frac{\gamma_2 s\beta + \mu_3(\alpha_2 d - \mu_5)}{\mu_3}\right)(1 - R_i^*)$$

where

$$R_i^* = \frac{\phi_1\alpha_1\mu_3}{\mu_1\left(\gamma_2 s\beta + \mu_3(\mu_5 - \alpha_2 d)\right)}, \quad at \quad k = 1$$

Since all the eigenvalues are negative i.e. $\delta_3 < 0$ and $\delta_4 < 0$. The Treatment Tumor-free equilibrium (TTFE) point of system (3.1.5) is locally asymptotically stable (LAS) if $R_i^* < 1$ otherwise unstable.

The treatment induced invasion reproduction number (R_i^*) measures the average number of new invasion generated by a single tumor cell in an entirely normal cell population. Theorem 3.4.1 thus implies that tumor cells can be eliminated from the population of normal cells if the invasion rate by invaded cell individual is small enough so that ($R_i < 1$).

Theorem 3.4.2. : *The type 1-dead equilibrium point P_{d1} of the system (3.1.5) is locally asymptotically stable if $\frac{(1-k)\lambda_1\epsilon\mu_4}{\alpha_1} > 1$ and $\frac{\alpha_2 dQ_3 - \mu_5 Q_3}{\gamma_2 s\beta(g\mu_4+\epsilon)} < 1$, otherwise unstable.*

Proof: We consider the case of the absence of normal and tumor cells (*i.e* $N_0^* = T_0^* = 0$) for the system (3.1.5), and then obtain a type 1 dead-equilibrium points.

$$P_{d1} = (N_0^*, T_0^*, M^*, E^*) = \left(0, 0, \frac{s\beta(g\mu_4 + \epsilon)}{\mu_3(g\mu_4 + \epsilon) + \lambda_3\epsilon(1-k)}, \frac{\epsilon}{\mu_4}\right) \tag{3.4.12}$$

At type 1 dead-equilibrium P_{d1}, the Jacobian matrix becomes

$$J(P_{d1}) = \begin{pmatrix} \alpha_1 - (1-k)\lambda_1 E^* & 0 & 0 & 0 \\ 0 & (\alpha_2 d - \gamma_2 M^* - \mu_5) & 0 & 0 \\ 0 & \frac{\rho M^* - \gamma_3 M^*\omega}{\omega} & -\left(\mu_3 + \frac{(1-k)\lambda_3 E^*}{g+E^*}\right) & \frac{-g\lambda_3 M^*(1-k)}{(g+E^*)^2} \\ 0 & 0 & 0 & -\mu_4 \end{pmatrix}$$

$$|J(P_{d1})| = \begin{vmatrix} B_0 - \delta & 0 & 0 & 0 \\ 0 & B_1 - \delta & 0 & 0 \\ 0 & B_2 & -B_3 - \delta & -B_4 \\ 0 & 0 & 0 & -\mu_4 - \delta \end{vmatrix} = 0$$

Obviously, $\delta_1 = \mu_4 < 0 \quad \& \quad \delta_2 = -B_3 < 0$ The remaining eigenvalues is given by $\delta_3 = B_0 < 0$ if,

$$\frac{(1-k)\lambda_1 \epsilon \mu_4}{\alpha_1} > 1, \quad k < 1$$

Also,

$\delta_4 = B_1 < 0$ provided that

$$\frac{Q_3(\alpha_2 d - \mu_5)}{\gamma_2 s \beta (g\mu_4 + \epsilon)} < 1, \quad \alpha_2 d < \mu_5, \text{ or } \alpha_2 < \frac{\mu_5}{d}$$

where

$Q_3 = (\mu_3(\mu_4 + \epsilon) + \lambda_3 \epsilon(1-k))$

Therefore, the type 1 -dead equilibrium point P_{d1} of the system (3.1.5) is locally asymptotically stable if δ_3 and δ_4 holds otherwise unstable.

Biologically, this implies that the net growth of tumor cells must be more than the value of immune cells in order to have the tumor cells overpower the normal cells. However, no fixed tissue is present and this can be as a result of whole breast tissue removal due to mastectomy or death.

Theorem 3.4.3. *The type 2-dead equilibrium point P_{d2} of the system (3.1.5) is locally asymptotically stable provided that following conditions holds:*

$$\left(\frac{\phi_1 \mu_4 \alpha_2 d + (1-k)\lambda_1 \mu_1 \epsilon}{\alpha_1 \mu_1 \mu_4 + \phi_1 \mu_4 \mu_5 + \phi_1 \mu_4 \gamma_2 M_1^*} \right) > 1, \quad \eta_0 < 0$$

$$\left(\frac{\rho M_1^* \omega}{\gamma_3 M_1^* G^*} \right) < 1, \eta_2 < 0$$

$$\left(\frac{\alpha_2 d\mu_1 + 2\mu_2\mu_5 + 2\mu_2\gamma_2 M_1^*}{2\mu_2\alpha_2 d + \gamma_2 M_1^*\mu_1 + \mu_1\mu_5}\right) < 1, \eta_1 < 0$$

$$\left(\frac{\gamma_2^2 M_1^* + \mu_5\gamma_2}{\gamma_2\alpha_2 d}\right) < 1, \eta_3 < 0$$

$$\left(\frac{\rho\mu_4 A_2}{A_1 + A_2\mu_3 + A_3}\right) < 1, \eta_4 < 0$$

otherwise unstable.

Proof: We linearised system (3.1.5) around the type 2-dead free equilibrium points and, the following Jacobian matrix $J(P_{d2})$ was obtained:

$$P_{d2} = (N_0^*, T_1^*, M_1^*, E^*) = \left(0, \frac{\alpha_2 d - \mu_5 - \gamma_2 M_1^*}{\mu_2}, M_1^*, \frac{\epsilon}{\mu_4}\right) \tag{3.4.13}$$

$$J(P_{d2}) = \begin{pmatrix} (\alpha_1 - \phi_1 T^* - (1-k)\lambda_1 E^*) & 0 & 0 & 0 \\ 0 & (\alpha_2 d - 2\mu_2 T^* - \gamma_2 M_1^* - \mu_5) & -\mu_2 T^* & 0 \\ 0 & \frac{\rho M_1^*\omega}{(\omega+T^*)^2} - \gamma_3 M_1^* & \eta_4 & \frac{-g\lambda_3 M_1^*(1-k)}{(g+E^*)^2} \\ 0 & 0 & 0 & -\mu_4 \end{pmatrix}$$

$$|J(P_{d2})| = \begin{vmatrix} \eta_0 - \delta & 0 & 0 & 0 \\ 0 & \eta_1 - \delta & \eta_3 & 0 \\ 0 & \eta_2 & \eta_4 - \delta & -\eta_5 \\ 0 & 0 & 0 & -\mu_4 - \delta \end{vmatrix} = 0$$

Obviously, $\delta_1 = \mu_4 < 0 \quad \& \quad \delta_2 = \eta_0 < 0$ even though a simple calculation can be used to analyse the remainder as follows:

$$\delta^2 - (\eta_1 + \eta_4)\delta + \eta_1\eta_4 - \eta_2\eta_3 = 0 \tag{3.4.14}$$

The eigenvalues are all real and negative (by Descartes' of positive solutions) if $(\eta_1 + \eta_4) < 0 \quad \text{and} \quad (\eta_1\eta_4 - \eta_2\eta_3) > 0$, that is

$\eta_1 < -\eta_4 \quad \text{and} \quad \eta_1\eta_4 > \eta_2\eta_3$

The remaining eigenvalues are all real and negative if the following conditions holds:

$$\left(\frac{\phi_1\mu_4\alpha_2 d + (1-k)\lambda_1\mu_1\epsilon}{\alpha_1\mu_1\mu_4 + \phi_1\mu_4\mu_5 + \phi_1\mu_4\gamma_2 M_1^*}\right) > 1, \eta_0 < 0 \quad \delta_2 < 0$$

$$\left(\frac{\rho M_1^*\omega}{\gamma_3 M_1^* G^*}\right) < 1, \eta_2 < 0$$

$$\left(\frac{\alpha_2 d\mu_1 + 2\mu_2\mu_5 + 2\mu_2\gamma_2 M_1^*}{2\mu_2\alpha_2 d + \gamma_2 M_1^*\mu_1 + \mu_1\mu_5}\right) < 1 \quad then, \quad \eta_1 < 0, \quad \delta_3 < 0,$$

$$\left(\frac{\rho\mu_4 A_2}{A_1 + A_2\mu_3 + A_3}\right) < 1, \quad then \quad \eta_4 < 0, \quad \delta_4 < 0$$

$$\left(\frac{\gamma_2^2 M_1^* + \mu_5\gamma_2}{\gamma_2\alpha_2 d}\right) < 1, \eta_3 < 0$$

where; $A_1 = \gamma_3\left(\omega\mu_2 + (\alpha_2 d - \mu_5 - \gamma_2 M_1^*)^2\right), \quad A_2 = (g\mu_4 + \epsilon)\left(\omega\mu_2 + \alpha_2 d - \mu_5 - \gamma_2 M_1^*\right)$

$A_3 = (1-k)\lambda_3\epsilon\mu_2\left(\omega\mu_2 + \alpha_2 d - \mu_5 - \gamma_2 M_1^*\right)$

$G^* = \omega^2\mu_2^2 + \alpha_2^2 d_2^2 + \mu_5^2 + \gamma_2^2(M_1^*)^2 + 2\omega\mu_2\alpha_2 d + 2\gamma_2 M_1^*\mu_5 - 2\omega\mu_2\mu_5 - 2\omega\mu_2\gamma_2 M_1^* - 2\alpha_2 d\gamma_2 M_1^*$

Biologically, for our solutions of system (3.1.5) around the type 2-dead equilibrium to be real and non-negative the above conditions must holds. This implies that the difference in the rates of immune response initiation and reduction should be greater than the rate at which they are lost. However, this explains that P_{d2} only occurs when there is no immune response which is rare. It is therefore uncommon to reach such an equilibrium point except when the patient is dead.

3.4.3 Co-existing equilibrium point

Theorem 3.4.4. *The co-existing equilibrium point ξ_e^* of system (3.1.5) is stable if the following Routh-Hurwitz criteria are satisfied:*

i $Trace(A) = (\varphi_0 + \varphi_3 + \varphi_6 - \mu_4) < 0$

ii $Det(A) = (-\mu_4 (\varphi_0\varphi_6\varphi_3 + \varphi_0\varphi_4\varphi_5 + \varphi_1\varphi_2\varphi_6)) > 0$

otherwise unstable.

Proof : We analysed and linearised system (3.1.5) around the co-existing equilibrium point ξ_e^* , we obtained the following Jacobian matrix $J(\xi_e^*)$ at $\xi_e^* = (N_4^*, T_4^*, M_4^*, E_4^*)$
A co-existing equilibrium state exists when all cells population would have survived the competition, where N_4^*, T_4^*, M_4^* & E_4^* respectively represent coexisting equilibrium values for normal cells, tumor cells, immune cells and estrogen levels.

$$N_4^* = \frac{2(1-k)^4\lambda_1^4\mu_1\mu_4\epsilon^2 + \phi_1\alpha_1^2\mu_4^2\mu_1 - 2(1-k)^2\mu_1\mu_4^2\alpha_1\lambda_1\phi_1\epsilon - 2\alpha_1\phi_1^2\mu_1\mu_4^3 - 2(1-k)^2\alpha_1\mu_1\mu_4^2\lambda_1\epsilon}{2\phi_1\alpha_1\mu_1^2\mu_4^3 - 2(1-k)^2\mu_1^2\mu_4^2\lambda_1\phi_1\epsilon}$$

$$T_4^* = \frac{\alpha_1^2\mu_1\mu_4^2 + 2\alpha_1\mu_1\mu_4^2\phi_1}{2\phi_1\alpha_1\mu_1\mu_4^2 - 2(1-k)^2\mu_1\mu_4\lambda_1\phi_1\epsilon}$$

$$M_4^* = \frac{G^{*^2}Z^*(1-k)^2\lambda_1\epsilon + (\alpha_1^2\alpha_2\mu_1\mu_4^3 d + 2\alpha_1\alpha_2\mu_1\mu_4^3\phi_1 d - \mu_4^3\mu_5\alpha_1^2 - 2\mu_4^3\mu_1\mu_5\alpha_1\phi_1)G^{*^2} - \mu_3\alpha_1^4\mu_1^2\mu_4^5 - 4\alpha_1^2\mu_1^2\mu_2\mu_4^5\phi_1 - 4\phi_1^2\alpha_1^2\mu_1^2\mu_4^5\mu_2}{G^{*^2}Q^*\mu_4}$$

$$E_4^* = \frac{\epsilon}{\mu_4}$$

Where;

$$G^{*^2} = 2\phi_1\alpha_1\mu_1\mu_4^2 - 2(1-k)^2\mu_1\mu_4\lambda_1\phi_1\epsilon$$

$$Z^* = \frac{2(1-k)^4\lambda_1^2\mu_1\mu_4\epsilon^2 + \phi_1\alpha_1^2\mu_4^2\mu_1 - 2(1-k)^2\mu_1\mu_4^2\alpha_1\lambda_1\phi_1\epsilon - 2\alpha_1\phi_1^2\mu_1\mu_4^3 - 2(1-k)^2\alpha_1\mu_1\mu_4^2\lambda_1\epsilon}{2\phi_1\alpha_1\mu_1^2\mu_4^3 - 2(1-k)^2\mu_1^2\mu_4^2\lambda_1\phi_1\epsilon}$$

$$Q^* = \frac{\alpha_1^2\mu_1\mu_4^2\gamma_2 - 2\alpha_1\mu_1\mu_4^2\phi_1\gamma_2}{2\phi_1\alpha_1\mu_1\mu_4^2 - 2(1-k)^2\mu_1\mu_4\lambda_1\phi_1\epsilon}$$

$$J = \begin{pmatrix} (\alpha_1 - 2\mu_1 N_4^* - (1-k)\lambda_1 E_4^*) & -N_4^*\phi_1 & 0 & -V_7 \\ (1-k)\lambda_1 E_4^* & (d\alpha_2 - 2\mu_2 T_4^* - \gamma_2 M_4^* - \mu_5) & -\gamma_2 T_4^* & \varphi_7 \\ 0 & \varphi_4 & \varphi_6 & \frac{\lambda_3 g M_4^*(1-k)}{(g+E_4^*)^2} \\ 0 & 0 & 0 & -\mu_4 \end{pmatrix}$$

$$A = \begin{pmatrix} \varphi_0 & -\varphi_2 & 0 & -\varphi_7 \\ \varphi_1 & \varphi_3 & -\varphi_5 & \varphi_7 \\ 0 & \varphi_4 & \varphi_6 & \varphi_8 \\ 0 & 0 & 0 & -\mu_4 \end{pmatrix}$$

$$|A| = \begin{vmatrix} \varphi_0 & -\varphi_2 & 0 & -\varphi_7 \\ \varphi_1 & \varphi_3 & -\varphi_5 & \varphi_7 \\ 0 & \varphi_4 & \varphi_6 & \varphi_8 \\ 0 & 0 & 0 & -\mu_4 \end{vmatrix} = 0$$

We need to show that $Trace(A) < 0$; that is

$$Tr(A) = (\varphi_0 + \varphi_3 + \varphi_6 - \mu_4) < 0$$

$$= \alpha_1(1 - A_0) - 2\mu_1 N_4^* + d\alpha_2(1 - \mu_5) - \mu_4 + \frac{T_4^* \left(\rho - \gamma_3(\omega - T_4^*)\right)}{\omega + T_4^*} - \mu_3 - \frac{(1-k)^4 \lambda_3 \epsilon}{(g\mu_4 + (1-k)\epsilon}$$

Thus,

$Tr(A) < 0, \quad$ if $A_0 > 1, \ \mu_5 > 1, \ \rho < \gamma_3(\omega - T_4^*)$ with $\quad A_0 = \frac{(1-k)^2 \lambda_3 \epsilon}{\alpha_1 \mu_4}, \quad N_4^* > 0$

To show that,

$$|A| = (-\mu_4 \left(\varphi_0 \varphi_3 \varphi_6 + \varphi_0 \varphi_4 \varphi_5 + \varphi_1 \varphi_2 \varphi_6\right)) > 0$$

Let $\ \zeta_1 = -\mu_4 \varphi_0 \varphi_3 \varphi_6, \ \zeta_2 = -\mu_4 \varphi_0 \varphi_4 \varphi_5, \ \zeta_3 = -\mu_4 \varphi_1 \varphi_2 \varphi_6$

$$\zeta_1 = \left(\alpha_1(1 - A_0) - 2\mu_1 N_4^*\right) \left(d\alpha_2(1 - \mu_5) - 2\mu_2 T_4^* - \gamma_2 \mu_4^*\right)) \Omega^*$$

where; $\Omega^* = \left(\frac{T_4^* \left(\rho - \gamma_3(\omega - T_4^*)\right)}{\omega + T_4^*} - \mu_3 - \frac{(1-k)^4 \lambda_3 \epsilon}{(g\mu_4 + (1-k)\epsilon} \right)$

this implies that, $\quad \zeta_1 > 0 \quad$ is a positive, if $A_0 > 1, \quad \mu_5 > 1, \quad \rho < \gamma_3(\omega - T_4^*)$ with $\quad A_0 = \frac{(1-k)^2 \lambda_3 \epsilon}{\alpha_1 \mu_4}$, $N_4^* > 0$

$$\zeta_2 = \left(\alpha_1(1 - A_0) - 2\mu_1 N_4^*\right) \left(\frac{M_4^*}{(\omega + T_4^*)^2} (\rho\omega - \gamma_3(\omega - T_4^*)) \right) (-\gamma_2 T_4^*)$$

Implies that, $\zeta_2 > 0$ is a positive , if $A_0 > 1$, $\mu_5 > 1$, $\rho\omega < \gamma_3(\omega - T_4^*)^2$, with $A_0 = \frac{(1-k)^2\lambda_3\epsilon}{\alpha_1\mu_4}$

$$\zeta_3 = -\mu_4(A_0)(-\phi_1 N_4^*)\left(\frac{T_4^*\left(\rho - \gamma_3(\omega - T_4^*)\right)}{\omega - T_4^*} - \mu_3 - \frac{(1-k)^4\lambda_3\epsilon}{(g\mu_4 + (1-k)\epsilon}\right)$$

This implies that $\zeta_3 < 0$ is negative and by Routh-Hurwitz's criteria, the system cannot be stable. The co-existing equilibrium point is always unstable with coexisting cells. Biologically, all cell populations survive in the competition for nutrients, resulting in the progression of all cell population where

$$\varphi_0 = \frac{\alpha_1\mu_4 - 2\mu_1\mu_4 N_4^* - (1-k)^2\lambda_1\epsilon}{\mu_4}, \quad \varphi_1 = \frac{(1-k)^2\lambda_1\epsilon}{\mu_4}, \quad \varphi_2 = -\phi_1 N_4^*,$$

$$\varphi_3 = \left(d\alpha_2 - 2\mu_2 T_4^* - \gamma_2 M_4^* - \mu_5\right), \quad \varphi_4 = \frac{\rho M_4^*\omega - \gamma_3 M_4^*(\omega - T_4^*)^2}{(\omega - T_4^*)^2}, \quad \varphi_5 = -\gamma_2 T_4^*$$

$$\varphi_6 = \frac{\rho T_4^*(g\mu_4+(1-k)\epsilon) - \gamma_3 T_4^*(\omega - T_4^*)(g\mu_4+(1-k)\epsilon) - \mu_3(\omega - T_4^*)(g\mu_4+(1-k)\epsilon) - (1-k)^2(\omega - T_4^*)\lambda_3\epsilon}{(\omega - T_4^*)(g\mu_4+(1-k)\epsilon)}$$

$$-\varphi_7 = -(1-k)\lambda_1 N_4^*, \quad \varphi_7 = (1-k)\lambda_1 N_4^*, \quad \varphi_8 = \frac{\lambda_3\mu_4^2 g M_4^*(1-k)}{(g\mu_4 + (1-k)\epsilon)^2}$$

3.4.4 Global stability analysis: for special case

Here, we explore the global asymptotic stability of the treatment tumor-free equilibrium (TTFE) for special case when $R_i^* \mid_{k=1} \leq 1$ with assumption that anti-cancer drug is very effective with the help of ketogenic diet as adjuvant therapy for the clearance of the tumor cells from the body system. However, it was established in [72] that, no global stability will exist whenever there is multiple steady states of equilibria point.

Theorem 3.4.5.

The treatment tumor-free equilibrium (TTFE), P_0^* of the breast cancer model (3.1.5) is globally asymptotically stable whenever the treatment invasion reproduction number $R_i^* \mid_{k=1} \leq 1$ otherwise unstable.

Proof: We consider the suitable combination of quadratic and linear Lyapunov functions [93,100] of the form:

$$L : \left\{(N, T, M, E) \in \Re_+^4 : N, T, M, E > 0\right\} \to \Re \;\; defined\ by$$

$$L = \frac{(N - N^*)^2}{2N^*} + T \tag{3.4.15}$$

The time derivative of the Lyapunov function (3.4.16) along with the solution of the breast cancer model (3.1.5) is given by

$$L = \left(\frac{N - N^*}{N^*}\right)\frac{dN}{dt} + \frac{dT}{dt}$$

$$L = \frac{N}{N^*}\left(1 - \frac{N^*}{N}\right)\frac{dN}{dt} + \frac{dT}{dt} \tag{3.4.16}$$

put $\frac{dN}{dt}$ and $\frac{dT}{dt}$ of model (3.1.5) into equation (3.4.17), we have

$$L' = \frac{N}{N^*}\left(1 - \frac{N^*}{N}\right)\left[N\alpha_1 - \mu_1 N^2 - \phi_1 NT - (1-k)\lambda_1 NE\right]$$

$$+ \left[T\alpha_2 d - \mu_2 T^2 - \gamma_2 MT - \mu_5 T + \phi_1 NT + (1-k)\left(\lambda_1 NE\right)\right]$$

Further expansion gives

$$L' = \frac{N}{N^*}\left[\left(1 - \frac{N^*}{N}\right)\left(N\alpha_1 - \mu_1 N^2\right) - \left(\phi_1 NT + (1-k)\lambda_1 NE\right) + \phi_1 N^* T + (1-k)\lambda_1 N^* E\right]$$

$$+ \left[T\alpha_2 d - \mu_2 T^2 - \gamma_2 MT - \mu_5 T + \phi_1 NT + (1-k)\left(\lambda_1 NE\right)\right]$$

$$L' = \frac{N}{N^*}\left[\mu_1\left(N - N^*\right)\left(\frac{\alpha_1}{\mu_1 - N}\right)\left(N\alpha_1 - \mu_1 N^2\right) - \left(\phi_1 NT + (1-k)\lambda_1 NE\right)\right]$$

$$+ \left(\phi_1 N^* T + (1-k)\lambda_1 N^* E\right) + \left[T\alpha_2 d - \mu_2 T^2 - \gamma_2 MT - \mu_5 T + \phi_1 NT + (1-k)\left(\lambda_1 NE\right)\right] \tag{3.4.17}$$

Since

$$N \leq \frac{\alpha_1}{\mu_1},\ it\ follows\ \ that\ \ N \leq N^*,\ where\ \ N^* \leq \frac{\alpha_1}{\mu_1}\ \ at\ \ k = 1$$

Consequently,

$$\frac{N}{N^*} \leq 1\ \ and\ \ M \leq M^*\ \ (boundedness\ \ of\ \ solution)$$

Similarly,

$$M^* = \frac{s\beta}{\mu_3}, \quad at \quad k = 1$$

Hence, equation (3.4.18) becomes:

$$L' \leq \mu_1 (N - N^*)(N^* - N) - \phi_1 NT + \phi_1 N^* T + \alpha_2 dT - \mu_2 T^2 - \gamma_2 M^* T - \mu_5 T + \phi_1 NT$$

$$= -\mu_1 (N - N^*)^2 - (\gamma_2 M^* + \mu_5 - \phi_1 N^* - \alpha_2 d) T - \mu_2 T^2$$

$$L' = -\mu_1 (N - N^*)^2 - \left(\gamma_2 \frac{s\beta}{\mu_3} + \mu_5 - \phi_1 \frac{\alpha_1}{\mu_1} - \alpha_2 d\right) T - \mu_2 T^2$$

$$L' = -\mu_1 (N - N^*)^2 - \left(\frac{\gamma_2 s\beta + \mu_3\mu_5 - \alpha_2 d\mu_3}{\mu_3} - \frac{\phi_1\alpha_1}{\mu_1}\right) T - \mu_2 T^2$$

$$L' = -\mu_1 (N - N^*)^2 - \left(\frac{\gamma_2 s\beta + \mu_3\mu_5 - \alpha_2 d\mu_3}{\mu_3}\right) \left(1 - \frac{\phi_1\alpha_1\mu_3}{\mu_1 (\gamma_2 s\beta + \mu_3(\mu_5 - \alpha_2 d))}\right) T - \mu_2 T^2$$

$$L' = -\mu_1 (N - N^*)^2 - \left(\frac{\gamma_2 s\beta + \mu_3\mu_5 - \alpha_2 d\mu_3}{\mu_3}\right) (1 - R_i^*) T - \mu_2 T^2 \tag{3.4.18}$$

where;

$$R_i^* = \frac{\phi_1\alpha_1\mu_3}{\mu_1 (\gamma_2 s\beta + \mu_3(\mu_5 - \alpha_2 d))}, \quad at \quad k = 1$$

Therefore, from (3.4.18), $L' \leq 1$ whenever $R_i^* \leq 1$ and that $L' = 0$ if and only if $R_i^* = 1$, $N = N^*$ and $T = 0$ if and only if $N = N^*$ and $T = 0$. It follows that the largest invariant set in $\{(N, T, M, E) : L' = 0\}$ is the treatment tumor-free equilibrium P_0^*. This means that P_0^* is globally asymptotically stable by Lasalle's Invariant Principle [72]. However, if the above condition did not hold for global stability of the TTFE, it may give rise to the phenomenon called bifurcation.

3.5 Bifurcation analysis

It is important to investigate the existence of the backward bifurcation phenomena as this can go a long way in determining parameter that could make it difficult to eradicate cancer cells when the invasion reproduction number is less than unity. Some models such as cancer models are known to exhibit the phenomenon of backward bifurcation, where the stable tumor-free equilibrium co-exists with a stable endemic equilibrium with the epidemiological requirement of having the invasion reproduction number less than unity being established. This phenomenon has been established in a number of epidemiological settings (Van Driessche and Watmough [132] and Garba *et al.,* [45]). In a backward bifurcation setting, disease control is only feasible if R_i is reduced to values below another sub-threshold less than unity. The implication of this phenomenon on public health is that the requirement of having the reproduction number less than unity, although necessary, is no longer sufficient for cancer control.

To demonstrate the possibility of the co-existence of the equilibria of the model (3.1.5) at $R_i < 1$ but near $R_i = 1$, the *Center Manifold Theory* is described by Castillo-Chavez and Song [25].

Theorem 3.5.1. *Castillo-Chavez and Song [25] consider the following general system of ordinary differential equations with a parameter* ϕ

$$\frac{dx}{dt} = f(x, \phi), \tag{3.5.19}$$

Where $f : \Re^n \times \Re \to \Re^n$ is C^2 with $f(0, \phi) = 0$ for all ϕ and satisfying the following:

1. The Jacobian matrix has $D_x f(0, 0)$ zero simple eigenvalue and the other eigenvalues have negative real parts;

2. $D_x f(0,0)$ has a nonnegative right eigenvector w and a left eigenvector v corresponding to the zero eigenvalue.

Let f_k be the k^{th} component of f and

$$a = \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0)$$

$$b = \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0).$$

The local dynamics of system (3.5.19) around 0, are totally determined by a and b. More precisely, we have following cases

1. If $a > 0$, and $b > 0$, then

   i. When $\phi < 0$ with $|\phi| \ll 1$, 0 is locally asymptotically stable and there exists a positive unstable equilibrium

   ii. When $0 < \phi \ll 1$, 0 is unstable and there exists a negative and locally asymptotically stable equilibrium.

2. If $a < 0$, and $b < 0$, then

   i. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable;

   ii. When $0 < \phi \ll 1$, 0 is locally asymptotically stable and there exists a positive unstable equilibrium.

3. If $a > 0$, and $b < 0$, then

   i. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable, and there exists a locally asymptotically stable negative equilibrium.

   ii. When $0 < \phi \ll 1$, 0 is stable, and a positive unstable equilibrium appears.

4. If $a < 0$, and $b > 0$, then as ϕ changes from negative to positive, 0, changes from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.

If $a > 0$ and $b > 0$, a backward bifurcation occurs at $\phi = 0$. We use the

Center Manifold theorem by Castillo-Chavez and Song [25], to carry out a bifurcation analysis. First, we consider the tumor progression rate ϕ_1 as a bifurcation parameter so that $R_i = 1$ if and only if

$$\phi_1 = \phi_1^* = \frac{\mu_1\mu_4(\gamma_2 s\beta(g\mu_4 + \epsilon) + (\mu_2 - \alpha_2 d)(\mu_3(\mu_4 + \epsilon) + \lambda_3\epsilon(1-k)))}{\alpha_1\mu_4 - \lambda_1\epsilon(1-k)(\mu_3(\mu_4 + \epsilon) + \lambda_3\epsilon(1-k))}$$

Then we make the following change of variables $N^* = x_1$, $T^* = x_2$, $M^* = x_3$, $E^* = x_4$ Furthermore, by using the vector notation $x = (x_1, x_2, x_3, x_4)^T$ the breast cancer model (3.1.5) can be written in the following form: Let the breast cancer (3.1.5) be written in the vector form

$\frac{dx}{dt} = F(x)$,

where

$x = (x_1, x_2, x_3, x_4)^T$ and $F = (f_1, f_2, f_3, f_4)^T$

Then

$$\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \alpha_1 x_1 - \mu_1 x_1^2 - \phi_1 x_1 x_2 - (1-k)\lambda_1 x_1 x_4 \\
\frac{dx_2}{dt} &= f_2 = \alpha_2 x_2 d - \mu_2 x_2^2 - \gamma_2 x_2 x_3 - \mu_5 x_2 + \phi_1 x_1 x_2 + (1-k)\lambda_1 x_1 x_4 \\
\frac{dx_3}{dt} &= f_3 = s\beta + \frac{\rho x_2 x_3}{w + x_2} - \gamma_3 x_2 x_3 - \mu_3 x_3 \frac{(1-k)\lambda_3 x_3 x_4}{g + x_4} \\
\frac{dx_4}{dt} &= f_4 = \epsilon - \mu_4 x_4
\end{aligned} \tag{3.5.20}$$

If the bifurcation parameter ϕ_1 be chosen so that at $R_i = 1$ in (3.4.12), we obtain

$$\phi_1^* = \frac{\mu_1\mu_4(\gamma_2 s\beta(g\mu_4 + \epsilon) + (\mu_2 - \alpha_2 d)(\mu_3(\mu_4 + \epsilon) + \lambda_3\epsilon(1-k)))}{\alpha_1\mu_4 - \lambda_1\epsilon(1-k)(\mu_3(\mu_4 + \epsilon) + \lambda_3\epsilon(1-k))} \tag{3.5.21}$$

The linearised matrix of the model (3.1.5) around the tumor-free equilibrium with P_0 and evaluated at $\phi_1 = \phi_1^*$ is given by

$$J(\varepsilon_0, \phi_1^*) = \begin{pmatrix} C_0^* & -C_2^* & 0 & -C_6^* \\ C_1^* & C_3^* & 0 & C_7^* \\ 0 & C_4^* & -C_5^* & C_8^* \\ 0 & 0 & 0 & -\mu_4 \end{pmatrix}$$

where

$$C_0^* = \frac{\alpha_1\mu_1\mu_4 - 2\mu_1^2\alpha_1 + 2\mu_1(1-k)\lambda_1\epsilon - (1-k)\lambda_1\mu_1\epsilon}{\mu_1\mu_4}$$

$$C_1^* = \frac{(1-k)\lambda_1\epsilon}{\mu_4}$$

$$C_2^* = \frac{\phi_1(1-k)\lambda_1\epsilon - \phi_1\alpha_1\mu_1}{\mu_1\mu_4}$$

$$C_3^* = \frac{\alpha_2 d\mu_1\mu_4(\mu_3\xi_2^* + \xi^* - \gamma_2(s\beta(g\mu_4+\epsilon))\mu_1\mu_4 - \mu_5\xi_1^* + \xi^*) + \phi_1(\mu_3\xi_2^* + \xi^*)(\alpha_1\mu_1 - \lambda_1\epsilon(1-k))}{\mu_1\mu_4(\mu_3\xi_2^* + \xi^*))}$$

where $\xi^* = \lambda_3\epsilon(1-k))$, $\xi_1^* = \mu_1\mu_4(\mu_3(\mu_4+\epsilon)$, $\xi_2^* = (\mu_4+\epsilon)$

$$C_4^* = \frac{\rho}{\omega}\left(\frac{s\beta(g\mu_4+\epsilon)}{(\mu_3(\mu_4+\epsilon) + \lambda_3\epsilon(1-k))}\right)$$

$$C_5^* = -\left(\frac{\mu_4^2 + (1-k)\lambda_3\epsilon}{g\mu_4+\epsilon}\right)$$

$$C_6^* = -\frac{(1-k)\lambda_1}{\mu_1\mu_4}(\alpha_1\mu_1 - (1-k)\lambda_1\epsilon)$$

$$C_7^* = \frac{(1-k)\lambda_1}{\mu_1\mu_4}(\alpha_1\mu_1 - (1-k)\lambda_1\epsilon)$$

$$C_8^* = \frac{g\mu_4^2\lambda_3}{(g\mu_4+\epsilon)^2}\left(\frac{s\beta(g\mu_4+\epsilon)}{(\mu_3(\mu_4+\epsilon) + \lambda_3\epsilon(1-k))}\right)$$

The Jacobian $J(P_0, \phi_1^*)$ of the linearized system has a simple zero eigenvalues with all other eigenvalues having negative real parts. It can be shown that, the associated left eigenvector, $V_i = (V_1, V_2, V_3, V_4)$, corresponding to the simple zero eigenvalue of $J(P_0, \phi_1^*)$ is obtained as:

$V_3 = 0, \quad V_2 > 0$ (positive constant)

$$V_1 = -\frac{C_1 V_2}{C_0}$$
$$V_4 = \left(\frac{C_6 C_1 + C_0 C_7}{\mu_4 C_0}\right) V_2$$

Furthermore, the associated right eigenvector corresponding to this simple zero eigenvalue denoted by $W_j = (W_1, W_2, W_3, W_4)^T$ so $J(\varepsilon_0, \phi_1^*)W = 0$

Therefore we have $W_4 = 0, \quad W_2 > 0$

$$W_1 = \frac{C_2 W_2}{C_0}$$
$$W_3 = \frac{C_4 W_2}{C_5}$$

Computation of a: It is clear, that all the second-order partial derivatives at P_0 and ϕ_1^* are zero except the following:

$$a = \sum_{i,j=1}^{k} V_k W_i W_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}$$

where $i, j, k = 1, 2, 3, 4$

$$\begin{aligned}
a = {} & V_1 W_1^2 \frac{\partial^2 f_1}{\partial x_1^2} + V_1 W_1 W_2 \frac{\partial^2 f_1}{\partial x_1 \partial x_2} + V_1 W_1 W_3 \frac{\partial^2 f_1}{\partial x_1 \partial x_3} + V_1 W_2 W_1 \frac{\partial^2 f_1}{\partial x_2 \partial x_1} + V_1 W_2^2 \frac{\partial^2 f_1}{\partial x_2^2} + \\
& V_1 W_2 W_3 \frac{\partial^2 f_1}{\partial x_2 \partial x_3} + V_1 W_3 W_1 \frac{\partial^2 f_1}{\partial x_3 \partial x_1} + V_1 W_3 W_2 \frac{\partial^2 f_1}{\partial x_3 \partial x_2} + V_1 W_3^2 \frac{\partial^2 f_1}{\partial x_3^2} + V_2 W_1^2 \frac{\partial^2 f_2}{\partial x_1^2} + \\
& V_2 W_1 W_2 \frac{\partial^2 f_2}{\partial x_1 \partial x_2} + V_2 W_1 W_3 \frac{\partial^2 f_2}{\partial x_1 \partial x_3} + V_2 W_2 W_1 \frac{\partial^2 f_2}{\partial x_2 \partial x_1} + V_2 W_2^2 \frac{\partial^2 f_2}{\partial x_2^2} + V_2 W_2 W_3 \frac{\partial^2 f_2}{\partial x_2 \partial x_3} + \\
& V_2 W_3 W_1 \frac{\partial^2 f_2}{\partial x_3 \partial x_1} + V_2 W_3 W_2 \frac{\partial^2 f_2}{\partial x_3 \partial x_2} + V_2 W_3^2 \frac{\partial^2 f_2}{\partial x_3^2} + V_4 W_1 \frac{\partial^2 f_4}{\partial x_1^2} + V_4 W_1 W_2 \frac{\partial^2 f_4}{\partial x_1 \partial x_2} + \\
& V_4 W_1 W_3 \frac{\partial^2 f_4}{\partial x_1 \partial x_3} + V_4 W_2 W_1 \frac{\partial^2 f_4}{\partial x_2 \partial x_1} + V_4 W_2^2 \frac{\partial^2 f_4}{\partial x_2^2} + V_4 W_2 W_3 \frac{\partial^2 f_4}{\partial x_2 \partial x_3} + V_4 W_3 W_1 \frac{\partial^2 f_4}{\partial x_3 \partial x_1} + \\
& V_4 W_3 W_2 \frac{\partial^2 f_4}{\partial x_3 \partial x_2} + V_4 W_3^2 \frac{\partial^2 f_4}{\partial x_3^2}
\end{aligned} \tag{3.5.22}$$

We can directly compute a at Tumor-free equilibrium, for $i = 1, 2, 3, 4$, and we have

$$\frac{\partial^2 f_1}{\partial x_1 \partial x_3} = \frac{\partial^2 f_1}{\partial x_2^2} = \frac{\partial^2 f_1}{\partial x_2 \partial x_3} = \frac{\partial^2 f_1}{\partial x_3 \partial x_1} = \frac{\partial^2 f_1}{\partial x_3 \partial x_2} = \frac{\partial^2 f_1}{\partial x_3^2} = \frac{\partial^2 f_2}{\partial x_1^2} = \frac{\partial^2 f_2}{\partial x_1 \partial x_2} = \frac{\partial^2 f_2}{\partial x_3 \partial x_1} = \frac{\partial^2 f_2}{\partial x_3^2}$$
$$= \frac{\partial^2 f_4}{\partial x_i^2} = \frac{\partial^2 f_4}{\partial x_1 \partial x_i} = 0$$

while,

$$\frac{\partial^2 f_1}{\partial x_1^2} = -2\mu_1,$$
$$\frac{\partial^2 f_1}{\partial x_1 \partial x_2} = \frac{\partial^2 f_1}{\partial x_2 \partial x_1} = -\phi_1,$$
$$\frac{\partial^2 f_2}{\partial x_1 \partial x_2} = \frac{\partial^2 f_2}{\partial x_2 \partial x_1} = \phi_1,$$
$$\frac{\partial^2 f_2}{\partial x_2^2} = -2\mu_2,$$
$$\frac{\partial^2 f_2}{\partial x_2 \partial x_3} = \frac{\partial^2 f_2}{\partial x_3 \partial x_2} = -\gamma_2$$

Thereafter, the value of a is given by:

$$a = \sum_{k,i,j=1}^{4} V_k W_i W_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(P_0, 0) = 2\mu_1 \left\{ \left(\frac{C_1 V_2}{C_0} \right) \left(\frac{C_2 V_2}{C_0} \right)^2 \right\} + 2\phi_1 W_2 \left(\frac{C_1 V_2}{B_0} \right) \left(\frac{C_2 W_2}{C_0} \right)$$
$$+2\phi_1 W_2 V_2 \left(\frac{C_2 V_2}{C_0} \right) - 2\mu_2 V_2 W_2^2 - 2\gamma_2 V_2 W_2 \left(\frac{C_4 W_2}{C_5} \right)$$

Computation of b : To compute b, we need the second order partial derivatives of f_2 with respect to x_i and ϕ_1 as the second variable, at tumor-free equilibrium P_0

$$b = \sum_{i,j=1}^{4} V_k W_i \frac{\partial^2 f_k}{\partial x_i \partial \phi_1}(P_0, \phi_1^*)$$

where ϕ_1 is a bifurcation parameter

$$b = V_1 W_1 \frac{\partial^2 f_1}{\partial x_1 \partial \phi_1} + V_1 W_2 \frac{\partial^2 f_1}{\partial x_3 \partial \phi_1} + V_1 W_3 \frac{\partial^2 f_1}{\partial x_3 \partial \phi_1} + V_2 W_1 \frac{\partial^2 f_2}{\partial x_1 \partial \phi_1} + V_2 W_2 \frac{\partial^2 f_2}{\partial x_2 \partial \phi_1} +$$
$$V_2 W_3 \frac{\partial^2 f_2}{\partial x_3 \partial \phi_1} + V_4 W_1 \frac{\partial^2 f_4}{\partial x_1 \partial \phi_1} + V_4 W_2 \frac{\partial^2 f_4}{\partial x_2 \partial \phi_1} + V_4 W_3 \frac{\partial^2 f_4}{\partial x_3 \partial \phi_1}$$

$$\frac{\partial^2 f_1}{\partial x_i \partial \phi_1} = \frac{\partial^2 f_4}{\partial x_i \partial \phi_1} = 0$$

for $i = 1, 2, 3, 4$ while,

$$\frac{\partial^2 f_2}{\partial x_2 \partial \phi_1} = x_2,$$
$$\frac{\partial^2 f_2}{\partial x_2 \partial \phi_1} = x_1,$$

the value of b is given by:

$$b = \sum_{k,i=1}^{n} V_k W_i \frac{\partial^2 f_k}{\partial x_i \partial \phi_1}(P_0, \phi_1^*) = V_2 W_1 x_2 + V_2 W_2 x_1$$

Theorem 3.5.2. *The breast cancer model (3.1.5) has backward bifurcation if a is positive.*

Proof: In line with Castillo-Chavez [25] and Diekmann *et al.* [35], the direction of the bifurcation is forward when $a < 0$ and $b > 0$, while it is backward when $a > 0$ and $b > 0$ as well. From the analysis of b above coupled with the fact that W_1 & W_2 are all positive which imply that $b > 0$, the direction of the bifurcation is governed by the sign of a such that if $a > 0$ it is backward, otherwise it is forward.

In conclusion,

$a = \frac{2C_2^2 C_1 V_2 W_2^2 \mu_1}{C_0^3} - \frac{2C_2 W_2^2}{C_0^2}(-C_1 V_2 \phi_1 - V_2 \phi_1 C_0) - \frac{2V_2 W_2}{C_5}(W_2 \mu_2 C_5 + C_4 W_2 \gamma_2)$

$$a = 2\left[\frac{C_2^2 C_1 V_2 W_2^2 \mu_1}{C_0^3} + \frac{C_2 W_2^2}{C_0^2}(C_1 V_2 \phi_1 + V_2 \phi_1 C_0) - \frac{V_2 W_2}{C_5}(W_2 \mu_2 C_5 + C_4 W_2 \gamma_2)\right] \tag{3.5.23}$$

If

$$\frac{C_2^2 C_1 V_2 W_2^2 \mu_1}{C_0^3} + \frac{C_2 W_2^2}{C_0^2}(C_1 V_2 \phi_1 + V_2 \phi_1 C_0) > \frac{V_2 W_2}{C_5}(W_2 \mu_2 C_5 + C_4 W_2 \gamma_2) \tag{3.5.24}$$

then $a > 0$. Also, if

$$\frac{C_2^2 C_1 V_2 W_2^2 \mu_1}{C_0^3} + \frac{C_2 W_2^2}{C_0^2}(C_1 V_2 \phi_1 + V_2 \phi_1 C_0) < \frac{V_2 W_2}{C_5}(W_2 \mu_2 C_5 + C_4 W_2 \gamma_2) \tag{3.5.25}$$

then $a < 0$ while

$b = V_2 W_2 N_n$

$$= V_2 W_2 \left(\frac{\alpha_1 \mu_1 - (1-k)\lambda_1 \epsilon}{\mu_1 \mu_4} \right) > 0$$

. If $k = 1$, $b > 0$, if $k < 1$, $b > 0$, if and only if $\alpha_1 \mu_1 > (1-k)\lambda_1 \epsilon$ and $b < 0$, if $\alpha_1 \mu_1 < \lambda_1 \epsilon$ Since the coefficient b is automatically positive, the breast cancer model (3.1.5) will undergo backward bifurcation as given by (3.5.24). The implication of the above result is represented in Figure 3.1, which shows that the reduction of R_i^* below unity alone is not sufficient to eradicate tumor cells from the body system. However, to rule-out this occurrence, the global dynamics of TTFE was investigated in section (3.4.4) for the special case with $k = 1$.

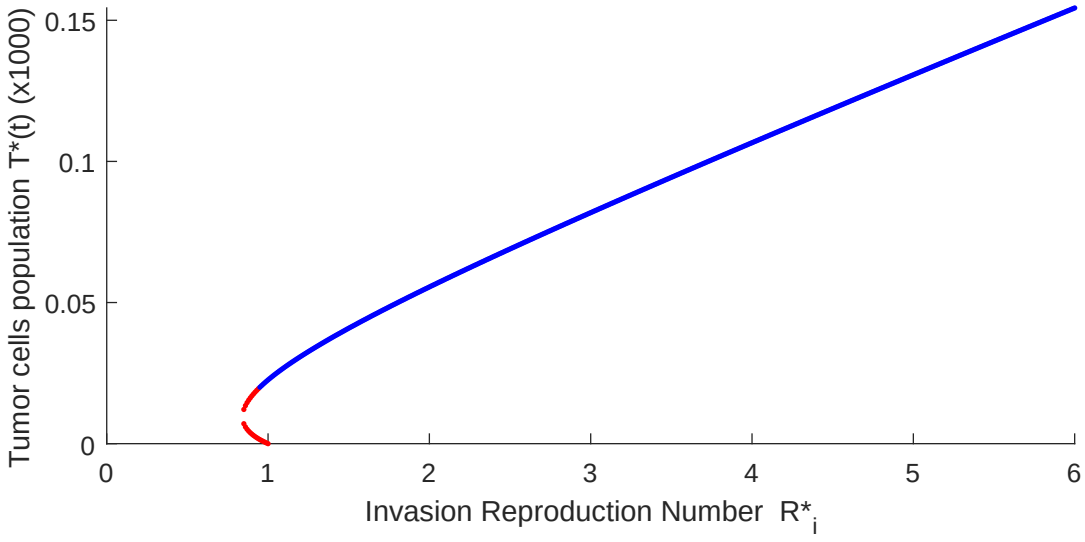


Figure 3.1: *Description of the backward bifurcation of the system (3.1.5) with* ϕ_1^*.

Additionally, the coefficient b is automatically positive and $a < 0$, the breast cancer model (3.1.5) will undergo forward bifurcation as given by (3.5.25). The implication of the above result is represented in Figure 3.2, which shows that the reduction of R_i^* above unity is sufficient to eradicate tumor cells from the body system. However, to rule-out this occurrence, the global dynamics of TTFE was investigated in section (3.4.4) for the

special case with $k = 1$.

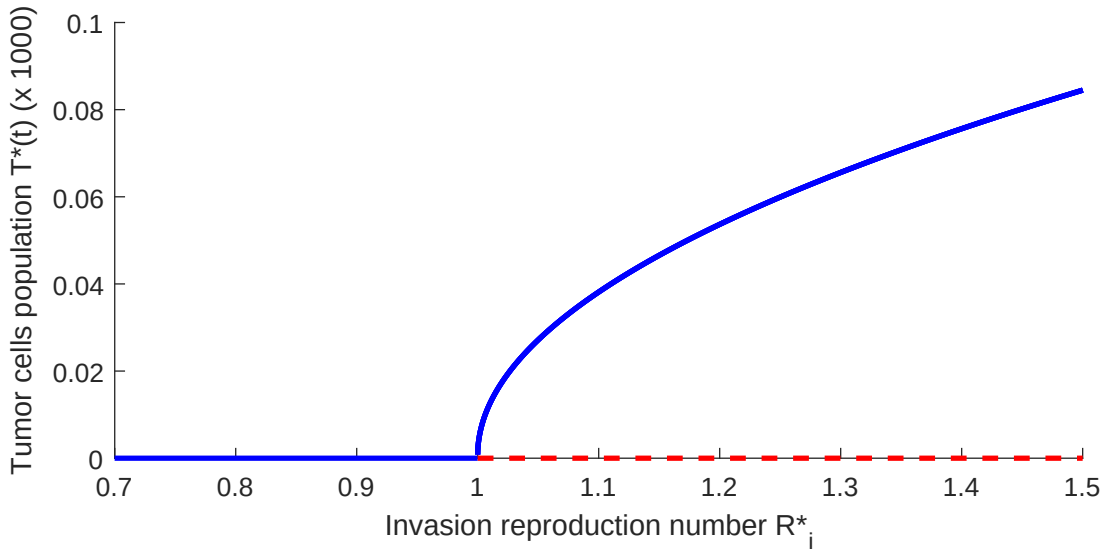


Figure 3.2: *Description of the forward bifurcation of the system (3.1.5) with* ϕ_1^*.

3.6 Sensitivity analysis of model parameters

We carried out a sensitivity analysis to determine the model's robustness to parameter values. This is to help us determine the parameters that have a high impact on tumor invasion, namely the invasion reproduction number (R_i). In carrying out the sensitivity analysis, we used the normalised forward sensitivity index of a variable to a parameter approach described in Chitins *et al.* [28]. This is defined as the ratio of relative change in the variable to relative change in the parameter. The sensitivity index may also be defined using partial derivatives when the variable is a differentiable function of the parameter.

3.6.1 Local sensitivity indices for R_i

Definition. *The normalised forward sensitivity index of a variable, h, that depends differentiably on a parameter, l, is defined as*:

$$\Upsilon_l^h := \frac{\partial h}{\partial l} \ \mathbf{x} \ \frac{l}{h}.$$

In particular, sensitivity indices of the invasion reproduction number R_i with respect to the model parameter are computed as follows:

$$
\begin{cases}
\dfrac{\partial R_i}{\partial \phi_1} \ \mathbf{x} \ \dfrac{\phi_1}{R_i} = \dfrac{\phi_1(\alpha_1\mu_4 - \lambda_1\epsilon\mu_3(1-k)(g\mu_4+\epsilon))}{\phi_1\alpha_1\mu_4 - \phi_1\lambda_1\epsilon\mu_3(1-k)(g\mu_4+\epsilon) + \lambda_3\epsilon(1-k)}, \\[2ex]
\dfrac{\partial R_i}{\partial \alpha_1} \ \mathbf{x} \ \dfrac{\alpha_1}{R_i} = \dfrac{\alpha_1\mu_4\phi_1}{\phi_1\alpha_1\mu_4 - \phi_1\lambda_1\epsilon\mu_3(1-k)(g\mu_4+\epsilon) + \lambda_3\epsilon(1-k)}, \\[2ex]
\dfrac{\partial R_i}{\partial \lambda_1} \ \mathbf{x} \ \dfrac{\lambda_1}{R_i} = -\left(\dfrac{\lambda_1\phi_1\mu_3\epsilon(1-k)(g\mu_4+\epsilon)}{\phi_1\alpha_1\mu_4 - \phi_2\lambda_1\epsilon\mu_3(1-k)(g\mu_4+\epsilon) + \lambda_3\epsilon(1-k)}\right), \\[2ex]
\dfrac{\partial R_i}{\partial \mu_3} \ \mathbf{x} \ \dfrac{\mu_3}{R_i} = \dfrac{\mu_3(\mu_5 - d\alpha_2)(g\mu_4+\epsilon)}{\gamma_2 s\beta(g\mu_4+\epsilon) + (\mu_5 - d\alpha_2)(\mu_3(g\mu_4+\epsilon) + \lambda_3\epsilon(1-k)}, \\[2ex]
\dfrac{\partial R_i}{\partial s} \ \mathbf{x} \ \dfrac{s}{R_i} = \dfrac{s\gamma_2(g\mu_4+\epsilon)}{\gamma_2 s\beta(g\mu_4+\epsilon) + (\mu_5 - d\alpha_2)(\mu_3(g\mu_4+\epsilon) + \lambda_3\epsilon(1-k)}, \\[2ex]
\dfrac{\partial R_i}{\partial \beta} \ \mathbf{x} \ \dfrac{\beta}{R_i} = \dfrac{s\gamma_2(g\mu_4+\epsilon)}{\gamma_2 s\beta(g\mu_4+\epsilon) + (\mu_5 - d\alpha_2)(\mu_3(g\mu_4+\epsilon) + \lambda_3\epsilon(1-k)}, \\[2ex]
\dfrac{\partial R_i}{\partial \gamma_2} \ \mathbf{x} \ \dfrac{\gamma_2}{R_i} = \dfrac{s\gamma_2(g\mu_4+\epsilon)}{\gamma_2 s\beta(g\mu_4+\epsilon) + (\mu_5 - d\alpha_2)(\mu_3(g\mu_4+\epsilon) + \lambda_3\epsilon(1-k)}, \\[2ex]
\dfrac{\partial R_i}{\partial \alpha_2} \ \mathbf{x} \ \dfrac{\alpha_2}{R_i} = -\left(\dfrac{d\alpha_2(\mu_3(g\mu_4+\epsilon) + \lambda_3\epsilon(1-k)}{\gamma_2 s\beta(g\mu_4+\epsilon) + (\mu_5 - d\alpha_2)(\mu_3(g\mu_4+\epsilon) + \lambda_3\epsilon(1-k)}\right), \\[2ex]
\dfrac{\partial R_i}{\partial d} \ \mathbf{x} \ \dfrac{d}{R_i} = -\left(\dfrac{d\alpha_2(\mu_3(g\mu_4+\epsilon) + \lambda_3\epsilon(1-k)}{\gamma_2 s\beta(g\mu_4+\epsilon) + (\mu_5 - d\alpha_2)(\mu_3(g\mu_4+\epsilon) + \lambda_3\epsilon(1-k)}\right), \\[2ex]
\dfrac{\partial R_i}{\partial \mu_1} \ \mathbf{x} \ \dfrac{\mu_1}{R_i} = -1,
\end{cases}
\tag{3.6.26}
$$

It is obvious from Table (3.2) above that the natural death rate of estrogen has the highest sensitivity index (S.I = 2.86) which indicates that increasing (or decreasing) the natural death rate of estrogen μ_4 by 10% decreases (or increases) the R_i by 28.61%. The second most sensitivity index (S.I =1.0406) is related to α_2 and d, which are the tumor growth rate and ketogenic-diet parameter respectively. These parameters can be increased (or decreased) by 10% each, then the R_i by 10.406%. Similarly, increasing(or decreasing) the rate at which normal cells grow α_1 and progression rate of tumor cells ϕ_1 by 10% decreases (or increases) the R_i by 9.55%. In the same way, increasing (or decreasing) the natural death rate for normal cells,μ_1 by 10% decreases (or increases) the R_i by 10%. Also, increasing (or decreasing) the source of estrogen, ϵ by 10% decreases(or increases) the R_i by 1.39%. However, increasing (or decreasing) the anti-cancer drugs efficacy, k by 10% decrease (or increases) the R_i by 0.45%. Nevertheless, the sensitivity indexes for the other parameters are very small, which indicates that they have no effect on R_i. In addition, our results show that the natural death rate has the most sensitivity index but increasing the death rate as a control measure is unreasonable biologically. The sensitivity index of the anti-cancer drugs of breast cancer is -0.0457, which indicates that to reduce R_i we need to increase the treatment rate. In fact, the constant rate of ketogenic-diet is also important in reducing R_i because it has sensitivity index of 1.0406.

In addition, the most effective control strategy is a strategy that involves control of tumor growth by increasing anti-cancer drugs or working on ketogenic-diet moderation. The positive sign of the sensitivity index of the invasion reproduction number to the model parameters indicated that an increase (or decrease) in the value of each of the parameter in this category will lead to an increase (or decrease) in the invasion reproduction number. For example, from Table 3.2, $\frac{\partial R_i}{\partial \mu_1} \times \frac{\mu_1}{R_i} = -1$ suggests that decreasing(or increasing) the natural death rate by 10 % decreases (or increases) the invasion reproduction

number, R_i, by 10%. However, the negative sign of the sensitivity index of the invasion reproduction number to the model parameters implies that an increase (or decrease) in the value of each of the parameter in this category leads to a corresponding decrease (or increase) in the invasion reproduction number of the tumor. Thus, sensitivity analysis of the breast cancer model (3.1.5) provides a very good insight the into the dynamics of tumor invasion of the disease. In particular, it helps public health authorities to focus on an intervention strategy for preventing and controlling the invasion of tumor cells to the other parts of the body.

3.6.2 Uncertainty analysis

We explored the dependence of the model solutions on the parameter values and we were able to figure out a feasible range of parameter values. We were also able to ascertain the most critical parameters in the model using a similar model to the Latin Hypercube Sampling (LHS) and the Partial Rank Coefficient (PRCC). The former is used in uncertainty analysis (the global sensitivity analysis method) while the latter is for analysing the sensitivity indexes of the parameters (see Malinzi *et al* [77] and Marino *et al* [78]). These were ran and analysed with a sample size of 100. The choice of this sample size is due to the fact that PRCC produces accurate results for a lower sample size compared to other technique like eFAST [78].

The parameter baseline values in Table 3.1 were varied in the range of 25%. Figure 3.2, displays a tornado plot of PRCCs plotted against the homogeneous parameter value with tumor compartment as the baseline dependent variable.

The parameter which are significantly positively correlated with tumor cells, at $p < 0.05$ level of significance, are α_1, g while $\mu_1, \gamma_3, \ and \ \omega$ are significantly negatively correlated. An increase in the production of normal cells α_1, leads to higher numbers of normal cells.

This means that the higher the α_1, the higher the normal cells while the most sensitive parameters are shown to be $p-values$ of s, γ_2, μ_3 and ρ in Figure 3.3.

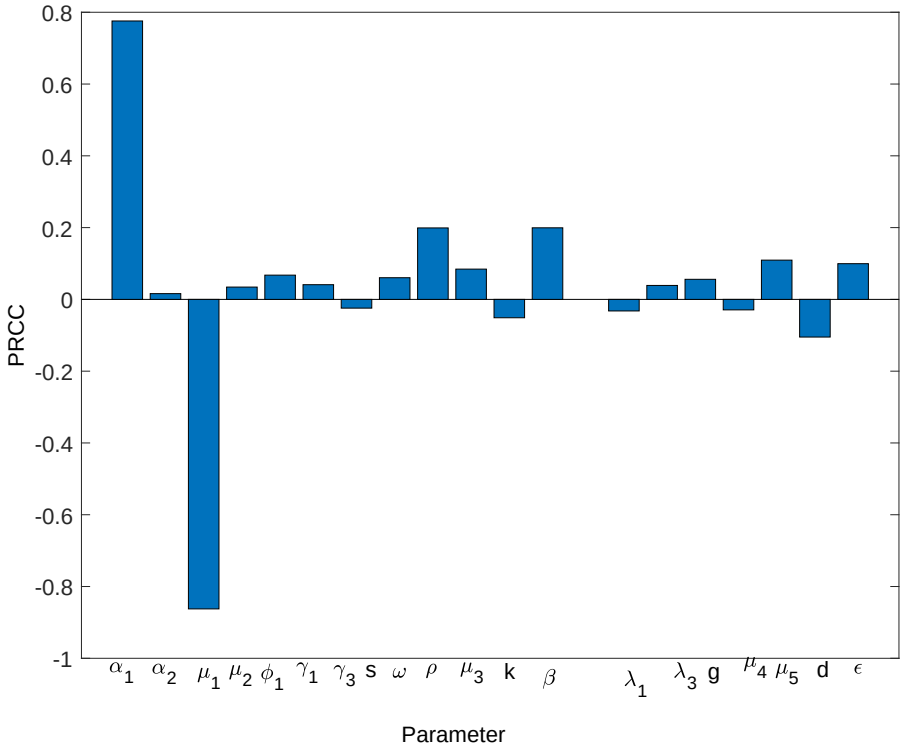


Figure 3.3: *PRCCs of homogeneous model parameters with the tumor cells as the baseline variable. All parameter values were varied in 25% of their baseline values in Table 3.1. The most sensitive parameters are shown to be $p-values$ of $\alpha_1, g, \mu_1, \gamma_3$ and ω are less than 0.01*

.

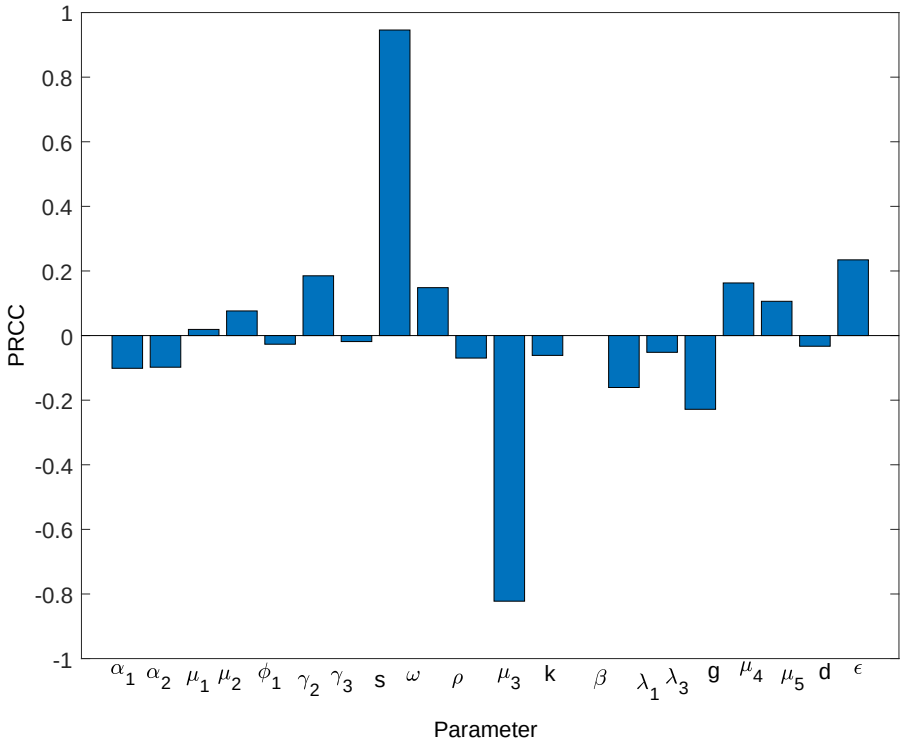


Figure 3.4: *PRCCs of homogeneous model parameters with the tumor cells as the baseline variable. All parameter values were varied in 25% of their baseline values in Table 1. The most sensitive parameters are shown to be* $p-values$ *of* s, γ_2, μ_3 *and* ρ *are less than 0.05*

.

Table 3.1: Description of parameters in the model

Parameter description	Symbol	Value	Units	References
Per capita growth rate of normal cells	α_1	0.70	day^{-1}	[31]
Per capita growth rate of tumor cells	α_2	0.514	day^{-1}	[108]
Natural death rate of normal cells	μ_1	0.00003	day^{-1}	Assumed
Natural death rate of tumor cells	μ_2	0.01	day^{-1}	[7]
Probabilistic rate of normal cells mutation into tumor cells	ϕ_1	6×10^{-8}	day^{-1}	[7]
Tumor cells death rate due to immune response	γ_2	3×10^{-6}	day^{-1}	[31]
Interaction coefficient rate with immune response	γ_3	1×10^{-7}	day^{-1}	[5]
Source rate of immune cells	s	1.3×10^4	day^{-1}	[31]
Source rate of estrogen	ϵ	1.3×10^4	day^{-1}	Estimated
Immune threshold rate	ω	3×10^5	day^{-1}	[108]
Immune response rate	ρ	0.20	day^{-1}	[34]
Natural death rate of immune cells	μ_3	0.29	day^{-1}	[108]
Efficacy of anti-cancer drug	k	$0 - 1$	day^{-1}	Assumed
Supplement for immune booster	β	0.01	day^{-1}	Estimated
Tumor formation rate as a result of DNA damage by excess estrogen	λ_1	0.20	$(Pg/mL)^{-1}$	Estimated
Immune suppression rate due to excess estrogen	λ_3	0.002	day^{-1}	Estimated
Assume constant of value of decay factor	g	0.1	day^{-1}	Estimated
Natural death rate of estrogen	μ_4	0.97	day^{-1}	[19]
Death rate due to ketogenic diet	μ_5	2.0	day^{-1}	Estimated
Constant rate of ketogenic diet	d	0.5	day^{-1}	Estimated

Table 3.2: Sensitivity Indexes of the model's parameters with respect to R_i

Parameter	Description	Sensitivity Index
α_1	Per capita growth rate of normal cells	0.9547
α_2	Per capita growth rate of tumor cells	1.0406
μ_1	Natural death rate of normal cells	-1.0000
μ_2	Natural death rate of tumor cells	- 0.0405
γ_2	Death rate of tumor cells as a result of immune response	-0.0001
s	Source rate of immune cells	-0.0001
ϵ	Source rate of estrogen	0.1391
μ_3	Natural death rate of immune cells	0.9998
k	Efficacy of anti-cancer drug	-0.0457
β	Supplement for immune booster	-0.0001
λ_1	Rate of tumor formation due to DNA damage by excess estrogen	-0.000004
λ_3	Immune suppression rate due to excess estrogen	0.0457
g	Assume constant of value of decay factor	-0.00005
μ_4	Natural death rate of estrogen	2.8609
ϕ_1	Probabilistic rate of normal cells mutation into tumor cells	0.9546
d	Constant rate of ketogenic diet	1.0406

Sensitivity Analysis Case II when $k = 1$

$$
\begin{cases}
\dfrac{\partial R_i^*}{\partial \phi_1} \ \mathbf{x} \ \dfrac{\phi_1}{R_i^*} = \\
\frac{1}{\phi_1 \alpha_1} \left\{ \mu_1(s\beta\gamma_2 + \mu_3(\mu_5 - d\alpha_2)) \left(\frac{\phi_1\alpha_1}{\mu_1(s\beta\gamma_2+\mu_3(\mu_5-d\alpha_2))} - \frac{\phi_1\alpha_1\mu_3(\mu_5-d\alpha_2}{\mu_1(s\beta\gamma_2+\mu_3(\mu_5-d\alpha_2))^2} \right) \right\}, \\
\dfrac{\partial R_i^*}{\partial \alpha_1} \ \mathbf{x} \ \dfrac{\alpha_1}{R_i^*} = 1, \\
\dfrac{\partial R_i}{\partial \mu_1} \ \mathbf{x} \ \dfrac{\mu_1}{R_i} = -1, \\
\dfrac{\partial R_i^*}{\partial \alpha_2} \ \mathbf{x} \ \dfrac{\alpha_2}{R_i^*} = \dfrac{\alpha_2\mu_3 d}{(s\beta\gamma_2 + \mu_3(\mu_5 - d\alpha_2)}, \\
\dfrac{\partial R_i}{\partial \mu_5} \ \mathbf{x} \ \dfrac{\mu_5}{R_i} = -\dfrac{\mu_3\mu_5}{(s\beta\gamma_2 + \mu_3(\mu_5 - d\alpha_2)}, \\
\dfrac{\partial R_i}{\partial \beta} \ \mathbf{x} \ \dfrac{\beta}{R_i} = -\dfrac{\gamma_2 s\beta}{(s\beta\gamma_2 + \mu_3(\mu_5 - d\alpha_2)}, \\
\dfrac{\partial R_i}{\partial \gamma_2} \ \mathbf{x} \ \dfrac{\gamma_2}{R_i} = -\dfrac{\gamma_2 s\beta}{(s\beta\gamma_2 + \mu_3(\mu_5 - d\alpha_2)}, \\
\dfrac{\partial R_i}{\partial s} \ \mathbf{x} \ \dfrac{s}{R_i} = -\dfrac{\gamma_2 s\beta}{(s\beta\gamma_2 + \mu_3(\mu_5 - d\alpha_2)}, \\
\dfrac{\partial R_i}{\partial d} \ \mathbf{x} \ \dfrac{d}{R_i} = \dfrac{\alpha_2 s\beta}{(s\beta\gamma_2 + \mu_3(\mu_5 - d\alpha_2)}, \\
\dfrac{\partial R_i}{\partial \phi_1} \ \mathbf{x} \ \dfrac{\phi_1}{R_i} = 0,
\end{cases}
\tag{3.6.27}
$$

Table 3.3: Case II for Sensitivity Indexes of the model's parameters with respect to R_i^*

Parameter	Description	Sensitivity Index
α_1	Per capita growth rate of normal cells	1.0000
α_2	Per capita growth rate of tumor cells	0.1474356
μ_1	Natural death rate of normal cells	-1.0000
γ_2	Tumor cells death rate due to immune response	-0.000077
s	Source rate of immune cells	-0.000077
μ_3	Natural death rate of immune cells	0.000077
β	Supplement for immune booster	-0.000077
μ_5	Death rate due to ketogenic diet	-1.147358
ϕ_1	Probabilistic rate of normal cells mutation into tumor cells	0.0000
d	Constant rate of ketogenic diet	0.1474355

Some parameters value have been taken from literature, as noted in the Table 3.1, others have been estimated, assumed in order to showcase the possible dynamics of our model. However, the focus of our work is to examine the mathematical implications of the model, we recognise that some of our parameters are not based on experimental data [34].

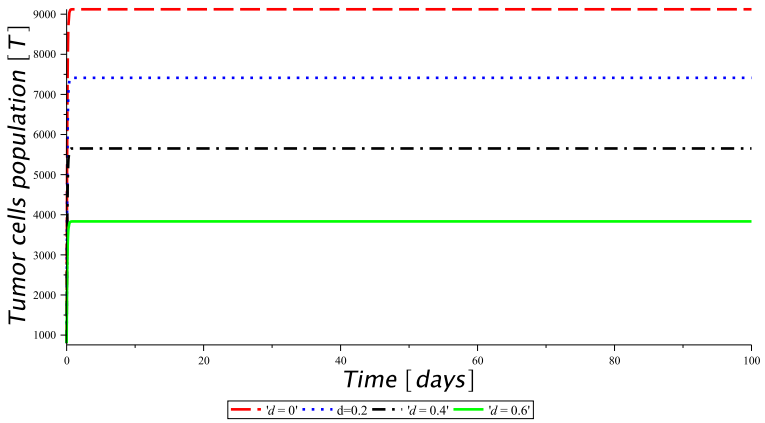


Figure 3.5: *The variation of proportion of Tumor cell population for different values of d with other parameters fixed*

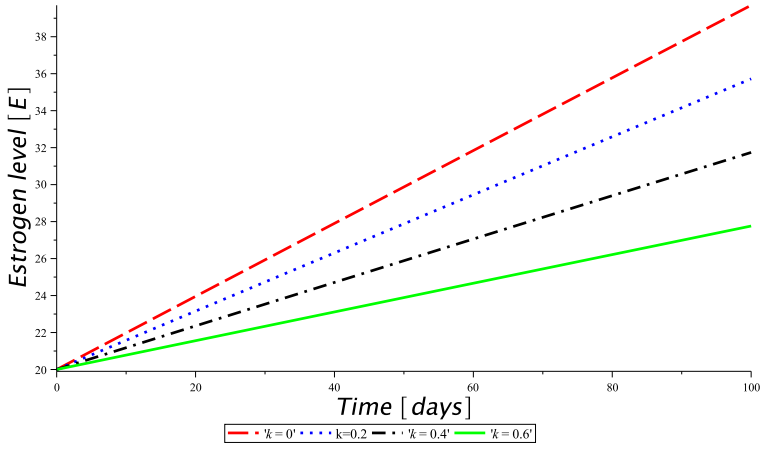


Figure 3.6: *The variation of proportion of Estrogen level for different values of k with other parameters fixed*

3.6.3 Numerical simulations

Key parameters are also noted in stabilising the model in system (3.1.5) such as ketogenic diet, anti-cancer drugs and immune booster. The initial values of variables are N(0)= 2000, T(0)= 800, M(0)= 500, E(0)= 20 and $s = 1.3 \times 10^4$ adopted from Abernathy *et al* [1]. All parameter values used for the numerical simulation are stated in Table 3.1.

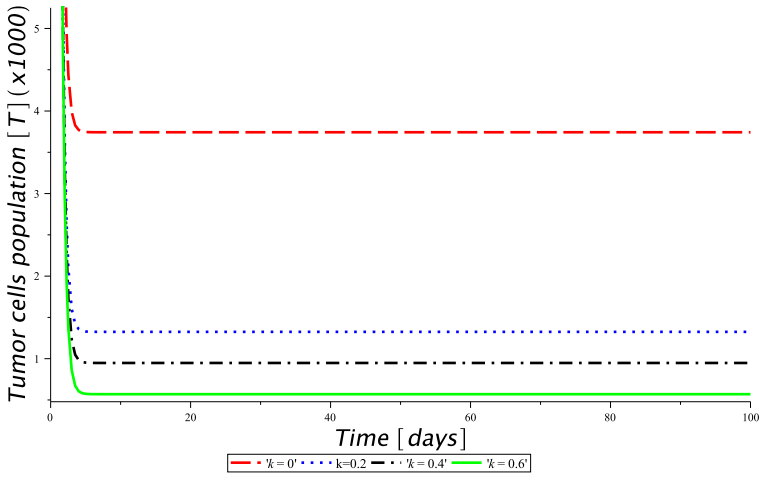


Figure 3.7: *The variation of proportion of Tumor cells population for different values of k with other parameters fixed*

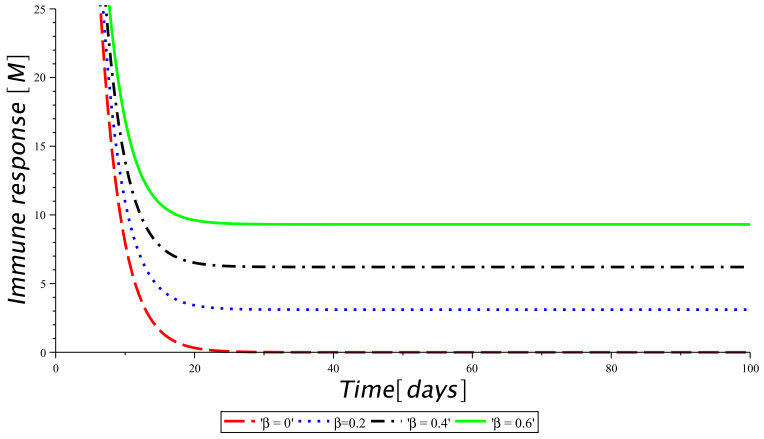


Figure 3.8: *The variation of proportion of Immune booster for different values of β with other parameters fixed*

3.6.4 Discussion

Figure 3.5 indicates that the introduction of a ketogenic diet results in the reduction of the activities of cancer cells. On the other hand, when ketogenic diet is in excess it can result into ketoacidosis, a combination of ketosis and acidosis. The former is the accumulation of ketone bodies while acidosis is increased acidity of the blood which can

cause frequent urination *Polyuria*, poor appetite and loss of consciousness. Therefore, our ketogenic diet's parameter rate is at its best at $d = 0.6$ and can compliment the activity of the anti-cancer drug (Tamoxifen). Figure 3.6, shows the impact of an anti-cancer drug in reducing the production of excess estrogen in the system, but when there is reduced production of estrogen there will not be the kind of rapid growth that is a characteristic of normal breast cells. However, the rapid production of estrogen results in abnormal breast cells expression which will lead to breast cancer. Figure 3.7 shows the obvious effects of anti-cancer drugs on tumor cells because there is no supply of nutrient or glucose (energy) to the cancer cells.

Figure 3.8 shows that the red line $\beta = 0$, during cancer formation when both innate and adaptive activities reduce drastically due to the expression of proteins other than those responsible for the activation of immune response. But the introduction of the immune booster into the system, reactivates the immune response to the cancer cells. The presence of abnormal estrogen levels without anti-cancer drugs or ketogenic diet will make the system unstable as shown in Figure 3.9.

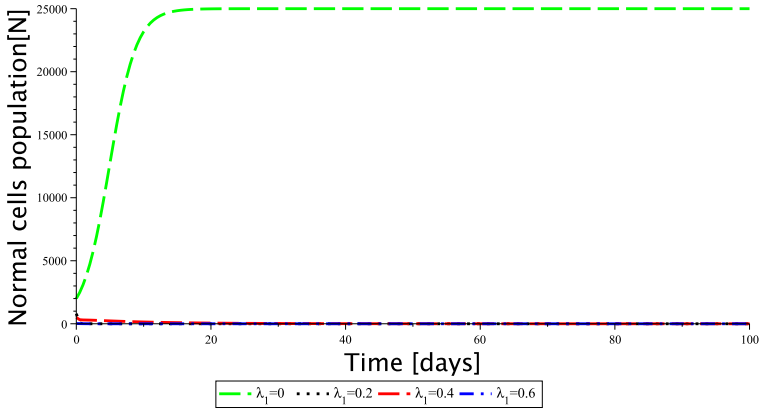


Figure 3.9: *The variation of proportion of Normal cells population for different values of* λ_1 *with other parameters fixed*

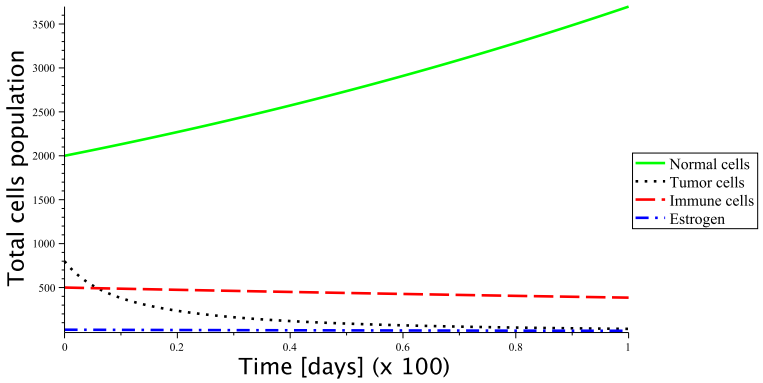


Figure 3.10: *The variation of Total cells population of the system (3.1.5)*

The system however becomes stable as we introduced chemotherapy and a ketogenic diet as represented in Figure 3.10. In addition, Figure 3.11, indicates that there is DNA damage at $\lambda_1 = 0$ which occurs naturally as a result of metabolic or hydrolytic processes. It is as a result of a Tumor Suppressor Gene (TSG) which is able to control the activity of DNA gene repair successfully. $\lambda_1 = 0.2, 0.4, 0.6$ shows that TSG (such as BRCA 1, BRCA 2, P53) compromises the pathway which leads to uncontrollable cell growth, the formation of tumors or accelerated aging.

The mathematical analysis of the model produced six equilibrium points all with epidemiological implications in relation to explaining the dynamics of breast cancer growth. P_0 represents a state of tumor-free equilibrium when only tumor cells died from competition with other cells.

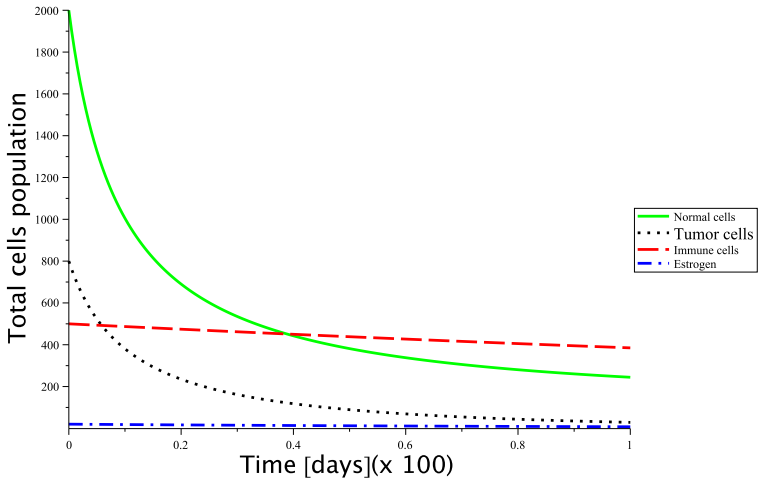


Figure 3.11: *The variation of Total cells population of the system (3.1.5)*

P_{d1} represents a type 1-dead equilibrium point where both normal and tumor cells die off as a result of breast tissue removal through mastectomy or death. P_{d2} could be described by a type 2-dead equilibrium point where only normal cells are forced into extinction leaving tumor cells surviving. P_{d3} represents a type 3-dead equilibrium point which means the immune system is weak and it cannot fight the tumor cells which eventually overpower normal cells and force them into extinction. P_{d4} shows that type 4-dead equilibrium point where the ketogenic diet is not effective, the immune booster is not active, and which leads to tumor cell overpowering normal cells as a result of the infusion of excess estrogen into the body system. We categorized this as "dead" because biologically, damaged normal cells do not recover. This could from the anti-cancer drug that destroys red blood cells that affected normal cells.

3.6.5 Summary

A four-dimensional compartmental deterministic model was designed and used to monitor the dynamics of breast cancer. The existing model in [87] was extended to incorporate treatments, ketogenic diet and immune booster. The system (3.1.5) was rigorously anal-

ysed to gain insight into their dynamical behaviours. The study shows the following:

i conditions of stability of the Treatment Tumor-Free Equilibrium (TTFE) was established and the system is for both Local Asymptotically Stable (LAS) if a certain threshold quantity, known as *treatment induced invasion reproduction number* is less than unity ($R_i^* < 1$) and Global Stability Analysis (GAS) for special case $R_i^* \mid_{k=1} \leq 1$. It implies that the number of tumor cells in the body will be brought to zero if proper treatments and ketogenic diet which can make the threshold to a value less than unity are monitored.

ii An individual has the chance of developing breast cancer depending on the level of immune system (s), efficacy of anti-cancer drug (k) and rate at which ketogenic diet (d) is being taken to fight tumor cells. This implies that any additional estrogen quantity introduced into the body through birth control pills and Hormone Replacement Therapy (HRT) enhances the rate of tumor formation [42]. Thus, the development of breast cancer is certain.

iii The transition from normal cells class to tumor cells class plays a crucial role in the breast cancer dynamics (λ_1). More tumor is formed if the DNA is damaged or altered as a result of excess estrogen; which reduces the number of normal cells that will be produced by red blood cells [82].

iv Furthermore, the results show that tumor cell formation depends on the level of excess estrogen introduced into the body system; an individual's DNA ability to resist changes in structure; and the amount of estrogen released during natural biological processes such as premenopause and menopause stages.

Other risk factors may also be incorporated in the model for future work.

Chapter 4

Application of optimal control

4.1 Introduction

Optimal control theory is a mathematical tool in decision making that includes the appropriate use of several strategies to reduce the occurrence of diseases in cost-effective ways. The application of optimal control theory to solve diverse epidemiological problems has been reported in several studies [69, 96, 104, 131]. Tsai [131] explored this techniques for improving multi-dose drug schedules, treatment times and drug toxicities in cancer chemotherapy. Also, Pang and Coworker [104] used the optimal control theory approach to investigate the implementation of immunotherapy and chemotherapy for a certain period to reduce the number of tumor cells and to minimise the implementation costs of the two therapeutic strategies. However, a quadratic objective function will be employed to measure the control cost for cancer treatment and application of anti-cancer drug control given the nonlinearity of costs of the relationships between the cost of intervention of the tumor cells population and the effects of intervention. These quadratic costs have been applied by several authors [4, 95, 96]. Lastly, we evaluate the incremental cost-effectiveness ratios to analyse the cost-effectiveness of all possible combinations of

the different treatments.

4.2 Formulation of optimal control model for breast cancer

In the previous section, the different forms of disease controls (ketogenic diet, immune booster and anti-cancer treatment) are considered as constants. This means there is no cost determination associated with their implementation. We formulate a corresponding optimal control problem for the model in system (3.1.5) using the ketogenic diet and chemotherapy as control interventions to reduce prevalence and economic burdens. This technique has been used successfully to determine the relevant control strategies with optimal cost [69]. We use a quadratic term for the rate of application of a anti-cancer drug control. Our goal is to minimize the number of tumor cells $T(t)$ and the cost control of u_1 (anti-cancer drug) & u_2 (ketogenic-diet) while maximising the tumor-free population. Mathematically, the objective functional J_1 formulates the optimisation problem of interest, namely that of identifying the most effective strategies. A few of the studies relevant to control problem are described in the following notes [43, 69, 90, 96].

As tumor formation rate increases due to DNA damage by excess estrogen, the tumor cells population increases as the density of normal cells population (that is prone to be cancerous). We implement a measure that will reduce the interaction by $(1-u_1(t))$, where $u_1(t)$ measures the level of successful treatment efforts, which has practical advantages in the reduction of cancer prevalence during the dead-free tumor or co-existing free tumor metastasis. The control variable $u_1(t)$ denotes the use of anti-cancer drugs, such as Tamoxifen of Taxol = Paclitaxel which are alternative preventive measures to minimise growth or eliminate tumors from the body system.

However, the ketogenic diet to tumor cells u_2 is chosen at a time dependent control intervention as $u_2(t)$. A control variable that represents the level of ketogenic diet in which cancer patient is placed on is $u_2(t)$. The ketogenic diet will aid the starvation of tumors the body system. It follows that the growth rate of the tumor population will be reduced by a factor $(1 - u_2(t))$, where u_2 also serves as a measures of the level of successful prevention (personal protection efforts). Thus, our main objective is to investigate optimal control policies which can minimise costs while limiting the disease. It is also our aim to determine the total costs of implementing control policies. The weighted sum of the total cost incurred is described as follows:

i) Cost incurred due to breast cancer: It is the weighted cost due to the patient's loss of opportunities [69] and is given as:

$$\int_0^{T_f} (A_1 T(t) + A_2 E(t))\, dt$$

Patients lose opportunities in several ways such as loss in efficiency due to sickness, loss of manpower, loss realised in searching for treatment and protection and care etc [44]; where T_f is final time .

ii) Cost incurred in treatment: This is the cost that providing treatment to tumor cells population during the metastasis stage and is given as:

$$\int_0^{T_f} \left(\frac{1}{2} A_3 u_1^2(t)\right) dt$$

The total weighted cost incurred in treatment includes the costs involved in the efforts and processes of treatment including mammography or X-rays scans, medication, diagnosis and hospital stays.

iii) Costs incurred in adopting a ketogenic diet: The weighted sum of costs realised in adopting a ketogenic diet includes the cost of a restricted diet that will starve tumor

cells from getting necessary nutrient from the body system and is given as:

$$\int_0^{T_f} \left(\frac{1}{2}A_4 u_2^2(t)\right) dt$$

Based on the severity and effect of treatment on tumor cells populations, we consider a nonlinear relationship between cost and the efforts made towards treatment and the use of a ketogenic diet.

We therefore define the control problem as per the above discussion for control policies and costs incurred, as follows:

$$J_1(u_1, u_2) = \int_0^{T_f} \left(A_1 T(t) + A_2 E(t) + \frac{1}{2}A_3 u_1^2(t) + \frac{1}{2}A_4 u_2^2(t)\right) dt \tag{4.2.1}$$

$$\min_{J_1(u_1,u_2)} (u_1, u_2 \in U) \quad U = \{u_1(t) \;\&\; u_2(t) : 0 \leq u_1(t) \leq 1, \;\; 0 \leq u_2(t) \leq 1, \;\; t \in [0, T_f]\}$$

and u_1 and u_2 are Lebesgue measurable subject to the model system (3.5):

$$\begin{aligned}
\frac{dN}{dt} &= N\alpha_1 - \mu_1 N^2 - \phi_1 TN - (1 - u_1(t))\,(\lambda_1 NE) \\
\frac{dT}{dt} &= (1 - u_2(t))\,T\alpha_2 - \mu_2 T^2 - \gamma_2 MT - \mu_5 T + \phi_1 TN + (1 - u_1(t))\,(\lambda_1 NE) \\
\frac{dM}{dt} &= s\beta + \frac{\rho MT}{\omega + T} - \gamma_3 MT - \mu_3 M - \left((1 - u_1(t))\,\frac{\lambda_3 ME}{g + E}\right) \\
\frac{dE}{dt} &= \epsilon - \mu_4 E
\end{aligned} \tag{4.2.2}$$

Following the initial conditions

$N(0) \geq 0,\; T(0) \geq 0,\; M(0) \geq 0,\; \&\; E(0) \geq 0.$

The objective function J_1 represents the total cost incurred as a result of the application of control plans and the burden of the disease.

$$L(N, T, M, E, u_1, u_2) = A_1 T(t) + A_2 E(t) + \frac{1}{2}A_3 u_1^2(t) + \frac{1}{2}A_4 u_2^2(t) \tag{4.2.3}$$

where A_1, A_2, A_3 & A_4 are positive weight constants related to the cost in unit effort and also balance the units integrand. For convenience, we consider $u_1(t) = u_1$ & $u_2(t) = u_2$. The system (4.2.2) which involves a system of coupled non-linear differential equation and

two controls will be introduced with initial conditions given at t=0. In order, to deal with the tumor-to-therapy trade-off, we used the approach in [34,49,109] to ensure optimal control. This requires the upper bounds on the system's (3.1.5) solutions to be analysed. Once it was established that the systems are bounded, the existence of an optimal control was done based on Madhi and Mohamed's [76] results. We proved, furthermore, the existence of an optimal control which reduces the objective function. This was done via established approaches (De Pillis *et al.*[34], Ghaddar [49], De Pillis*et al.* [33], Acar and Aplak [2], and Kirschner *et al.* [63]). We use the fact that super-solutions $\overline{N}$, $\overline{T}$, $\overline{M}$, $\overline{E}$ of

$$\begin{aligned} \frac{d\overline{N}}{dt} &= N\alpha_1, \quad \frac{d\overline{T}}{dt} = T\alpha_2(1-u_2), \\ \frac{d\overline{M}}{dt} &= s\beta + \frac{\rho MT}{\omega + T}, \quad \frac{d\overline{E}}{dt} = 1 \end{aligned} \tag{4.2.4}$$

are bounded on a finite time interval. Given that the sub-solutions are zero, the result obtained shows that our system is bounded. Also, our next mission was to ensure the existence of the optimal control using a result from Fleming and Rishel [41] as well as Oke *et al.* [95] in view of the fact that we had a bounded system.

4.2.1 Existence of an optimal control

Theorem 4.2.1. : *Given the objective functional in (4.2.1), where* $U = \{u_i^*(t),$ *Lebesgue measure* $: 0 \leq u_i^*(t) \leq 1, \forall t \in [0,t]\}$ *subject to system (4.2.2) with* $N(0) = N_0$, $T(0) = T_0$, $M(0) = M_0$, *and* $E(0) = E_0$, *there exists an optimal control* $\overline{u_i^*}$ *such that* $\min_{\overline{u_i^*}(t)\in[0,1]} J_1(\overline{u_i^*}) = J_1(u_i^*(t))$ *if the following conditions holds:*

(i) f *is not empty*

(ii) The admissible control set U *is closed and convex*

(iii) Each right hand side of the state system is continuous, is bounded above by the sum of the bounded control and the state, and can be written as a linear function of $\overline{u_i^*(t)}$

with coefficients depending on time and the state.

(iv) The integrand of $J_1(\overline{u_i^*})$ *is convex on* U *and is bounded below by* $-c_2 + c_1\overline{u}^2$ *with* $c_1 > 0$

Proof : Since the system (4.2.2) has bounded coefficients and the solutions are bounded on the finite time interval, we can apply the result of Helton *et al.* [54] (*Theorem* 9.2.1, *page* 182), to obtain the existence of the solution of the system (4.2.2). Furthermore, we note that U is closed and convex by definition. For the third conditions, the right hand side of the system (4.2.2) must be continuous. The right hand side is continuous since the denominators of all fractions from the right hand side of the system consists solely of positive entities. We let $\overrightarrow{\varphi}(t, \overrightarrow{X})$ be right hand side of the system (4.2.2) except for the terms of $\overline{u_i^*}$ and define.

$$\mid \overrightarrow{f}(t, \overrightarrow{X}, u_i^*) \mid = \overrightarrow{\varphi}(t, \overrightarrow{X}) + \begin{pmatrix} 0 \\ \lambda_1 NE \\ 0 \\ u_1 \end{pmatrix}, with \quad \overrightarrow{X} = \begin{pmatrix} N \\ T \\ M \\ E \end{pmatrix}$$

using the boundedness of the solutions (4.4), we have

$$\mid \overrightarrow{f}(t, \overrightarrow{X}, u_i^*) \mid \leq \left| \begin{pmatrix} \alpha_1 & 0 & 0 & 0 \\ 0 & \alpha_2(1-u_2) & 0 & 0 \\ 0 & 0 & \rho & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} N \\ T \\ M \\ E \end{pmatrix} \right| + \left| \begin{pmatrix} 0 \\ (1-u_1)\lambda_1 NE \\ s\beta \\ -u_1\epsilon \end{pmatrix} \right| \leq c_1 \left(\mid \overrightarrow{X} \mid + \mid \overrightarrow{u_i^*} \mid \right)$$

where c_1 depends on the coefficients of the system. For the fourth condition, we need to show

$$J\left(t, T, E, (1-P_i)u_i + P_i V_i\right) \leq (1-P_i) J\left(t, T, E, u_i\right) + P_i(t, T, E, V_i)$$

we analyze the difference of

$$J\left(t,T,E,(1-P_i)u_i+P_iV_i\right)-\left[(1-P_i)J\left(t,T,E,u_i\right)+P_i(t,T,E,V_i)\right]$$

$$=T(t)+E(t)+\frac{\epsilon}{2}\left(u_i^2-2P_iu_i^2+P_i^2u_i^2+P_i^2V_i^2-2P_i^2V_i^2u_i^2+2P_iV_iu_i\right)$$

$$-\left(T(t)+E(t)+\frac{\epsilon}{2}u_i^2-\frac{\epsilon}{2}P_iu_i^2+\frac{\epsilon}{2}P_iV_i^2\right)$$

$$=\frac{\epsilon}{2}(P_i^2-P_i)(u_i-V_i)^2$$

since, $P_i\in(0,1)$ implies $(P_i^2-P_i)<0$ and $(u_i-V_i)^2>0$ but $(P_i^2-P_i)<0$, which implies $\frac{\epsilon}{2}(P_i^2-P_i)(u_i-V_i)^2$ is negative. This implies that,

$$J\left(t,T,E,(1-P_i)u_i+P_iV_i\right)\leq(1-P_i)J\left(t,T,E,u_i\right)+P_i(t,T,E,V_i)$$

Lastly,

$$T(t)+E(t)+\frac{\epsilon}{2}u_i^2(t)\geq\frac{\epsilon}{2}u_i^2(t)\geq-c+\frac{\epsilon}{2}u_i^2(t)$$

which gives $-c+\frac{\epsilon}{2}u_i^2(t)$ as the lower bound. With the existence of the optimal control established, we now characterize the optimal control using Pontryagin's Maximum Principle [112]. However, we only examined these three alternative strategies:

- Strategy A : Anti-cancer drug treatment control on tumor cells (control $u_1(t)$ only)
- Strategy B : Anti-cancer drug and ketogenic diet treatment combined control on tumor cells growth and excess estrogen (controls $u_1(t)$ and $u_2(t)$)
- Strategy C : Ketogenic diet control on excess estrogen and tumor cells (control $u_2(t)$ only)

Thus, strategies use the objective functionals (4.2.1).

We assumed that there are practical limitations on the maximum rate at which the anti-cancer treatment may be applied in a given period. We defined the positive constant

u_{max} accordingly. We also defined the set U of admissible controls to be all Lebesgue measurable functions which take on values in the control set [4,64,98,99,110,111,125] $u = [0, u_{max}]$ almost everywhere on $[0, T]$. We looked for an optimal control $u^* \in U$ in (4.1.1) [38]. To find the optimal solutions, we first traced the Lagrangian and Hamiltonian for the optimal control problem (4.2.5) and (4.1.2). The Lagrangian of the optimal control problem is given by:

$$L(N, T, M, E, u_1, u_2) = A_1 T(t) + A_2 E(t) + \frac{1}{2} A_3 u_1^2(t) + \frac{1}{2} A_4 u_2^2(t) \tag{4.2.5}$$

$$H = \begin{cases} A_1 T(t) + A_2 E(t) + \frac{1}{2} A_3 u_1^2(t) + \frac{1}{2} A_4 u_2^2(t) \\ +\theta_1 \left(N\alpha_1 - \mu_1 N^2 - \phi_1 TN - (1 - u_1(t)) (\lambda_1 NE) \right) \\ +\theta_2 \left((1 - u_2(t)) T\alpha_2 - \mu_2 T^2 - \gamma_2 MT - \mu_5 T + \phi_1 NT + (1 - u_1(t)) (\lambda_1 NE) \right) \\ \quad + \theta_3 \left(s\beta + \frac{\rho MT}{\omega + T} - \gamma_3 MT - \mu_3 M - \left((1 - u_1(t)) \frac{\lambda_3 ME}{g + E} \right) \right) \\ +\theta_4 \left(\epsilon - \mu_4 E \right) \end{cases}$$

where $\theta_1, \theta_2, \theta_3, \theta_4$

are adjoints variable for the states N,T,M,E. Using Pontryagin's Maximum Principle, we can obtain minimised Hamiltonian that minimizes objective function or cost functional.

4.2.2 Characterisation of optimal control

We describe the optimal control pair u_1^* & u_2^* using Pontryagin's Maximum Principle [112] as follows.

Theorem 4.2.2.

Given that optimal control variables u_1^* & u_2^* and $N^*, T^*, M^* \& E^*$ are corresponding optimal state variables of the control system (4.2.1) and (4.2.2), there exists an adjoint

variable

$\theta = (\theta_1, \theta_2, \theta_3, \theta_4) \in \Re_+^4$ *that satisfies the following equations.*

$$-\frac{d\theta_1}{dt} = 2\theta_1\mu_1 N + (\phi_1\theta_1 + \phi_1\theta_2)T + (\theta_1 + \theta_2)\left(1 - u_2(t)\right)\lambda_1 E - \alpha_1\theta_1$$

$$-\frac{d\theta_2}{dt} = -A_1 + \theta_1\phi_1 N + \theta_2\left(2T\mu_2 + \gamma_2 M + \mu_5 - \alpha_2(1 - u_2)\right) + \theta_3\left(\gamma_3 M - \frac{\rho\omega M}{(\omega + T)^2}\right)$$

$$-\frac{d\theta_3}{dt} = \theta_2\gamma_2 T + \theta_3\left(\gamma_3 T + \mu_3 - \frac{\rho T}{\omega + T} + (1 - u_1)\frac{\lambda_1 E}{g + E}\right)$$

$$-\frac{d\theta_4}{dt} = -A_2 + (\theta_1 - \theta_2)(1 - u_1)\lambda_1 N + \theta_3\left((1 - u_1)\frac{\lambda_3 M g}{(g + E)^2}\right) + \theta_4\mu_4$$

with transversality conditions

$\theta_1(T_f) = \theta_2(T_f) = \theta_3(T_f) = \theta_4(T_f) = 0$

The corresponding optimal controls u_1^* & u_2^* are given as,

$$u_1^* = min\left\{max\left\{0, \frac{1}{A_3}\left(\theta_2\lambda_1 N^* E^* - \theta_1\lambda_1 N^* E^* - \frac{\theta_3\lambda_3 M^* E^*}{g + E^*}\right)\right\}, 1\right\}$$

and

$$u_2^* = min\left\{max\left\{0, \frac{1}{A_4}\left(\theta_2\alpha_2 T^*\right)\right\}, 1\right\}$$

Proof: Let u_1^* & u_2^* be the given optimal control functions and $N^*, T^*, M^* \& E^*$ be the corresponding optimal state variables of the system (4.2.2) which minimise the cost functional or objective (4.2.1). Then by Pontryagin's Maximum Principle [112], there exist adjoint variables $\theta_1, \theta_2, \theta_3,$ & θ_4 which satisfy following equations:

$$-\frac{d\theta_1}{dt} = \frac{\partial H}{\partial N} = 2\theta_1\mu_1 N + (\phi_1\theta_1 + \phi_1\theta_2)T + (\theta_1 + \theta_2)\left(1 - u_2(t)\right)\lambda_1 E - \alpha_1\theta_1$$

$$-\frac{d\theta_2}{dt} = \frac{\partial H}{\partial T} = -A_1 + \theta_1\phi_1 N + \theta_2\left(2T\mu_2 + \gamma_2 M + \mu_5 - \alpha_2(1 - u_2)\right) + \theta_3\left(\gamma_3 M - \frac{\rho\omega M}{(\omega + T)^2}\right)$$

$$-\frac{d\theta_3}{dt} = \frac{\partial H}{\partial M} = \theta_2\gamma_2 T + \theta_3\left(\gamma_3 T + \mu_3 - \frac{\rho T}{\omega + T} + (1 - u_1)\frac{\lambda_1 E}{g + E}\right)$$

$$-\frac{d\theta_4}{dt} = \frac{\partial H}{\partial E} = -A_2 + (\theta_1 - \theta_2)(1 - u_1)\lambda_1 N + \theta_3\left((1 - u_1)\frac{\lambda_3 M g}{(g + E)^2}\right) + \theta_4\mu_4$$

and with transversality conditions

$$\theta_1(T_f) = \theta_2(T_f) = \theta_3(T_f) = \theta_4(T_f) = 0$$

Therefore, we obtain (see [75])

$$0 = \frac{\partial H}{\partial u_1} = A_3 u_1 + \theta_1\lambda_1 NE - \theta_2\lambda_1 NE + \theta_3\frac{\lambda_3 ME}{g + E}$$

$$0 = \frac{\partial H}{\partial u_1} = A_4 u_2 - \theta_2\alpha_2 T$$

which in a more explicit form becomes

$$-\frac{d\theta_1}{dt} = 2\theta_1\mu_1 N + (\phi_1\theta_1 + \phi_1\theta_2)T + (\theta_1 + \theta_2)\left(1 - u_2(t)\right)\lambda_1 E - \alpha_1\theta_1$$

$$-\frac{d\theta_2}{dt} = -A_1 + \theta_1\phi_1 N + \theta_2\left(2T\mu_2 + \gamma_2 M + \mu_5 - \alpha_2(1 - u_2)\right) + \theta_3\left(\gamma_3 M - \frac{\rho\omega M}{(\omega + T)^2}\right)$$

$$-\frac{d\theta_3}{dt} = \theta_2\gamma_2 T + \theta_3\left(\gamma_3 T + \mu_3 - \frac{\rho T}{\omega + T} + (1 - u_1)\frac{\lambda_1 E}{g + E}\right)$$

$$-\frac{d\theta_4}{dt} = -A_2 + (\theta_1 - \theta_2)(1 - u_1)\lambda_1 N + \theta_3\left((1 - u_1)\frac{\lambda_3 M g}{(g + E)^2}\right) + \theta_4\mu_4$$

Thus, we obtain

$$u_1^* = \frac{1}{A_3}\left\{\theta_1\lambda_1 NE - \theta_1\lambda_1 NE - \theta_3\frac{\lambda_3 ME}{g+E}\right\} \tag{4.2.6}$$

$$u_2^* = \frac{1}{A_4}\left\{\theta_2\alpha_2 T\right\} \tag{4.2.7}$$

And we have, (4.2.6) and (4.2.7) which can also be writing as

$$u_1^* = min\left\{max\left\{0, \frac{1}{A_3}\left(\theta_2\lambda_1 N^*E^* - \theta_1\lambda_1 N^*E^* - \frac{\theta_3\lambda_3 M^*E^*}{g+E^*}\right)\right\}, 1\right\}$$

and

$$u_2^* = min\left\{max\left\{0, \frac{1}{A_4}\left(\theta_2\alpha_2 T^*\right)\right\}, 1\right\}$$

By standard control arguments involving the bounds on the controls, we conclude that

$$u_1^* = \begin{cases} 0 & if \quad Z_1^* \leq 0, \\ Z_1^* & if \quad 0 < \ Z_1^* < 1, \\ 1 & if \quad Z_1^* \geq 1, \end{cases}$$

and

$$u_2^* = \begin{cases} 0 & if \quad G_1^* \leq 0, \\ G_1^* & if \quad 0 < \ G_1^* < 1, \\ 1 & if \quad G_1^* \geq 1, \end{cases}$$

where;

$$Z_1^* = \frac{1}{A_3}\left(\theta_1\lambda_1 N^*E^* - \theta_1\lambda_1 N^*E^* - \theta_3\frac{\lambda_3 M^*E^*}{g+E^*}\right)$$

$$G_1^* = \frac{1}{A_4}(\theta_2 \alpha_2 T^*)$$

4.3 Cost-Effectiveness Analysis (CEA)

This is used to determine the cost implication of the benefit derived from the use of restricted diets (ketogenic - diet) and anti-cancer drugs. There are three types of cost-effectiveness ratios (CER) namely:

(i) Marginal Cost-Effectiveness Ratio (MCER): Which is used to determine the particular changes in cost and effect when a programme is extended.

(ii) Average Cost-Effectiveness Ratio (ACER): This is a single intervention against its baseline option (for example: no intervention or current practice). It is calculated by the ACER numerator which includes total cost produced by strategy A (anti-cancer drugs) while the ACER denominator includes total decrement of tumor cells caused by anti-cancer drugs.

(iii) Incremental Cost-Effectiveness Ratio (ICER): It is the differences between the costs and health outcomes of two different intervention strategies that compete for the same resources and it is generally described as the additional cost per additional health outcome.

In order to achieve our aim, a comparison was done between the cost and health benefit of these strategies by calculating the incremental cost-effectiveness ratio (ICER) which is known as additional cost per additional health benefit. However for the purpose of comparison, one less effective strategy is compared with a more potent intervention. The ICER numerator includes the differences in intervention costs, averted disease costs, costs of prevented cases and averted productivity losses if applicable. The ICER denominator

is the differences in health outcomes (e.g total decrement of tumor cells). It is assumed that the cost of the controls are directly proportional to the number of controls used. In addition to the model simulation outputs, the control strategies are ranked in increasing order of effectiveness in averting infection, which include: anti-cancer drugs only (Strategy A), ketogenic-diet combined with anti-cancer drugs (Strategy B) and ketogenic-diet only as a treatment (Strategy C)[4-7, 47, 96-98, 104].

4.3.1 Strategy A: Using anti-cancer drugs only.

Strategy A, involving the use of anti-cancer drugs (chemotherapy) only that is, $u_1(t)$ while setting $u_2(t) = 0$. In Figure 4.1(a), we observe that the optimal therapeutic strategy A adopts low-dose chemotherapy in the first 20 weeks and it controls the level of invaded cells population. Similarly, Figure 4.1(b) shows that the number of immune cells increases in the first 60 weeks and then starts to decrease gradually after 95 weeks while Figure 4.1(c) indicate that the level of estrogen decreases gradually after 40 weeks of anti-cancer drugs administration. We observed that, in the Figure 4.1(d) the number of normal cells population increases significantly in the first 15 weeks of the introduction of anti-cancer drugs.

However, in order to show clearly the efficacy of strategy A clearly, we define the efficacy function of treatment strategy A as

$$E_{FA} = \frac{Y_0(0) - Y_1^*(t)}{Y_0(0)} \tag{4.3.8}$$

where

$Y_0(0)$ is the initial condition (that is number of tumor cells in the tumor-present equilibrium)

$Y_1^*(0)$ is the corresponding optimal state associated with optimal controls $u_1^*(t)$ and $u_2^*(t)$.

This function measures the proportional decrease in the number of tumor cells caused by the intervention with optimal controls of strategy A.

To perform the cost-effectiveness analysis, we first determine the total decrement of tumor cells caused by strategy A during the treatment period T as

$$D_a = Y_0^*(0) - Y_1^*(T) \tag{4.3.9}$$

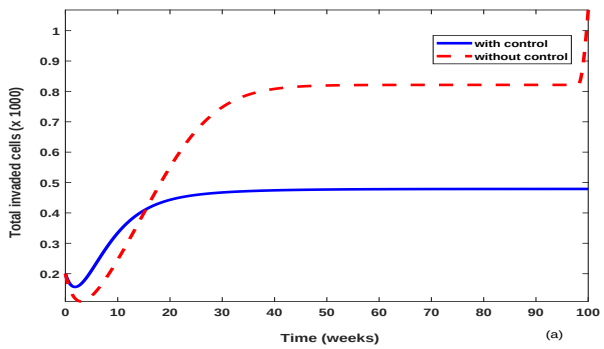
where;

$Y_1^*(T)$ represent the number of tumor cells at the end of treatment period.

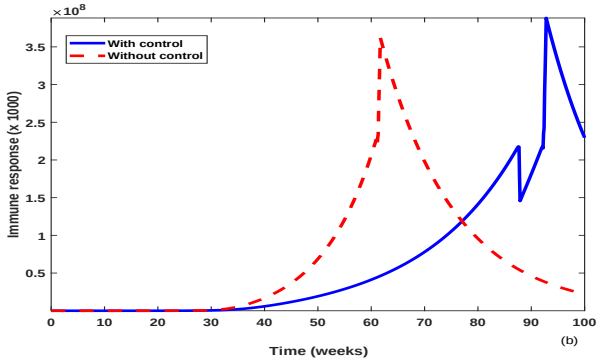
Following the method in [4, 46, 95, 97,104] we define the average cost-effectiveness ratio of treatment strategy A by:

$$ACER_A = \frac{Total\ cost\ produced\ by\ strategy\ A\ (Anti-cancer\ drugs\ only)}{Total\ decrement\ of\ tumor\ cells\ caused\ by\ (Anti-cancer\ drugs)} \tag{4.3.10}$$

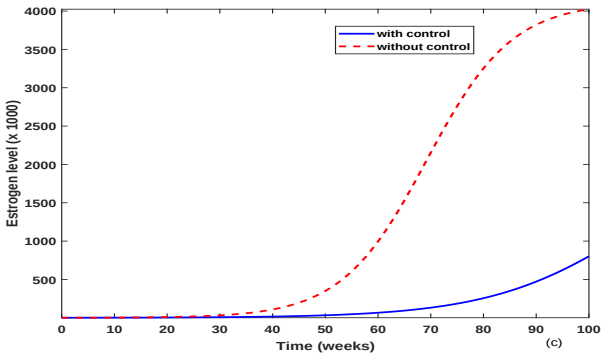
Figure 4.5 shows that the most cost-effective strategy B, followed by strategy A and, strategy C (see Table 4.2).



(a)



(b)



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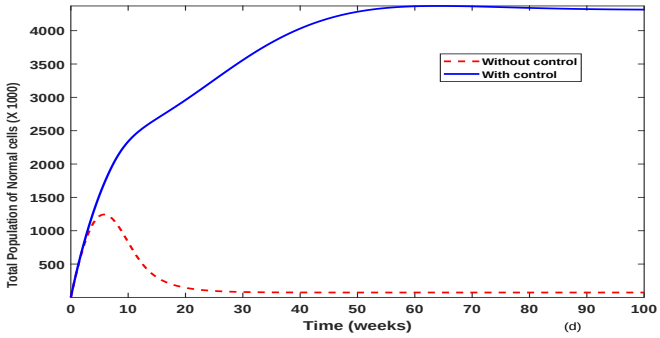
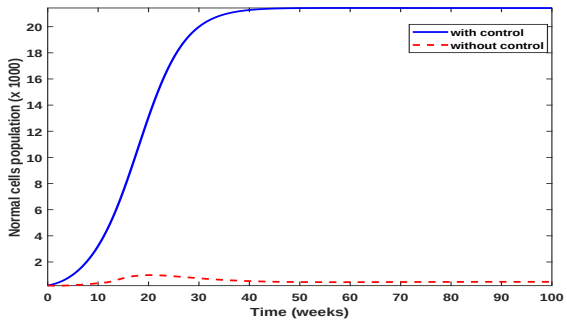


(d)

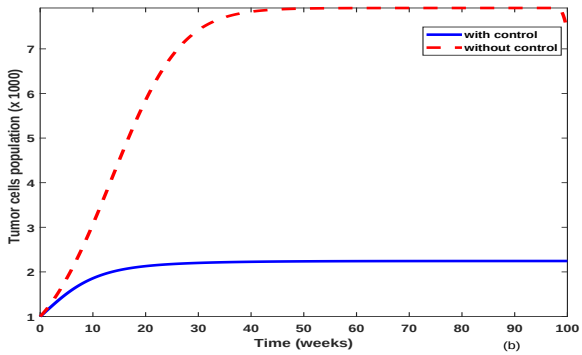
Figure 4.1: *Diagram depicting the strategy A (The use of anti-cancer drugs only as control)*

4.3.2 Strategy B: Combination of anti-cancer drugs and ketogenic-diet.

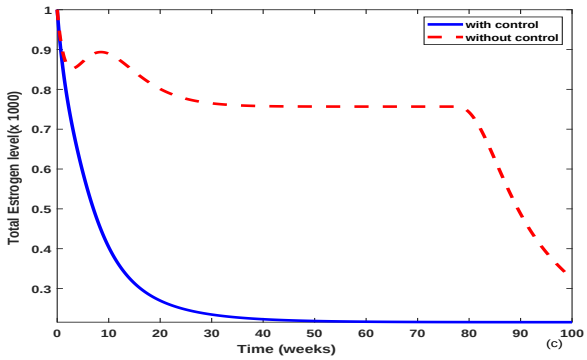
Strategy B, which involves the use of anti-cancer drugs and ketogenic-diet (i.e $u_1^*(t)$ and $u_2^*(t)$) is a gradual increase in the population of normal cells from the first week to the twentieth weeks after the introduction of both a ketogenic-diet and anti-cancer drugs as shown in Figure 4.2(a). In Figure 4.2(b), there is a drastic reduction in the population of tumor cells due to the activity of both control variables. As shown in Figure 4.2(c),



(a)



(b)



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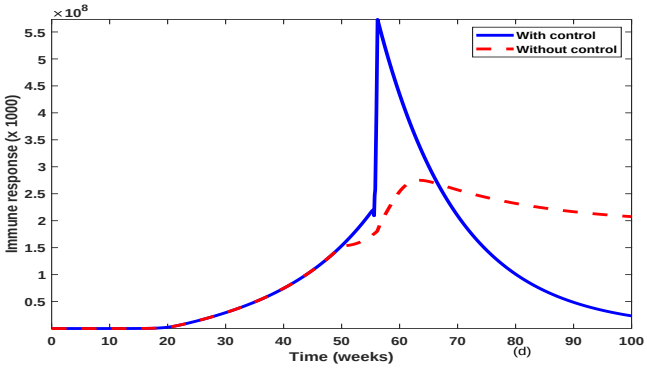


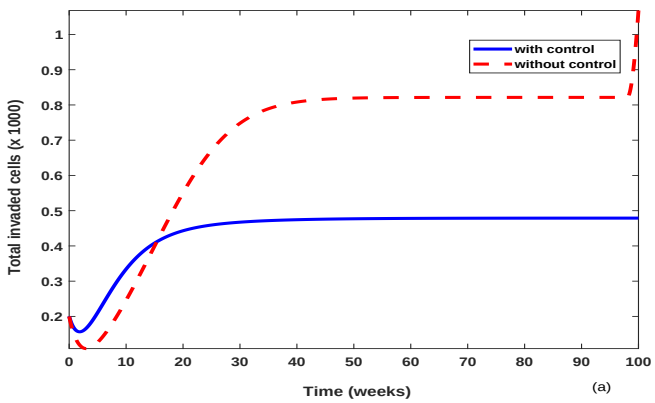
(d)

Figure 4.2: *Diagram depicting the strategy B (The combination of both anti-cancer drugs and ketogenic diet as control)*

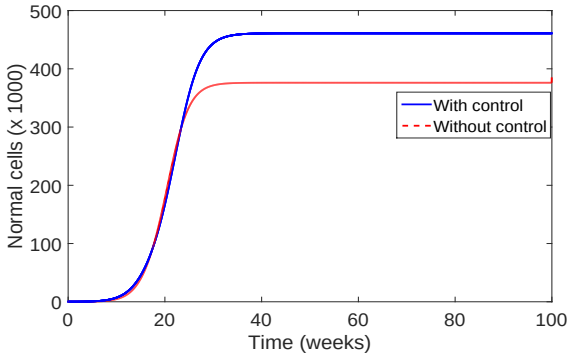
we observed significant decrease in the activity of estrogen levels after the introduction of both control strategies in the first 20 weeks. However, in Figure 4.2(d) there is a steady increase in the activity of immune response in the first 20 weeks after the introduction of combined control variables. We noticed a drastic increase in the activity of immune response around week 55 and a steady decrease after 60 weeks to prevent auto-immune diseases which may later results in such as *Neurodegenerative diseases* like Diabetes Type I , Alzheimer and so on.

4.3.3 Strategy C: Ketogenic-diet only.

Strategy C, involves the use of ketogenic diet i.e $u_2(t)$ as a control strategy reduces the population of invaded cells within the first 20 weeks as shown in Figure 4.3(a). It slightly increases the activity of normal cells as shown in Figure 4.3(b) which indicates that the, ketogenic-diet alone has a little or no effects on normal cells. In Figure 3(c), the introduction of a ketogenic-diet has a significant influence on tumor cells. The control profiles for strategies A, B and C is shown in Figure 4.3(d) and 4.3(e) and the ICER is calculated as



(a)



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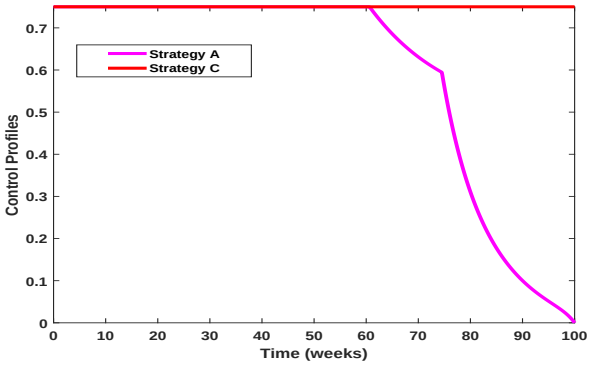

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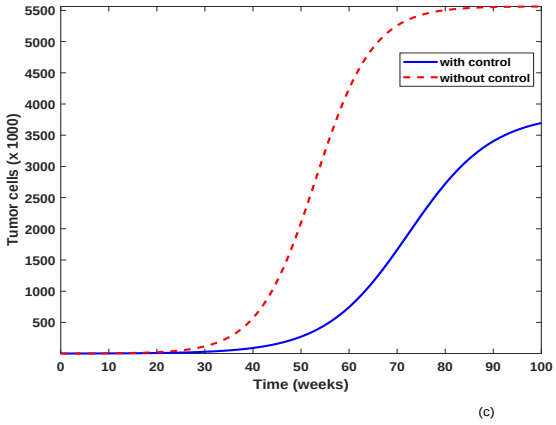

(d)

Figure 4.3: *Diagram depicting the strategy C (The use of ketogenic diet only as control)*

$$ICER = \frac{Difference\ in\ infection\ averted\ costs\ in\ strategies\ i\ and\ j}{Difference\ in\ total\ number\ of\ decrement\ of\ tumor\ cells\ in\ strategies\ i\ and\ j} \tag{4.3.11}$$

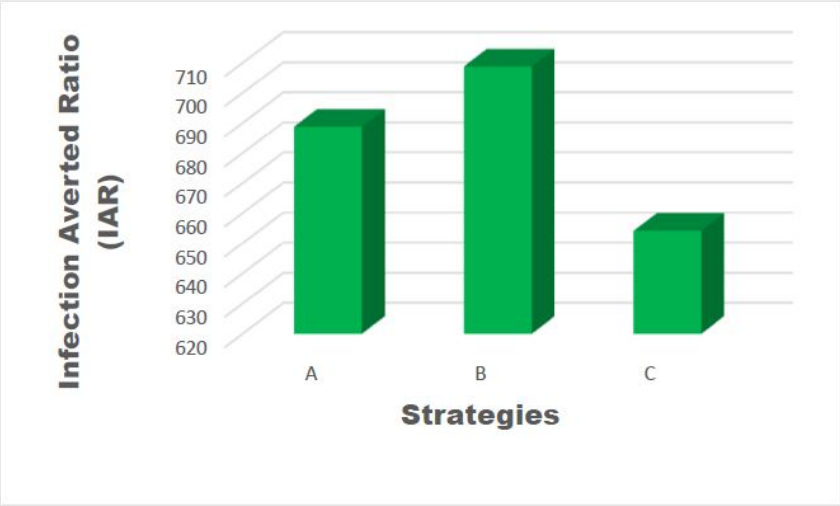

Figure 4.4: *IAR plots indicating the effect of the control strategies A, B and C*

Based on the model simulation results, we rank the strategies in order of increasing effectiveness

Table 4.1: *Total decrement of tumor cells, the total cost, IAR, ACER*

Strategies	Total decrement of tumor cells (A_i)	Total costs (\$) (J_i)	IAR	ACER
Strategy A(u_1)	327.70	\$6001.80	688.73	18.3149
Strategy B(u_1, u_2)	337.10	\$5997.90	708.79	17.7926
Strategy C(u_2)	310.90	\$6002.00	654.11	19.3052

Figure 4.4 shows the IAR for the three strategies implemented (see Table 4.2). Strategy B which is the use of anti-cancer drugs and ketogenic-diet ($u_1(t)$ and $u_2(t)$) combined was the most effective. This is followed by strategy A which involves the use of anti-cancer drugs alone $u_1(t)$ with $u_2(t) = 0$. Strategy C involving the use of ketogenic-diet only was

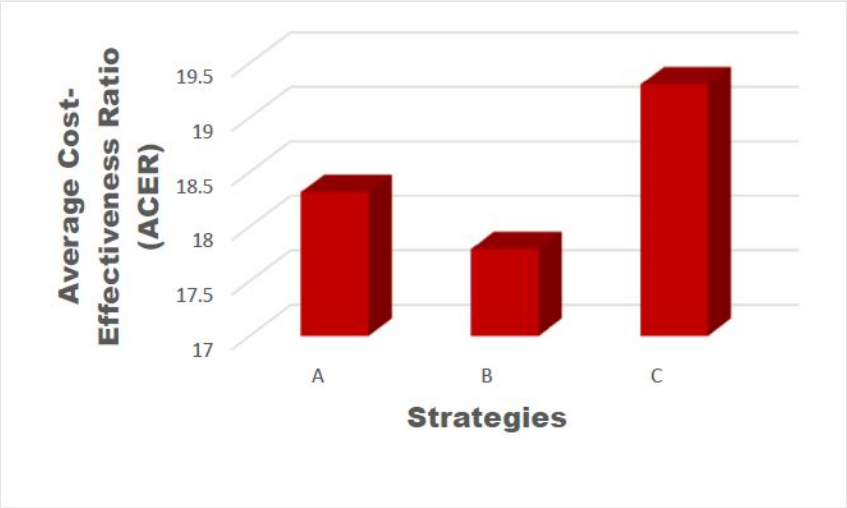

Figure 4.5: *ACER plots indicating the effect of the control strategies A, B and C* the least effective having the lowest number of infections averted(see also Table 4.2).

Table 4.2: *Incremental cost-effectiveness ratio in increasing order of total decrement of tumor cells I*

Strategies	Total decrement of tumor cells (A_i)	Total costs (\$) (J_i)	IAR	ICER
No Strategy	0	0	0	–
Strategy C(u_2)	310.90	\$6002.00	654.11	19.3052
Strategy A(u_1)	327.70	\$6001.80	688.73	-0.0119
Strategy B(u_1, u_2)	337.10	\$5997.90	708.79	-0.4149

The use of incremental cost-effectiveness ratio mentioned in Pang *et al.*[104]; Okosun *et al.* [97], and Agusto *et al.*[5] to determine the cost-effectiveness of the three different strategies. The difference between the total decrements of tumor cells and total cost for the alternative control strategies was determined using the cost-effectiveness ratio which

predicts the additional cost per additional tumor cells decrements. To find the ranking of strategies used in the increasing order of their effectiveness, we measured the total decrements of tumor cells caused by strategy i where (i = A,B,C) as shown in(Table 4.3).

The ICER, is calculated as follows:

$$\textbf{ICER}(C) = \frac{J_c}{A_c} = \frac{6002.00}{310.90} = 19.3052$$

$$\textbf{ICER}(A) = \frac{J_a - J_c}{A_a - A_c} = \frac{6001.80 - 6002.00}{327.70 - 310.90} = -0.0119$$

The comparison between strategies A and C shows a cost saving of \$11.9 for strategy A over strategy C and indicates that strategy C is more costly and less effective than strategy A. Therefore, strategy C is excluded from the set of alternatives. We exclude strategy C and similarly compare strategy A and B to get the following values of the ICER

Table 4.3: Incremental cost-effectiveness ratio in increasing order of total decrements of tumor cells II

Strategies	Total decrements of tumor cells (A_i)	Total costs (\$) (J_i)	IAR	ICER
Strategy A(u_1)	327.70	\$6001.80	688.73	-0.0119
Strategy B(u_1, u_2)	337.10	\$5997.90	708.79	-0.4149

$$\textbf{ICER}(A) = \frac{J_a}{A_a} = \frac{6001.80}{327.70} = 18.3149$$

$$\textbf{ICER}(B) = \frac{J_b - J_a}{A_b - A_a} = \frac{5997.90 - 6001.80}{337.10 - 327.70} = -0.4149$$

Comparing between strategies A and B shows a cost saving of \$414.8936 for strategy B over strategy A. Similarly, the negative ICER for strategy B indicates that strategy B is strongly dominant. That is, strategy A is more expensive and less effective than strategy B. Therefore, strategy A, is excluded from the set of alternatives so that it does not consume limited resources. (see Table 4.3 and 4.4)

Table 4.4: *Incremental cost-effectiveness ratio in increasing order of total decrements of tumor cells III*

Strategies	Total decrements of tumor cells (A_i)	Total costs (\$) (J_i)	IAR	ICER
Strategy B(u_1, u_2)	337.10	\$5997.90	708.79	- 0.41489
Strategy A(u_1)	327.70	\$6001.80	688.73	18.3149

With this result, we therefore conclude that strategy B (a combination of treatment of anti-cancer drugs (u_1) and Ketogenic-diet (u_2)) with the least ICER is a more cost-effective strategy than strategy A for treating breast cancer. This result agree with the results obtained in Figure 4.6

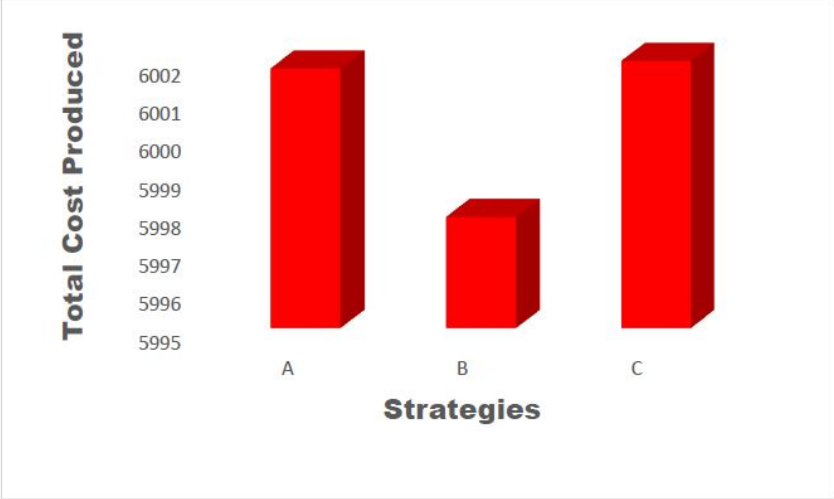

Figure 4.6: *The objective functional indicating the effect of the control strategies A, B and C*

It is clearly shown that strategies A and B had the highest number of tumor decrements while strategy C performed less (see Figure 4.7 below).

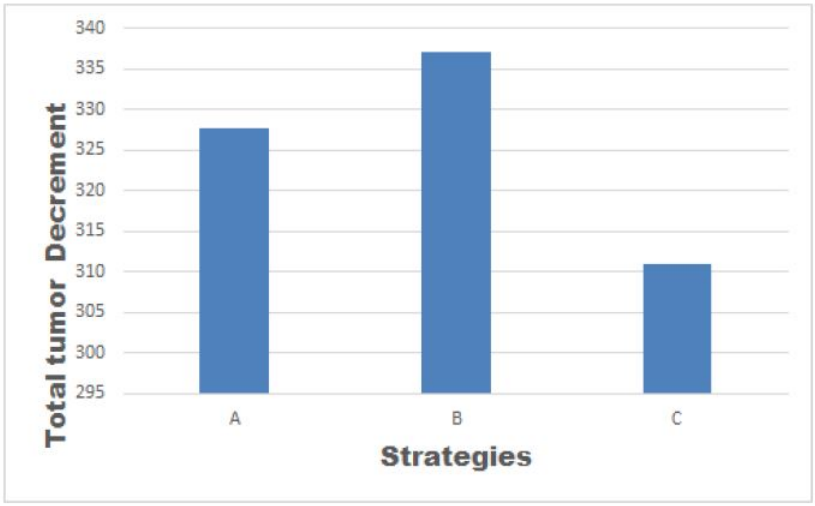

Figure 4.7: *The objective functional indicating the effect of the control strategies A, B and C*

The weights on cost considered here are for illustration purposes. More realistic results will be obtained if real data on the cost of the implementation of control strategies are available because time to treatment and some direct and indirect costs need to be considered in real life scenario.

Chapter 5

Conclusion

In this study, we investigated the impact of a nutritional diet (ketogenic diet) and anti-cancer drugs such as *Tamoxifen* in the treatment breast cancer. We determined a cost-effective and appropriate optimal control strategy for tumor cells elimination or control. We also derived and analysed a deterministic model for breast cancer and performed an optimal control analysis of the model. We began with a detailed background on breast cancer and cancer biology in Chapter 1. We then discussed the most common types of cancer and presented graphics showing the numbers of new breast cancer cases occurring worldwide. Chapter 2 highlighted some factors responsible for breast cancer and offered a limited of the literature reviews on the breast cancer models such as the tumor growth model, Angiogenesis model, and the treatment response model. A figure depicting the genesis of cancer formation was presented. Furthermore, the study explored the use of Tamoxifene as an anti-cancer drug as well as the use of a ketogenic diet as (adjuvant therapy).

The formulation of the breast cancer model was presented in Chapter 3. The qualitative analysis of the four compartment model was shown to be epidemiologically feasible and mathematically well-posed. The researcher investigated the existence and stability of

the treatment tumor-free equilibrium points (TTFE) and the next generation matrix technique was applied to drive the invasion reproduction number R_i and used it to show the treatment tumor-free equilibrium (TTFE) which is locally asymptotically stable whenever $R_i < 1$, and unstable otherwise. However, the possibility of the occurrence of backward bifurcation where both equilibria co-exists as the invasion reproduction number crosses unity was investigated using the center manifold theory. Moreover, to extend the stability analysis of the model beyond small region near the equilibria, we explored the global dynamical behavior of the model around the equilibria. At this point, a suitable Lyapunov function was constructed at TTFE to prove that the model is globally asymptotically stable at a threshold parameter less than unity and $k = 1$. Furthermore, a sensitivity analysis was carried out with a view to examining the factors most responsible for the tumor cells growth and the spread of cancer disease. The sensitivity index of the invasion reproduction number relative to the associated parameters were obtained. It was revealed that the natural death rate of estrogen, among other parameters with positive sensitivity index, has major effects on the cancer cells. On the other hand, the natural death rate of the normal cells was shown to be most sensitive to the invasion reproduction number of the model among the parameters with negative sensitivity indices.

To complement the sensitivity analysis index, we ran an uncertainty analysis on all non-dimensional system parameters in the system using the Latin Hypercube Sampling (LHS) and Partial Rank Correlation Coefficient (PRCC). Numerical simulations of the model was carried-out to validate the analytical results. In Chapter 4, two time dependent controls namely, anti-cancer drugs ($u_1(t)$) and ketogenic diets ($u_2(t)$) were introduced into the model for the treatment. The existence of an optimal control was established with the application of Pontryagin's Maximum Principle. This was used to explain the tumor-to-therapy trade-off following the approach adopted by Perko [109] and De pillis *et al.*

[34]. It required an analysis of the super-solutions (the upper bounds on solutions) of the system (3.1.5). Furthermore, we derived the conditions for the cancer cells eradication as well as the necessary conditions for disease control when eradication is not achievable. We also investigated the cost-effectiveness of the controls to determine the most effective strategy to eradicate tumor cells with minimum costs. However, the weights on cost considered here are for illustration purposes. Using the decrement of tumor cells and the incremental cost-effectiveness ratio (ICER), the total costs for using anti-cancer drugs only to treat a breast cancer patient was found to be \$6001.80 requiring 20 weeks to be sustained, even though it is not effective for tumor cells clearance from the body. Also, the total costs of using a ketogenic diet alone is \$6002.00, with a time requirement of, 55 weeks. However, the costs for using all controls at the same time, \$5997.90 and it needs about 100% of the anti-cancer drugs and 50% of ketogenic diet for 15 weeks. This implies, hypothetically, that the strategy will be effective in eradicating the disease. It should be noted, as earlier stated, that more realistic results will be obtained if real data on the cost of the implementation of control strategies are available because time to treatment and some direct and indirect costs need to be considered in real life scenario.

5.1 Recommendations

Based on the quantitative and qualitative results of the breast cancer model analysis, the following recommendations are made towards increasing a tumor-free cell population:

- Efforts should be made to reduce the treatment induced invasion reproduction number of breast cancer model since the sensitivity analysis has helped to identify that α_2 (tumor growth rate) and d (ketogenic-diet) are the most sensitive parameters. Medically, it is advisable to find a way of reducing the tumor growth by monitoring

level of estrogen in the body system; and to encourage the patients on ketogenic-diet for inhibition on tumor cells population.

- The combination of the therapies will reduce or eliminate the tumor cells from the body system, hence use of ketogenic diet and anti-cancer drugs should be encouraged;

- Ketoacidosis must be avoided when taking ketogenic-diet; hence the patients must adhere to advice of nutritionist advice;

- The ministry of health and other policy makers should create awareness and sensitize the public, especially breast cancer patients, on the use of diet (especially ketogenic diet) in the treatment of cancer. It is hoped that this will foster recovery and in turn reduce national economic burden in treating breast cancer.

5.2 Limitations of the study

The present study did not explore the possibility of the resistance of tumor cells to therapy. We assumed that $Tamoxifen$ is highly effective when combined with a ketogenic diet in the treatment of breast cancer. Also, the study, in order to reduce the complexity of the model, did not take all the possible dynamics of breast cancer into account. For instance, such other risk factors as genetics and the environmental were not considered. The major challenge we encountered during this study was the fact that we were unable to obtain data for breast cancer treatment to validate the model.

5.3 Areas of further study

In view of the limitations outlined above, it is suggested that the stochastic version of the breast cancer model may be considered to explore the possibility of randomness which may exist in the dynamics and spread of tumor cells in the population. The role and treatment of co-infections (for example, breast cancer and cardiovascular diseases or diabetes) in the dynamics of non-communicable diseases have become of global concern and should be considered for future research. The study also suggests that linear control, using the switching function to investigate Bang-bang control (i.e Bang-bang solutions also arise when the Hamiltonian is linear in the control variable; application of Pontryagin's minimum or maximum principle will then lead to pushing the control to its upper or lower bound depending on the sign of the co-efficient of U in the Hamiltonia) be considered for future study.

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