ΣΧΟΛΗ ΘΕΤΙΚΩΝ ΕΠΙΣΤΗΜΩΝ
ΤΜΗΜΑ ΜΑΘΗΜΑΤΙΚΩΝ

MODELLING AND OPTIMAL CONTROL METHODS FOR BREAST CANCER THERAPY

ΕΝΑ ΜΑΘΗΜΑΤΙΚΟ ΜΟΝΤΕΛΟ ΓΙΑ ΤΟΝ ΚΑΡΚΙΝΟ ΤΟΥ ΜΑΣΤΟΥ ΚΑΙ ΜΕΘΟΔΟΙ ΒΕΛΤΙΣΤΟΥ ΕΛΕΓΧΟΥ ΓΙΑ ΤΗ ΘΕΡΑΠΕΙΑ

ΑΓΓΕΛΟΣ ΓΚΙΚΑΣ

Διπλωματική Διατριβή για την απόκτηση του Μεταπτυχιακού Τιτλου
Σπουδών στα Εφαρμοσμένα Μαθηματικά

ΕΠΙΒΛΕΠΩΝ ΚΑΘΗΓΗΤΗΣ

ΓΕΩΡΓΙΟΣ ΧΑΛΙΚΙΑΣ - Αναπληρωτής Καθηγητής τμήματος
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ABSTRACT

In this master thesis we describe a mathematical model for breast cancer based on a system of ordinary differential equations in the presence of chemotherapy treatment and ketogenic diet. Analytic methods are being used to examine the stability of the model. Moreover we seek out the sufficient conditions for the parameter values to test cancer tumor persistence when different therapies are being applied. Optimal control theory is being used adapted to verify the optimal drug dosage as an input control of the system therapies,in order to minimize the population of tumor cells under different control combinations of cure strategies utalizing the maximum principle of Pontryagin. Last but not least, numerical simulations verify the theoritical results for both the non linear and the linear model using LQR and H_∞ algorithms.

ΠΕΡΙΛΗΨΗ

Στόχος αυτής της διπλωματικής διατρίβής, είναι η μελέτη ενός μαθηματικού μοντέλου για τον καρκίνο του μαστού. Το μοντέλο αυτό αποτελείται από ένα σύστημα Συνήθων Διαφορικών Εξισώσεων, το οποίο μελετάμε όταν εφαρμόζεται χημειοθεραπεία ή κετονική δίαιτα. Αναλυτικές μέθοδοι χρησιμοποιούνται για τη μελέτη ευστάθειας του μοντέλου καθώς και την εύρεση κατάλληλων συνθηκών για τις παραμέτρους ώστε να ελεγχθεί η εξαπλωση του καρκίνου κάτω από την χρησιμοποίηση διαφορετικών μεθόδων θεραπείας. Η θεωρία βέλτιστου ελέγχου καθώς και η αρχή του Pontryagin εφαρμόζεται για να βρεθεί η βέλτιστη παροχή φαρμάκου που χρησιμοποιείται ως εισαγωγικός έλεγχος στο σύστημα θεραπειών, έτσι ώστε να ελαχιστοποιηθεί ο πληθυσμός των κυττάρων του καρκινικού όγκου, όταν χρησιμοποιούμε διαφορετικούς συνδυασμούς θεραπειών. Τέλος, με αριθμητική προσωμοίωση, επιβεβαιώνουμε τα θεωρητικά δεδομένα,τοσο για το μη γραμμικο μοντελο οσο και για το γραμμικο χρησιμοποιωντας 2 μεθοδους την LQR και τον αλγοριθμο H_∞.

ΤΡΙΜΕΛΗΣ ΕΠΙΤΡΟΠΗ

ΕΠΙΒΛΕΠΩΝ

ΓΕΩΡΓΙΟΣ ΧΑΛΙΚΙΑΣ - Αναπληρωτής Καθηγητής τμήματος Μαθηματικών του Ε.Κ.Π.Α.

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First of all i would like to thank my family colleagues and professors for their support during my studies, my supervisor professor G. Halikias for his precious help on my masterstr thesis. This work is dedicated to all patients who suffer from breast cancer, and other types of cancer.

Contents

CHAPTER 1

Biology of Cancer

SECTION 1.1

Cell Circle

Cell in an adult organism can be viewed as a steady-state system. The DNA is constantly read out into a particular set of mRNA's, which specify a particular set of proteins. As these proteins function, they are also being degraded and replaced by new ones, and the system is so balanced that the cell neither grows, shrinks, nor changes its function. Nevertheless, cell circle is not that static but a dynamic replication program.The cell-replication program is encoded in the DNA and executed by proteins. This program usually involves a period of cell growth, during which proteins are made and DNA is replicated, followed by cell division, when a cell divides into two daughter cells. Most eukaryotic cells live according to an internal clock; that is, they proceed through a sequence of phases, called the cell cycle, during which DNA is duplicated during the synthesis (S) phase and the copies are distributed to opposite ends of the cell during mitotic (M) phase (see figure below). Progress along the cycle is controlled at key checkpoints, which monitor the status of a cell, for instance, the internal amount of DNA or the presence of extracellular nutrients. When certain conditions are met, the cell proceeds to the next checkpoint. The cycle begins after the cell divides into two daughter cells, each containing an identical copy of the parental cell's genetic material. Whether a given cell will grow and divide is a highly regulated decision of the body, assuring that an adult organism replaces worn out cells or makes more cells in response to a new need.

In eukaryotic cells, or cells with a nucleus, the stages of the cell cycle are divided into two major phases:

- Interphase.
- Mitotic (M) phase.

During interphase, the cell grows and makes a copy of its DNA. During the mitotic (M) phase, the cell separates its DNA into two sets and divides its cytoplasm, forming two new cells.

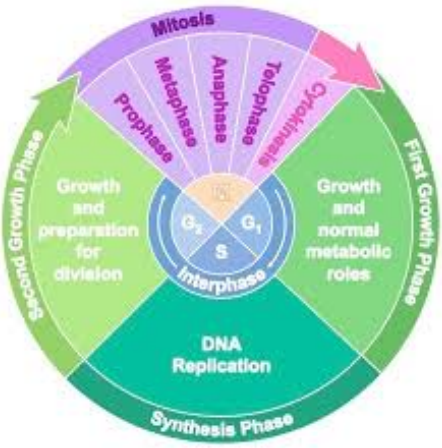
Interphase

1. G_1 phase.
    - During the G_1 phase, also called the first gap phase, the cell grows physically larger, copies organelles, and makes the molecular building blocks it will need in later steps.
2. S phase.
    - In S phase, the cell synthesizes a complete copy of the DNA in its nucleus. It also duplicates a microtubule-organizing structure called the centrosome. The centrosomes help separate DNA during M phase.
3. G_2 phase.
    - During the second G phase,the cell grows more, makes proteins and organelles, and begins to reorganize its contents in preparation for mitosis. G_2 phase ends when mitosis begins.

M phase

During the mitotic (M) phase, the cell divides its copied DNA and cytoplasm to make two new cells. M phase involves two distinct division-related processes:

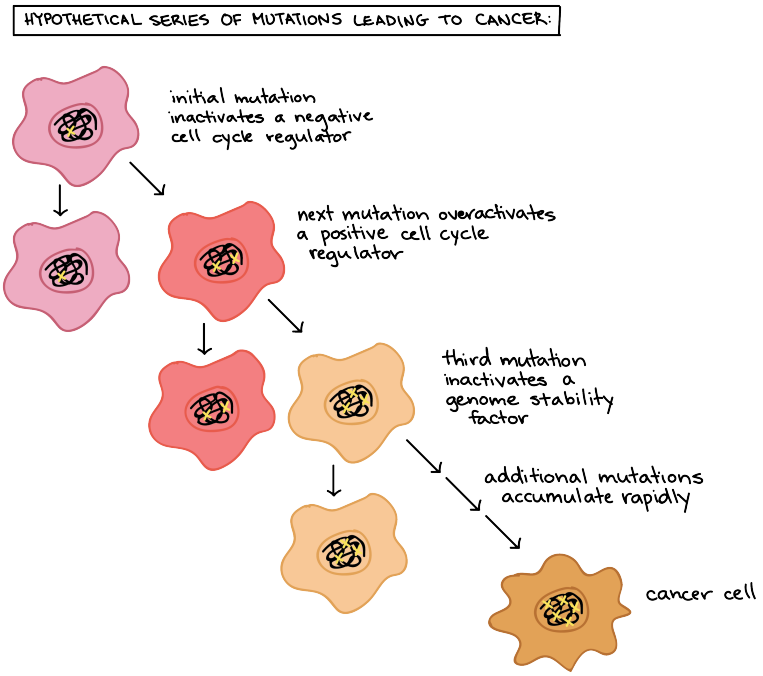
1. Mitosis
    - In mitosis, the nuclear DNA of the cell condenses into visible chromosomes and is pulled apart by the mitotic spindle, a specialized structure made out of microtubules. Mitosis takes place in four stages:prophase(sometimes divided into early prophase and prometaphase), metaphase, anaphase, and telophase.
2. Cytokinesis
    - In cytokinesis, the cytoplasm of the cell is split in two, making two new cells. Cytokinesis usually begins just as mitosis is ending, with a little overlap. The cell cycling process is carefully regulated and responds to the specific needs of a certain tissue or cell type. Normally, in adult tissue, there is a delicate balance between cell death (programmed cell death or apoptosis) and proliferation (cell division) producing a steady state. Disruption of this equilibrium by loss of cell cycle control may eventually lead to cancer.



SECTION 1.2

Cancer Development

Cancer development Cancer is a disease in which some of the body's cells begin to divide without stopping and spread into surrounding tissues. Cells can experience uncontrolled growth if there are mutations to DNA, and therefore, alterations to the genes involved in cell division. They have many different mechanisms to restrict cell division, repair DNA damage, and prevent the development of cancer. Because of this, it's thought that cancer develops in a multi-step process, in which multiple mechanisms must fail before a critical mass is reached and cells become cancerous. Specifically, most cancers arise as cells acquire a series of mutations (changes in DNA) that make them divide more quickly, escape internal and external controls on division, and avoid programmed cell death. Firstly a cell might lose activity of a cell cycle inhibitor, an event that would make the cell's descendants divide a little more rapidly.It's unlikely that they would be cancerous, but they might form a benign tumor, a mass of cells that divide too much but don't have the potential to invade other tissues (metastasize).Over time, a mutation might take place in one of the descendant cells, causing increased activity of a positive cell cycle regulator. The mutation might not cause cancer by itself either, but the offspring of this cell would divide even faster, creating a larger pool of cells in which a third mutation could take place. Eventually, one cell might gain enough mutations to take on the characteristics of a cancer cell and give rise to a malignant tumor, a group of cells that divide excessively and can invade other tissues.



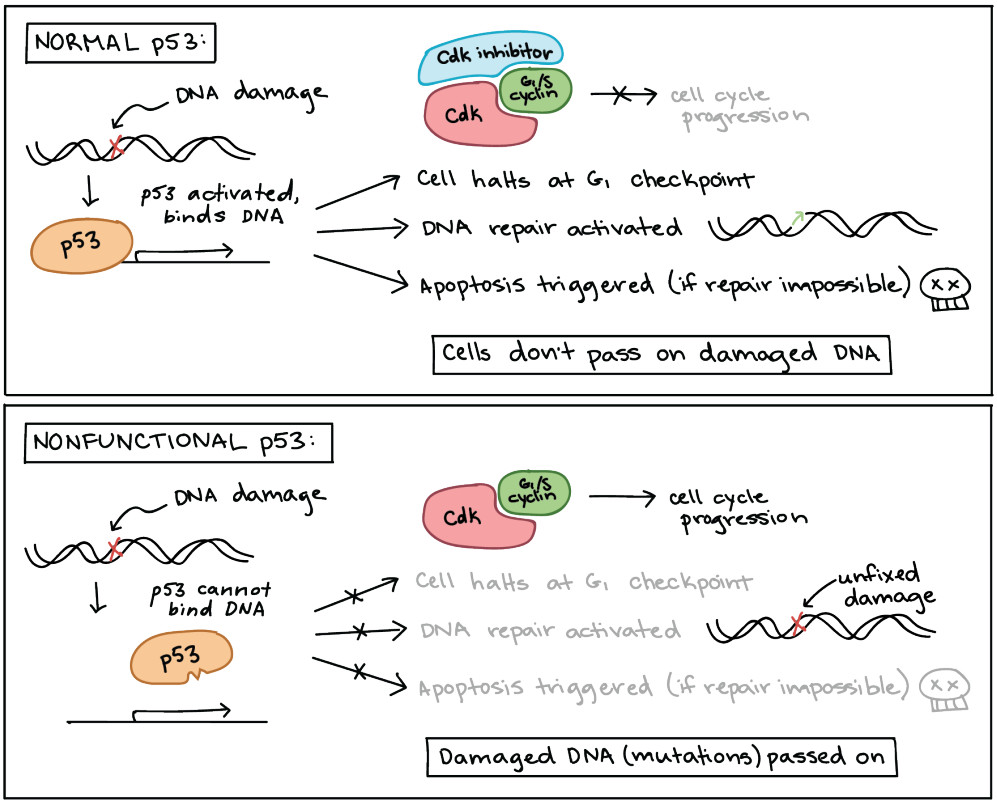
Four key types of gene are responsible for the cell division process:

- suicide genes which control apoptosis and tell the cell to kill itself if something goes wrong
- DNA-repair genes which instruct a cell to repair damaged DNA.
- oncogenes oncogenes tell cells when to divide.

  Positive cell cycle regulators may be overactive in cancer. For instance, a growth factor receptor may send signals even when growth factors are not there, or a cyclin may be expressed at abnormally high levels. The overactive (cancer-promoting) forms of these genes are called oncogenes, while the normal, not-yet-mutated forms are called proto-oncogenes. This naming system reflects that a normal proto-oncogene can turn into an oncogene if it mutates in a way that increases its activity.

- tumor suppressor genes tell cells when not to divide.

  Negative regulators of the cell cycle may be less active (or even nonfunctional) in cancer cells. For instance, a protein that halts cell cycle progression in response to DNA damage may no longer sense damage or trigger a response. Genes that normally block cell cycle progression are known as tumor suppressors. Tumor suppressors prevent the formation of cancerous tumors when they are working correctly, and tumors may form when they mutate so they no longer work. One of the most important tumor suppressors is tumor protein p_{53} , which plays a key role in the cellular response to DNA damage. p_{53} acts primarily at the checkpoint (controlling the G_1 to S transition), where it blocks cell cycle progression in response to damaged DNA and other unfavorable conditons. When a cell's DNA is damaged, a sensor protein activates p_{53} , which halts the cell cycle at the G_1 checkpoint by triggering production of a cell-cycle inhibitor. This pause buys time for DNA repair, which also depends on p, whose second job is to activate DNA repair enzymes. If the damage is fixed, p will release the cell, allowing it to continue through the cell cycle. If the damage is not fixable, p will play its third and final role: triggering apoptosis (programmed cell death) so that damaged DNA is not passed on.



In cancer cells, p_{53} is often missing, nonfunctional, or less active than normal. For example, many cancerous tumors have a mutant form of p_{53} that can no longer bind DNA. Since p_{53} acts by binding to target genes and activating their transcription, the non-binding mutant protein is unable to do its job. When p_{53} is defective, a cell with damaged DNA may proceed with cell division. The daughter cells of such a division are likely to inherit mutations due to the unrepaired DNA of the mother cell. Over generations, cells with faulty p_53 tend to accumulate mutations, some of which may turn proto-oncogenes to oncogenes or inactivate other tumor suppressors. p_{53} is the gene most commonly mutated in human cancers, and cancer cells without p_{53} mutations likely inactivate p_{53} through other mechanisms (e.g., increased activity of the proteins that cause p_{53} to be recycled)

SECTION 1.3

Breast Cancer

In this thesis we will study a model for breast cancer

Breast Cancer

Breast cancer starts when cells in the breast begin to grow out of control,forming a tumor. The tumor is malignant (cancer) if the cells can grow into (invade) surrounding tissues or spread (metastasize) to distant areas of the body. Breast cancer occurs almost entirely in women, but men can get breast cancer, too.It is estimated that 1 out of 8 women will develop breast cancer during their lifetime. If left untreated, malignant cells may eventually spread beyond the original tumor to other parts of the body, a process called metastasis which eventually causes death. Breast cancer is the most commonly occurring cancer in women and the second most common cancer overall. There were over 2 million new cases in 2018. The mortality rate from cancer is projected to continue to rise, with an estimated 13 million deaths by 2030.

Causes of Breast Cancer

Researchers have identified hormonal, lifestyle and environmental factors that may increase your risk of breast cancer. But it's not clear why some people who have no risk factors develop cancer, yet other people with risk factors never do. It's likely that breast cancer is caused by a complex interaction of your genetic makeup and your environment. Several factors are associated with an increased risk of breast cancer. First of all women are much more likely than men are to develop breast cancer.Breast cancer is more likely to occur as age increases.Moreover if a woman had a breast biopsy that found lobular carcinoma in situ (LCIS) or atypical hyperplasia of the breast, you have an increased risk of breast cancer. Moreover women who have a history of breast cancer have greater chance of suffering from the disease because of the genes inherited from their ancestors.Certain gene mutations that increase the risk of breast cancer can be passed from parents to children. The most well-known gene mutations are referred to as BRCA1 and BRCA2. These genes can greatly increase your risk of breast cancer and other cancers, but they don't make cancer inevitable. Last but not least, exposure to high dosage of radiations also increase chance of breast cancer, while obesity and other abuses such as alcohol and drug overconsumtion also increase the likelihood.

Types of breast cancer

Breast cancers can start from different parts of the breast. Most breast cancers begin in the ducts that carry milk to the nipple (ductal cancers). Some start in the glands that make breast milk (lobular cancers). There are also other types of breast cancer that are less common. A small number of cancers start in other tissues in the breast. These cancers are called sarcomas and lymphomas and are not really thought of as breast cancers. Although many types of breast cancer can cause a lump in the breast, not all do. Many breast cancers are found on screening mammograms which can detect cancers at an earlier stage, often before they can be felt, and before symptoms develop. There are other symptoms of breast cancer you should watch for and report to a health care provider. It's also important that most breast lumps are benign and not cancer (malignant). Non-cancerous breast tumors are abnormal growths, but they do not spread outside of the breast and they are not life threatening. But some benign breast lumps can increase a woman's risk of getting breast cancer. Any breast lump or change needs to be checked by a health care professional to determine if it is benign or malignant (cancer) and if it might affect your future cancer risk.

Treatment methods

- radiation therapy
- surgery
- biological therapy, or targeted drug therapy
- hormone therapy
- chemotherapy

Direct Therapies

Radiation therapy

Controlled doses of radiation are targeted at the tumor to destroy the cancer cells. Used from around a month after surgery, along with chemotherapy, it can kill any remaining cancer cells.Each session lasts a few minutes, and the patient may need three to five sessions per week for 3 to 6 weeks, depending on the aim and the extent of the cancer.The type of breast cancer will dictate what type of radiation therapy, if any, is most suitable. Adverse effects include fatigue,lymphedema, darkening of the breast skin, and irritation of the breast skin.

Chemotherapy

Medications known as cytotoxic drugs may be used to kill cancer cells, if there is a high risk of recurrence or spread. This is called adjuvant chemotherapy.If the tumor is large, chemotherapy may be administered before surgery to shrink the tumor and make its removal easier. This is called neo-adjuvant chemotherapy.Chemotherapy can also treat cancer that has metastasized, or spread to other parts of the body, and it can reduce some symptoms, especially in the later stages.It may be used to reduce estrogen production, as estrogen can encourage the growth of some breast cancers. The most common drug used in chemotherapy is Tamoxifen which is an anti-estrogen agent. Adverse effects include nausea, vomiting, loss of appetite, fatigue, sore mouth, hair loss, and a slightly higher susceptibility to infections.Other Medications can help control many of these.

Hormone blocking therapy

Hormone blocking therapy is used to prevent recurrence in hormone-sensitive breast cancers. These are often referred to as estrogen receptive (ER) positive and progesterone receptor (PR) positive cancers.Hormone blocking therapy is normally used after surgery, but it may sometimes be used beforehand to shrink the tumor.It may be the only option for patients who cannot undergo surgery, chemotherapy, or radiotherapy. The effects normally last for up to 5 years after surgery. The treatment will have no effect on cancers that are not sensitive to hormones. Some of the common hormone therapies are drugs such as tamoxifen,use of aromatase inhibitors ovarian ablation or suppression and a luteinising hormone-releasing hormone agonist (LHRHa) drug called Goserelin, to suppress the ovaries.

The Ketogenic Diet (KD), a high-fat/low-carbohydrate/adequate-protein diet, has recently been proposed as an adjuvant therapy in cancer treatment . KDs target the Warburg effect, a biochemical phenomenon in which cancer cells predominantly utilize glycolysis instead of oxidative phosphorylation to produce ATP. In this regard, these dietary modifications might be expected to reduce tumor size and growth rate which depend on glucose as an energy source during anaerobic glycolysis. Also the inability of ketone bodies metabolization due to various deficiencies in mitochondrial enzymes, is one of the metabolic

modification found in malignant cells. Further, ketone bodies possibly result in a decreasing the supply of gluconeogenic precursors by restriction of the branch chain amino acids oxidation. Thus, the rationale in providing a fat-rich, low-carbohydrate diet in cancer therapy is to reduce circulating glucose levels and induce ketosis such that cancer cells are starved of energy while normal cells adapt their metabolism to use ketone bodies and survive. Furthermore, by reducing blood glucose also levels of insulin and insulin-like growth factor, which are important drivers of cancer cell proliferation, drop.

CHAPTER 2

Thesis Brief Explanation

SECTION 2.1

System formulation

Culling useful aspects of previously developed mathematical models, we combine the following features in this model:

- competition terms
- immune response
- estrogen dependence

Tumor cells population, CD8+T cell population, and Natural Killer cell population competed in a way almost similar to that suggested by Lotka-Volterra's competition models Cell populations have also been known to compete for nutrients and natural cell requirements resulting in nutrient consumption models. Tumor cell proliferation and death are considered to be dependent on only one generic nutrient (most often oxygen). However, some consider the effect of several nutrients and pH on the cell population.

Normal cells : Based on many previous useful models done on tumor growth we here consider a model which subdivides the total population N(t) of cells of the breast tissue at any given time t into three groups which include normal or host cells, tumor cells and immune cells classes. The normal cells class, denoted by N(t) is in form of epithelial cells that make up the breast tissue. The cells differentiate and die normally as they have unaltered DNA which controls all cell actions. We assumed that the normal and tumor cells compete for space and resources in a small volume. The normal cells grow exponentially at a per capita growth rate of a_1 as a result of DNA initiation. μ_1 is the depletion rate resulting from competition for resources such as nutrients and oxygen or the accumulation of substances released from cell metabolism within themselves.

Tumor cells : Tumor cells, denoted by T at any time t, represent a class of breast cancer cells with damaged DNA. Actually, there are about 51 breast cancer cell lines which mirror the 145 primary breast tumors . These can be classified into 2 major branches, the luminal, which has estrogen receptors (ESR1 positive), and basal-like, without estrogen receptors (ESR1 negative). In this thesis we assume a homogeneous luminal type of cancer cells . Several tumor growth laws have been proposed which include an exponential growth, Gompertz growth and logistic growth. We assume the presence of a small tumor mass, that is, a tumor size that is close to zero relative to carrying capacity, and therefore the choice of growth law does not significantly affect the qualitative behaviour of the model since they only differ for large tumor sizes. We therefore assume an exponential growth of tumor cells with per capita rate of a_2 which results from the damaged DNA. Analogously μ_2 is a factor restricting their growth competition for space and food within themselves. The normal cells N(t) and tumor cells T(t) also compete for space and natural cell requirements like oxygen as they are supplied by the blood vessels. We assume cancer cells have uncontrolled cycle than the normal cells due to changed DNA which makes them fail to regulate a cell cycle and thus their interaction with normal cells results in an inhibitory effect on normal cells at rate ϕ_1

Immune system cells : The model includes an immune cells class, M(t), in form of Natural Killer (NK) cells and CD8+ T cells. Their growth 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 system does not necessarily imply that the tumor has completely escaped active immunosurveillance. Although 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 the tumor cell population and the eventual development into a tumor. The population of immune cells is considered to be outside of the

system and we assume a background level of NK cells, even in the absence of tumor with CD8+ T cells only present as a result of activation. It is therefore reasonable to assume a constant source, s, of the immune cells from the thymus gland. Furthermore, in the absence of any tumor, the cells will die off naturally at a per capita rate of μ_3 . The presence of tumor cells stimulates the immune response resulting in growth of immune cells. This is represented by a positive nonlinear growth term for immune cells which as a function of T(t), where ϱ is the immune response rate and ω is the immune threshold rate, which is inversely proportional to the steepness of the immune response curve. Thus immune cell proliferation is controlled and will never result in immune crowding which might in turn be detected as a threat. Furthermore, the reaction of immune cells and tumor cells can result in either the death of tumor cells at a rate μ_3 or the inactivation of the immune cells, with γ_3 as the interaction coefficient.

Estrogen dependance : Finally, we considered estrogen compartment denoted by E(t)in the form of 17-β estradiol to the dynamics of breast cancer cells. Estrogen is a female steroid hormone that is produced by the ovaries in lesser amounts, and by the adrenal cortex, placenta and male testes. The assumption here is that as women take hormonal birth control methods they increase a constant level of the estrogen hormonal level. We therefore assume a constant source, π of 17-β estradiol, the primary biologically most active estrogen which is all the estrogen in the system at any given time. Human breast cells, the epithelial cells, contain estrogen receptors termed estrogen receptor-1 (EP-α)and estrogen receptor-2 (EP-β). These are intracellular receptors, which when activated by ligand binding, translocate to the nucleus and act as transcription factors by binding to DNA in the promoter regions of target genes. Both EP-α and EP-β bind 17-β estradiol in the nucleus of the cell with similar affinity and act as transcription factors to regulate gene expression. This will lead to gene transactivation which may also result from tethering of estrogen receptors to nuclear transcription factors such as NFYB and SPI .We assumed that the majority of cancer cells are estrogen-receptor positive and only a small propotion of epithelial cells are estrogen-receptor positive which can be only blocked by anti-cancer drug (1-κ). It is also consistent to assume that the estrogen modulation of the inflammatory response is a contributing factor in estrogen-stimulated growth of breast tumor which also has an effect on the host innate immune response. This can however result in damage to DNA primary structure of the double helix as a result of estrogen oxidation products. Therefore, normal cell population N will be reduced as some of the normal cells are being converted into tumor cells by a factor μ_4*NE , where μ_4 is the rate of tumor formation as a result of DNA damage by estrogen. Damaged normal cells will now form the class of tumor cells and therefore tumor cell population will also increase at a rate μ_4 resulting in a growth factor of μ_4*NE on tumor cell population. Here $\mu_4 < \lambda_1$ since some of the damaged cells can be destroyed as a result of antitumor immunity from Natural Killer cells. Estrogen is oxidised to catechol estrogens by recombinant phase 1 enzymes (CYP1A1 and CYP1B1) which also die naturally at a rate θ represented by the death factor θ*E . The molecule 17-β estradiol stimulates growth in estrogen-responsive breast cancer cells. As shown by in a series of experiments, ER-positive cells can stimulate surrounding benign cells to proliferate through similar paracrine effects involving stromal-epithelial cell interactions. The presence of estrogen has also been shown to reduce immune cell proliferation. We therefore assume that if estrogen deficiency increases immune cell proliferation and lifespan, then its presence will inhibit immune cell proliferation.

SECTION 2.2

System Analysis

System equilibrium analysis

The model system admits six steady states in which there are four dead equilibria, one tumor-free equilibrium point and one co-existing equilibrium point.In this section, we mainly analyzed the stability behaviors of system the by means of eigenvalues. We apply Hartman–Grobman Theorem which states that in the neighborhood of a hyperbolic equilibrium point, a nonlinear dynamical system is topologically equivalent to its linearization.

Pontryagin's optimal control

In this section, we formulated a corresponding optimal control problem for the model in the system considering ketogenic diet and anticancer drugs as control interventions to minimize the breast cancer and tumor burden at finite time. The units of cells were normalized in order for the carrying capacity of normal cells to be kept above threshold of time. On the other hand, the aim is to reduce the tumor size which indicates the degree of the disease in the body and it requires the application of as much anticancer drugs as much as possible. However, it also minimized the systemic cost, which is based on the quantities of anticancer drugs, since large drug concentrations can be harmful and cause toxic side effects. In brief, the drug doses were minimized because the smaller the dose, the better.

Numerical Simulation of the non linear system

A picture of the dynamical behavior of breast cancer cells in the presence of normal cells, tumor cells, immune cells, and estrogen is given by the numerical simulations of the model. The optimal control is acquired by solving the optimality system of four ordinary differential equations from the state variables and the adjoint system. Simulations on this model give us a portrait of the general behaviour of breast cancer cells in the presence of normal cells and immune cells. We are also concerned on the parameters which are of importance in stabilising the model and the ranges in which the system is stable and unstable.

Simulation of the linearized system using 2 different robust controllers

We synthesized two controllers using Matlab r2018a for the linearized system around P_0 steady point.Each controller simulates the solution of the system.*

SECTION 2.3

Objectives

The design of a mathematical model of a biological system is governed by the need to distill the essential behavior of the system and the need to answer specific questions about that system. In our case, our goal was to use the model to design a protocol for chemo-therapy that would produce an improved outcome by way of reducing final tumor size without causing large losses in the normal cell population. In order to do this we incorporated time dependent control parameters (use of ketogenic diet, immune booster, and anti-cancer drugs) based on the assumption that there is an interaction between normal cells and tumor cells that is due to a mutation in DNA as a result of excess estrogen in the body system Furthermore,we analyzed and applied an optimal control to the improved model to determinethe possible impacts of ketogenic-diet use and anti-cancer drugs as a treatment on tumor cells. We carried out a rigorous qualitative optimal control analysis of the resulting model and found the necessary conditions foroptimal control of the disease using Pontryagin's maximum principle in order to determine the optimal strategies for controlling the metastatic of the tumor cells. Last but least we used 2 modern rebust control methods LQR,and H_∞ to simulate system's theoritical data.

CHAPTER 3

Mathematical Model Analysis

SECTION 3.1

Formulation of the System of Equations

For the growth law terms, we considered several possible models, including exponential growth, Gompertz growth, logistic growth and Lotka-Volterra competition models.

Exponential growth law

The exponential growth law in the context of a tumor cell population assumes that the rate of increase in the population at a certain point in time is directly proportional to the size of the tumor population at that time; the exponential curve is unbounded as time increases

$$\frac{\partial P}{\partial t} = kP,\ P(0) = P_0 \tag{3.1}$$

Gompertz growth

Benjamin Gompertz originally designed the function for the royal society in 1825 to detail his law of human mortality. The law rests upon a priori assumption that a person's resistance to death decreases as his years increase. The model can be written in this way:

$$N(t) = N_0 e^{-ce^(at-1)} \tag{3.2}$$

where N(0) is the initial number of cells-orgamisms when time is zero a is an asymptote c denotes the rate of growth N(t) represents the number of individuals in the given time period, t. The letters c and a are constants. This model is a modification of a demographic model of Robert Malthus It was commonly used by insurance companies to calculate the cost of life insurance.

Logistic growth Verhulst

A typical application of the logistic equation is a common model of population growth, originally due to Pierre Francois Verhulst in 1838, where the rate of reproduction is proportional to both the existing population and the amount of available resources, all else being equal. Verhulst derived his logistic equation to describe the self-limiting growth of a biological population. The equation was rediscovered in 1911 by Mckendrik for the growth of bacteria in broth and experimentally tested using a technique for nonlinear parameter estimation.
Letting P represent population size (N is often used in ecology instead) and t represent time, this model is formalized by the ordinary differential equation

$$\frac{\partial P}{\partial t} = rP(1 - P/K) \tag{3.3}$$

where the constant r defines the growth rate and K is the carrying capacity where

$$\lim_{t\to\infty} P(t) = K$$

Lotka-Volterra

Lotka-Volterra model is the simplest model of predator-prey interactions. The model was developed independently by Lotka (1925) and Volterra (1926)

$$\begin{cases} \dfrac{\partial H}{\partial t} = rH - aHP \\ \dfrac{\partial P}{\partial t} = bHP - mP \end{cases} \tag{3.4}$$

It has two variables P and H and several parameters which denote

- H : the density of prey
- P : the density of predators
- r : the intrinsic rate of prey population increase
- a : the predation rate coefficient
- b : the reproduction rate of predators per one prey eaten
- m : the predator mortality rate

In this section, we considered tumor progression and regression as a prey-predator like system. The predator is the immune system which slaughters the tumor cells (prey). In most of the mathematical models of the tumor-immune system, the response of the immune system is considered as a single population of cells, namely, effector cell , which perform the task of destroying cancer cells. This simplifying assumption allows decreasing the complexity of the dynamics of the immune system. The predator, that is, immune system, is eradicating tumor cells in two stages: one is hunting cells and another is resting cells. Here, we are considering that hunting cells can slaughter tumor cells, but resting cells cannot. The cellular immune response identifies and eliminates the tumor cells from the host because tumor cells produce some antigens on its outer surface. The strength of the immune response depends on the tumor antigenicity . The cellular response of the immune system is carried by T lymphocytes. During maturation, T cells surface contains specialized antibody like receptors that see fragments of antigens on the surface of tumor cells. In most of the cases, T cells can recognize only antigen that is bound to a cell membrane protein called major histocompatibility complex (MHC) molecule. MHC molecule is a protein recognized by resting T cells, which distinguish between self and nonself. Resting T cells engulf the tumor cells and then produce various growth factors known collectively as cytokines, but they cannot kill tumor cells. Cytokines are chemical messenger switches which turn on the cytotoxic T lymphocytes (hunting cells). In contrast to the resting T cell, the cytotoxic T lymphocytes generally not only secrete many cytokines but also eliminate tumor cells by mounting a cytotoxic reaction that lyses their target . Considering the above biological mechanism, we have produced a mathematical model of tumor development in immune response. The model involves certain assumptions as follows:

1. logistic growth function is assumed for the growth of tumor cells in the absence of hunting CTL cells;
2. the tumor cells and hunting cells are being eradicated at a rate proportional to the densities of tumor cells and hunting predator cells according to the law of mass action;
3. the resting predator cells are converted to the hunting cells, either by direct contact with them or by contact with a fast diffusing substance (cytokines) produced by the hunting cells;
4. resting cells also follow logistic growth in absence of tumor cells;
5. once a hunting T cell has been converted, it will never return to the resting stage;
6. resting cells also were stimulated due to the presence of tumor cells, and this is considered by the Michaelis-Menten function.

Normal cells equation

The normal cells are modeled by a logistic growth law, with parameters a_i and m_i representing the per capita growth rates and reciprocal carrying capacities of the two types of cells: i = 1 identifies the parameters associated with the tumor, and i = 2 identifies those associated with the normal tissue. In addition, there are two terms representing the competition between tumor and host cells. The first equation is

$$\frac{\partial N(t)}{\partial t} = N(t)\alpha_1 - \mu_1 N(t)^2 - \phi_1 N(t)T(t) - (1-k)\lambda_1 N(t)E(t) \tag{3.5}$$

where

- $N(t)$ is the number of normal cells around a tumor
- $\alpha_1 N(t)$ is the logistic growth rate of normal cells which are breast tissues made of epithelial cells
- $\mu_1 N(t)^2$ is the rate of natural death of normal cells
- $\phi_1 N(t)T(t)$ is the rate which normal cells inhibit due to an alteration in DNA that is responsible for cancer cells having an uncontrolled cycle that normal cells dont have
- $(1-k)\lambda_1 N(t)E(t)$ describes the gene transactivation that can be a contributing growth factor responsible for estrogen stimulation of breast cancer which can result in damage of DNA

there will be a reduction in population of normal cells $N(t)$ being trasformed into tumor cells by $\lambda_1 N(t)E(t)$ where λ_1 represents the tumor formation rate resulting from DNA mutation caused by the presence of excess estrogen and $(1-k)$ represents the effectiveness of anticancer drugs such as tamoxifen .

Tumor cells

Tumor cells can be denoted by T(t) in the form of an abnormal mass of tissue. Tumors are classic signs of inflammation, and can be benign or malignant (cancerous). Breast cancer types can be classified into two major branches: the luminal, which has estrogen receptors, and the basal-like, which has no estrogen receptors.

$$\frac{\partial T(t)}{\partial t} = T(t)d\alpha_2 - \mu_2 T(t)^2 - \gamma_2 M(t)T(t) - \mu_5 T(t) + (1-k)\lambda_1 N(t)E(t) \tag{3.6}$$

where

- $T(t)\alpha_2 d$ is a limited growth term for tumor cells that depends on d (ketogenic diets) if d=0 tumor cells are eradicated but any DNA mutation that is caused by excess estrogen will repopulate the tumor again by $\lambda_1 N(t)E(t)$.
- μ_5 is the induced death rate as a result of tumor starvation of nutrients and glycose due to ketogenic diet.
- γ_2 is the rate tumor cells are removed from effectiveness of immune response.

Immune response cells

M(t) is the immune system response in the form of natural killer NK cells and CD8+T cells. Their growth may be stimulated by the presence of tumor and they can destroy tumor through the kinetic process.

$$\frac{dM}{dt} = s\beta + \frac{\rho MT}{\omega + T} - \gamma_3 MT - \mu_3 M - (1-k)\frac{\lambda_3 ME}{g+E} \tag{3.7}$$

where

- s denotes the source rate of immune response fully infused in the body daily.
- β immune booster (a supplement as ketone bodies) to assist the immune response whenever tumor cells overpower immune cells in order to activate immune response.
- $\frac{\rho MT}{\omega + T}$ is a non linear growth term for immune response, where
  - ρ is the rate of immune response
  - ω is the immune cell threshold
  - γ_3 is the rate immune response is inactivated
  - μ_3 is immune cells natural death rate, as a result of necrosis
  - λ_3 is rate immune suppression
- $(1-k)\frac{\lambda_3 ME}{g+E}$ is the limited rate at which estrogen suppress immune cells activation, where g is the rate of immune suppression

Estrogen

Estrogen is a female steroid hormone.Estrogen helps to the growth of tumor cells.It also serves as a mitogen by triggering cell division in breast tissue. Estrogen acts as a carcinogen by directly damaging DNA forcing healthy epithelial cells to have a higher likehood of malignantt conversion

$$\frac{\partial E}{\partial t} = (1-k)\epsilon - \mu_4 E \tag{3.8}$$

where ϵ is the process of constantly replenishing excess estrogen We assumed that the majority of cancer cells are estrogen-receptor positive and only a small propotion of epithelial cells are estrogen-receptor positive which can be only blocked by anti-cancer drug (1-k) and μ_4 is the rate at which estrogen is being washed out. Thus our model is:

$$\begin{cases} \frac{\partial N}{\partial t} = N\alpha_1 - \mu_1 N^2 - \phi_1 NT - (1-k)\lambda_1 NE \\ \frac{\partial T}{\partial t} = Td\alpha_2 - \mu_2 T^2 - \gamma_2 MT - \mu_3 M + (1-k)\lambda_1 NE \\ \frac{dM}{dt} = s\beta + \frac{\rho MT}{\omega+T} - \gamma_3 MT - \mu_3 M - (1-k)\frac{\lambda_3 ME}{g+E} \\ \frac{\partial E}{\partial t} = (1-k)\epsilon - \mu_4 E \end{cases}$$

SECTION 3.2

Math definitions and Theorems

We will commence analysing the system properties but before that its important to quote some definitions and theorems,from Ordinary Differential Equation theory,being used in this analysis.

Definitions

Definition 1

Homeomorphism

A function $h : X \to Y$ is a homeomorphism between X and Y if it is a continuous bijection (1-1) and onto function) with a continuous inverse denoted as h^{-1}. The existence of homeomorphisms tell us that X and Y have analogous structures.

Definition 2

Topological Conjugacy

Given two maps,$f : X \to X$ and $gY \to Y$, the map $hX \to Y$ is a topological semi conjugacy if it is continuous, onto and

$$h(f(x)) = g(h(x)) \tag{3.9}$$

where **x** is a point in X. Furthermore, h is a topological conjugacy if it is a homeomorphism between X and Y (h is also 1-1 and has a continuous inverse). We then say that X and Y are homeomorphic.

Definition 3

Hyperbolic Fixed Point

A hyperbolic fixed point for a system of differential equations a point at which the eigenvalues of the Jacobian for the system evaluated at that point all have nonzero real part.

Definition 4

Flow

Let

$$\vec{x'} = F(\vec{x}) \tag{3.10}$$

$$\vec{x'} = F(\vec{x}) \tag{3.11}$$

be a system of differential equations and $\vec{x_0}$ be an initial condition for $F(\vec{x})$. Provided that the solutions to the differential equation exist and are unique (the conditions of which are given in the existence and uniqueness theorem. Then $f(t; \vec{x_0})$, the flow of $F(\vec{x})$, gives the spatial solution of $F(\vec{x})$ given the initial condition over time. An important result of flows is that changing initial conditions in phase space will change flows in a continuous fashion because we have a continuous vector field in $\mathbb{R}^n$

Definition 5

Orbit/trajectory

The set all all points in a flow $f(t; \vec{x_0})$ for the set of differential equations

$$\vec{x'} = F(\vec{x}) \tag{3.12}$$

is called the orbit or trajectory of $F(\vec{x})$ with initial condition $\vec{x_0}$. We write the orbit as $f(t; \vec{x_0})$. When we consider only t, we say we consider the forward orbit or forward trajectory.

Definition 6

Lyapunov Stability

Consider an autonomous nonlinear dynamical system :

$$\vec{x'} = F(\vec{x}), x(0) = x_0 \tag{3.13}$$

where $x(t) \in D \subseteq \mathbb{R}^n$ denotes the system state vector,D an open set containing the origin, and $f : D \to \mathbb{R}^n$ continuous on D. Suppose f has an equilibrium point at x_e so that

$$f(x_e) = 0 \tag{3.14}$$

then:

1. This equilibrium is said to be Lyapunov stable if for every $\epsilon > 0$,there exist a δ such that,if $\parallel x(0) - x_e \parallel < \delta$ then for every $t \geq 0$ $\parallel x(t) - x_e \parallel < \epsilon$
2. The equilibrium of the above system is said to be asymptotically stable if it is Lyapunov stable and there exists a δ such that,if $\parallel x(0) - x_e \parallel < \delta$ then for every $t \geq 0$ $\parallel x(t) - x_e \parallel < \epsilon$

Definition 7

Positively invariant set

Let $f(t; \vec{x_0})$ be the flow for the set of differential equations

$$\vec{x'} = F(\vec{x}) \tag{3.15}$$

defined on $\mathbb{R}^n$. If, for $S \subset \mathbb{R}^n$ and $f(t; \vec{x_0}) \in$ S for any point $\vec{x_0} \in S$, $t \geq 0$, then S is positively invariant. In other words, if the forward orbits of all initial conditions in S are subsets of S, then S is positively invariant.

Definition 8

ω-limit point,ω-limit set

Let $f(t; \vec{x_0})$ be the flow for the set of differential equations

$$\vec{x'} = F(\vec{x}) \tag{3.16}$$

defined on $\mathbb{R}^n$ with initial condition $\vec{x_0}$. $\vec{z}$ is called an ω-limit point of $\vec{x_0}$ if $\exists$ an infinite sequence of times t_0,t_1,...,t_n,t_{n+1},... such that $f(t; \vec{x_0})$ converges to $\vec{z}$. The ω-limit set of $\vec{x_0}$, denoted $\omega(\vec{x_0})$, is the set of all ω-limit points of $\vec{x_0}$.

Theorems

The Hartman-Grobman Theorem

Let x $\in \mathbb{R}^n$. Consider the nonlinear system

$$\vec{x'} = f(\vec{x}) \tag{3.17}$$

with the flow ϕ_t and the linear system

$$\vec{x'} = A\vec{x*} \tag{3.18}$$

where A is the Jacobian maxtrix of f and $\vec{x*}$ is a hyperbolic fixed point. Assume that we have appropriately translated $\vec{x*}$ to origin.

$$\vec{x*} \neq 0 \tag{3.19}$$

. Let f be C^1 on some $E \subset \mathbb{R}^n$ with $\vec{0}$. Let $I_0 \subset R$, $U \subset \mathbb{R}^n$ and $V \subset \mathbb{R}^n$ such that U, V and I_0 each contain the origin. Then $\ni$ a homeomorphism $H : U \to V$ such that, $\forall$ initial points $\vec{x_0}$ ϵ U and all $t \in I_0$,

$$H \circ f\phi(\vec{x_0}) = e^{At}H(\vec{x_0}) \tag{3.20}$$

Thus the flow of the non-linear system is homeomorphic to the flow, e^{At}, of the linear system given by the fundamental theorem for linear systems.

Comparison Theorem

Let

$$x' = f(x), x(0) = x_0 \tag{3.21}$$

and suppose $x' \leq cx, \forall t \geq 0$ Then there is a $T_1 > 0$ such that: $x \leq c \ \forall \ t \geq T_1$ thus x is oultimately bounded.

Lyapunov global stability Theorem

Let

$$\vec{x'} = f(\vec{x}) \tag{3.22}$$

suppose there is a function V such that:

- V is positive definite
- $V(z)' < 0$ for all $z > 0$, $V(0) = 0$

then every trajectory of $\vec{x'} = f(\vec{x})$ converges to 0 as $t \to \infty$ which implies the system is globally asymptotically stable.

LeSalle Invariance principle

We consider $\vec{x'} = f(\vec{x})$ suppose there is a function $V : \mathbb{R}^n \to \mathbb{R}$ such that:

- V is positive definite
- $V'(x) \leq 0$
- the only solution of $\vec{x'} = f(\vec{x})$, $V(x) = 0$ is $x(t) = 0$ for all $t > 0$ then

the system $\vec{x'} = f(\vec{x})$ is globally asymptotically stable.

Summary theorem

Consider:$\vec{x'} = f(\vec{x})$ The following statements are equivalent:

- $x = 0$ is a globally asymptotically stable equilibrium of the system
- there exists a quadratic Lyapunov function $V(x) = x^T Px, P\epsilon S^n$
- there exists a matrix $P\epsilon S^n$ such that $P > 0, A^T PA - P < 0$

- matrix $P \epsilon S^n$ that solves the Stein equation $A^T P A - P + Q = 0$ is positive definite. $P > 0$ for some $Q > 0$

Ruth-Hurwitz criterion

We will use a modified version of Ruth-Hurwitz criterion for stability, for a 2x2 matrix. Let:

$$\vec{x'} = A\vec{x}, x(0) = x_0 \tag{3.23}$$

where A is linearitation matrix of the system above. All the eigenvalues of A are negative meaning that the equilibrium points P_i for $i = 1, ..., n$ are asymptotically stable if and only if $Det(A) > 0$ and $Tr(A) < 0$

Dulac-Bendixson criterion

Let the autonomous system:

$$\frac{\partial x}{\partial t} = f(x,t), \frac{\partial y}{\partial t} = g(x,t) \tag{3.24}$$

if there exists a C^1 function $\phi(x,y)$ such that the expression $\frac{\partial f\phi}{\partial x} + \frac{\partial g\phi}{\partial y}$ has the same sign ($\neq 0$)almost everywhere in a simply connected region of the plane, then the plane autonomous system above as no non-constant periodic solutions lying entirely within the region.

SECTION 3.3

Properties of the system

Invariance of non-Negativity, and Dissipativity

All solutions with positive values remain positive. The system of equations * has initial conditions $N(0) = N_0 \geq 0$, $T(0) = T_0 \geq 0$, $M(0) = M_0 \geq 0$, $E(0) = E_0 \geq 0$ since our model is to investigate cellular populations,therefore all the variables and parameters of the model are all non negative. Based on the biological finding, the system of will be studied in

$$D = \{(N,T,M,E) \in \mathbb{R}^4_+ \ | N(t) \leq \frac{\alpha_1}{\mu_1}, E(t) \leq \frac{(1-k)\epsilon}{\mu_4}, T(t) \leq \frac{(1-k)^2\lambda_1\alpha_1\epsilon}{\mu_1\mu_4(\mu_5 - \alpha_2 d)},$$
$$M(t) \leq \frac{-s\beta\omega(\mu_5 - \alpha_2 d)}{\frac{\rho(1-k)^2\lambda_1\alpha_1\epsilon}{\mu_1\mu_4} - \mu_3\omega(\mu_5 - \alpha_2 d)}\}$$

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

Theorem

Let the region $D \subset \mathbb{R}^4_+$ descripted above then:

1. D is positively invariant
2. All solutions of the system are within $\mathbb{R}^4_+$ are eventually uniformly bounded and are attracted into the region D
3. System is dissipative

Proof

Let $D = \{(N,T,M,E) \in \mathbb{R}^4_+ \ | N(t) \leq \frac{\alpha_1}{\mu_1}, E(t) \leq \frac{(1-k)\epsilon}{\mu_4}, T(t) \leq \frac{(1-k)^2\lambda_1\alpha_1\epsilon}{\mu_1\mu_4(\mu_5-\alpha_2 d)}$,
$M(t) \leq \frac{-s\beta\omega(\mu_5-\alpha_2 d)}{\frac{\rho(1-k)^2\lambda_1\alpha_1\epsilon}{\mu_1\mu_4} - \mu_3\omega(\mu_5-\alpha_2 d)}\}$

- Boundary for N(t)

  It is obvious from the first compartment of the system that
  $\frac{\partial N(t)}{\partial t} \leq N(t)\alpha_1 - \mu_1(N(t))^2$
  Solving with Bernoulli method and taking $N(0) = N_0$, we have: $N(t) \leq \frac{\alpha_1}{\mu_1 + \upsilon\alpha_1 e^{\alpha_1 t}}$ with $\upsilon = \frac{\alpha_1 - N_0\mu_1}{N_0\alpha_1}$ and $N_0 = \frac{\alpha_1}{\alpha_1 + \upsilon\mu_1}$

  hence by all the above and the comparison Theorem we conclude to $limsup(N(t)) \leq \frac{\alpha_1}{\mu_1}$ as $t \to \infty$

- Boundary for E(t)

  From the forth differential equation of the system which is linear and first order, we solve and find $\frac{\partial N(t)}{\partial t} \leq \frac{(1-k)\epsilon}{\mu_4} + (E_0 - \frac{(1-k)\epsilon}{\mu_4})e^{-\mu_4 t}$
  for simplicity reasons we set $\zeta = E_0 - \frac{(1-k)\epsilon}{\mu_4}$ and we assume that $\frac{\partial E(t)}{\partial t} \leq \frac{(1-k)\epsilon}{\mu_4}$ if and only if $\zeta > 0$ By all the above and the comparison theorem we deduce $limsup(E(t)) \leq \frac{(1-k)\epsilon}{\mu_4}$ as $t \to \infty$

- Boundary for T(t)

  Now let T_n be so large that $0 \leq N(t) \leq \frac{\mu_1}{\alpha_1}$ for all $t > T_n$
  and $0 \leq E(t) \leq (1-k)\frac{\epsilon}{\mu_4}$ for all $t > T_e$

and choose $T_t = max(T_n, T_e)$
$\frac{\partial T(t)}{\partial t} \leq T(t)(\alpha_2 d - \mu_5) + (1-k)^2 \frac{\lambda_1 \alpha_1 \epsilon}{\mu_1 \mu_4}$
we set $q = (1-k)^2 \frac{\lambda_1 \alpha_1 \epsilon}{\mu_1 \mu_4}$ and $g = \mu_5 - \alpha_2 d$
$\frac{\partial T(t)}{\partial t} \leq \frac{(1-k)^2 \lambda_1 \alpha_1 \epsilon}{\mu_1 \mu_4 (\mu_5 - \alpha_2 d)}$ which infers that for every $\frac{q}{g} > 0$
$limsup(T(t)) \leq \frac{(1-k)^2 \lambda_1 \alpha_1 \epsilon}{\mu_1 \mu_4 (\mu_5 - \alpha_2 d)}$ as $t \to \infty$

- Boundary for M(t) Lastly,we choose $T_m = max(T_n, T_e)$ for all $t > T_m$
  $\frac{\partial M(t)}{\partial t} \leq s\beta + \frac{\rho M T}{g\omega} - \mu_3 M$
  we set $w = \frac{\rho q - \mu_3 g \omega}{\omega + g}$
  $\frac{\partial M(t)}{\partial t} \leq \frac{-s\beta\omega(\mu_5 - \alpha_2 d)}{\frac{\rho(1-k)^2 \lambda_1 \alpha_1 \epsilon}{\mu_1 \mu_4} - \mu_3 \omega(\mu_5 - \alpha_2 d)}$ and if $w < 0$
  we conclude : $limsup(M(t) \leq \frac{-s\beta\omega(\mu_5 - \alpha_2 d)}{\frac{\rho(1-k)^2 \lambda_1 \alpha_1 \epsilon}{\mu_1 \mu_4} - \mu_3 \omega(\mu_5 - \alpha_2 d)}$
  Hence the system of equations is ultimately bounded and the Theorem is proved

The Equilibrium Points of the System

The steady states occur by setting the left hand side of the system to zero

$$\frac{\partial N(t)}{\partial t} = \frac{\partial T(t)}{\partial t}\frac{\partial M(t)}{\partial t} = \frac{\partial E(t)}{\partial t} = 0$$

The model system admits six steady states in which there are four dead equilibria, one tumor-free equilibrium point and one co-existing equilibrium point $P = (N^*, T^*, M^*, E^*)$ where N^*, T^*, M^*, E^* represent the tumor free equilibrium values for the normal cells, tumor cells, immune cells and estrogen hormone respectively We have $N^* > 0, M^* > 0, E^* > 0, T^* > 0$ since cell populations are non-negative and real. Therefore, all parameters $s, \beta, g, \mu_1, \mu_3, \mu_4, \epsilon, \lambda_3, k, \alpha_1$, and λ_1 are positive.

1. **Tumor free equilibrium**

   $$P_0 = (\frac{\alpha_1\mu_4 - (1-k)^2\lambda_1\epsilon}{\mu_1\mu_4}, 0, \frac{s\beta(g\mu_4 + (1-k)\epsilon)}{\mu_3(g\mu_4 + (1-k)\epsilon) + (1-k)^2\lambda_3\epsilon}, \frac{(1-k)\epsilon}{\mu_4})$$

   In principle, we would like the tumor-free equilibrium to be stable so that the possibility exists of moving the state of the system toward the tumor-free point. P_0 represents the situation where there is tumor free equilibrium, that is when only tumor cell population has died off due to competition with other cells.

   Theorem 1

   The tumor-free equilibrium point P_0 of the system is locally asymptotically stable if $R_0 < 1$, otherwise unstable.

   Linearizing the system of equations around P_0 we obtained the following Jacobian Matrix $J(P_0)$:

$$J_{(P_0)} = \begin{bmatrix} B_0 & B_2 & 0 & -B_6 \\ B_1 & B_3 & 0 & B_6 \\ 0 & B_4 & -B_5 & -B_7 \\ 0 & 0 & 0 & -\mu_4 \end{bmatrix} \tag{3.25}$$

   where :

$$B_0 = \frac{2\mu_1\lambda_1(1-k)^2\epsilon - \alpha_1\mu_1\mu_4 - (1-k)^2\lambda_1\mu_1\epsilon}{\mu_1\mu_4}$$

$$B_1 = \frac{(1-k)^2\lambda_1\epsilon}{\mu_4}$$

$$B_2 = \frac{(1-k)^2\lambda_1\phi_1\epsilon - \phi_1\alpha_1\mu_4}{\mu_1\mu_4}$$

$$B_3 = \frac{\alpha_2\mu_3 d\psi^* + \alpha_2\lambda_3 d\epsilon(1-k)^2 - \gamma_2 s\beta\psi^* - \mu_5\mu_3\psi^* - \mu_5\lambda_3\epsilon(1-k)^2}{\mu_3\psi^* + (1-k)^2\lambda_3\epsilon}$$

$$\psi^* = (g\mu_4 + (1-k)\epsilon)$$

$$B_4 = -\frac{s\beta(g\mu_4 + (1-k)\epsilon(\rho - \gamma_3\omega))}{\omega\mu_3(g\mu_4 + (1-k)\epsilon)}$$

$$B_5 = -\frac{\mu_3\mu_4 g + \mu_3(1-k)\epsilon + \lambda_3(1-k)^2\epsilon}{g\mu_4 + (1-k)\epsilon}$$

$$B_6 = \frac{(1-k)\lambda_1\alpha_1\mu_4 - (1-k)^3\lambda_1^2\epsilon}{\mu_1\mu_4}$$

$$B_7 = \frac{\mu_4^2(1-k)\lambda_3 g s\beta(g\mu_4 + (1-k)\epsilon)}{(g\mu_4 + (1-k)\epsilon)^2(\mu_3(g\mu_4 + (1-k)\epsilon) + (1-k)^2\lambda_3\epsilon)}$$

$$|J(P_0)| = \begin{vmatrix} B_0 & B_2 & 0 & -B_6 \\ B_1 & B_3 & 0 & B_6 \\ 0 & B_4 & -B_5 & -B_7 \\ 0 & 0 & 0 & -\mu_4 \end{vmatrix} \tag{3.26}$$

Then the characteristic equation at P_0 of the linearized system of the model is given below.Obviously there exists two negatives characteristics roots $\delta_1 = -\mu_4$, $\delta_2 = -B_5$ However we only need to consider: $\delta^2 - (B_0 + B_3)\delta + B_0B_3 - B_1B_2 = 0$
$\delta^2 - (B_0 + B_3)\delta + B_0B_3(1 - \frac{B_1B_2}{B_0B_3}) = 0$ from where we get basic reproduction number $R_0 = \frac{B_1B_2}{B_0B_3}$ so finally $\delta^2 - (B_0 + B_3)\delta + B_0B_3(1 - R_0) = 0$ where in order to use the Routh-Hurwitz ($Tr(A) < 0$, $Det(A) > 0$) provided
$\alpha_0 = 1, \alpha_1 = (B_0 + B_3) < 0, (B_0B_3(1 - R_0) > 0$ if $R_0 < 1$
$B_0B_3 > B_1B_2$, $B_1 > 0$, $B_2 > 0$, $B_3 < 0$, $B(0) < 0$

Epidemiological implication
Tumor cells population that are governed by the system of equations can be eliminated from the population whenever an influx by tumor cells into the normal cells is small such that $R_0 < 1$. Therefor the existence of a tumor-free equilibrium in this case depends on the estrogen level.

2. **Dead free type 1 equilibrium**

$P_{d1} = (0, 0, \frac{s\beta(g\mu_4 + (1-k)\epsilon)}{\mu_3(g\mu_4 + (1-k)\epsilon + (1-k)^2\lambda_3\epsilon)}, \frac{(1-k)\epsilon}{\mu_4})$

P_{d1} represents Type 1 dead equilibrium point where both normal cells and tumor cells die-off as a result of breast tissue removal through mastectomy surgery or death. This is because overtime the cancer cells which are depending on estrogen to develop into independent cells that grow regardless of estrogen receptors.

Theorem 2

The Type 1 Dead equilibrium point P_{d1} of the system is locally asymptotically stable if $\frac{(1-k)^2\lambda_1\epsilon}{\alpha_1\mu_4} > 1$

Proof

Linearizing the system around Type 1 dead free equilibrium point P_{d1} we obtained the following Jacobian matrix $J(P_{d1})$

$$J(P_{d1}) = \begin{bmatrix} C_0 & 0 & 0 & 0 \\ C_1 & C_2 & 0 & 0 \\ 0 & C_3 & -C_4 & -C_5 \\ 0 & 0 & 0 & -\mu_4 \end{bmatrix} \tag{3.27}$$

where:

$C_0 = \alpha_1 - (1-k)\lambda_1 E_0^*$

$C_1 = (1-k)\lambda_1 E_0^*$

$C_2 = d\alpha_2 - \gamma_2 M_0^* - \mu_5$

$C_3 = \frac{M_0^*\rho\omega - \gamma_3 M_0^*\omega^2}{\omega^2}$

$C_4 = \frac{\mu_3(g + E_0^*) + (1-k)\lambda_3 E_0^*}{g + E_0^*}$

$C_5 = \frac{\lambda_3 g M_0^*(1-k)}{(g + M_0^*)^2}$

$$|J(P_d1)| = \begin{vmatrix} C_0 - \xi & 0 & 0 & 0 \\ C_1 & C_2 - \xi & 0 & 0 \\ 0 & C_3 & -C_4 - \xi & -B_7 \\ 0 & 0 & 0 & -\mu_4 - \xi \end{vmatrix} \tag{3.28}$$

Clearly two eigenvalues of the system at P_{d1} are negative and real: $\xi_1 = -\mu_4$, $\xi_2 = -C_4 = -\frac{\mu_3(g + E_0^*) + (1-k)\lambda_3 E_0^*}{g + E_0^*}$ while the remaining two eigenvalues are obtained from a $2x2$ matrix:

$$A = \begin{bmatrix} C_0 & C_1 \\ C1 & C_2 \end{bmatrix} \tag{3.29}$$

Applying the Routh-Hurwitz criterion state above we have:

(a) $Tr(A) = C_0 + C_2 \Rightarrow (\frac{\alpha_1\mu_4 - (1-k)^2\lambda_1\epsilon}{\mu_4} + \frac{(\mu_3\alpha_2 d - \gamma_2 s\beta - \mu_5\mu_3)A^* + d\alpha_2\lambda_3(1-k)^2\epsilon - (1-k)^2}{\mu_3 A^* + (1-k)^2\lambda_3\epsilon}$

0 if $\alpha_1(1 - \frac{(1-k)^2\lambda_1\epsilon}{\alpha_1\mu_4}) > 0 \Rightarrow \frac{(1-k)^2\lambda_1\epsilon}{\alpha_1\mu_4}) > 0$ therefore $Tr(A) < 0$

(b) $Det(A) = C_0C_2$

$(\frac{\alpha_1\mu_4 - (1-k)^2\lambda_1\epsilon}{\mu_4})(\frac{(\mu_3\alpha_2 d - \gamma_2 s\beta - \mu_5\mu_3)A^* + d\alpha_2\lambda_3(1-k)^2\epsilon - (1-k)^2\lambda_3\mu_5\epsilon}{\mu_3 A^* + (1-k)^2\lambda_3\epsilon}) > 0$

if $\alpha_1(1 - \frac{(1-k)^2\lambda_1\epsilon}{\alpha_1\mu_4}) > 0$ provided that $(\frac{(1-k)^2\lambda_1\epsilon}{\alpha_1\mu_4}) > 1$ and

$(\alpha_1(1 - \frac{(1-k)^2\lambda_1\epsilon}{\alpha_1\mu_4})(\frac{\mu_3\alpha_2 d - \gamma_2 s\beta - \mu_5\mu_3)A^* + d\alpha_2\lambda_3(1-k)^2\epsilon - (1-k)^2\lambda_3\mu_5\epsilon}{\mu_3 A^* + (1-k)^2\lambda_3\epsilon} > 0$

which implies that $Det(A) > 0$. Thus, the remaining eigenvalues ξ_3 and ξ_4 are negative and real since R-H criterion has been satisfied. Hence, the type 1 Dead equilibrium point P_{d1} of the system is locally asymptotically stable.

Epidemiological implication

Epidemiologically it is implied that the net growth of the tumor cells must be more than the immune cells values in order to have the tumor cells overpower the normal cells as the reactivation of the immune cells is due to the estrogen effects that are greater than the reactivation of the immune cells due to the tumor effect. However, ketogenic diet is inactive at the type 1 Dead equilibrium point

3. **Dead free type 2 equilibrium**

$P_{d2} = (0, \frac{d\alpha_2 - \gamma_2 M_1^* - \mu_5}{\mu_2}, M_1^*, \frac{(1-k)\epsilon}{\mu_4})$

P_d2 could be described by Type 2 dead equilibrium point where normal cells were only forced to extinction leaving the tumor cells surviving.

Theorem 3

The Type 2 Dead equilibrium point P_{d2} of the system is locally asymptotically stable if $\frac{(1-k)^2\lambda_1\epsilon}{\alpha_1\mu_4} > 1$ and $\omega > \frac{A^*}{\mu_2}(\frac{\mu_2 C^*\rho}{\gamma_3 A^* C^* + \mu_2\mu_3 C^* + ((1-k)^2\lambda_3\epsilon} - 1)$ otherwise unstable

Proof

Linearizing the system around Type 2 dead free equilibrium point P_{d2} we obtained the following Jacobian matrix $J(P_{d2})$

$$J(P_{d2}) = \begin{bmatrix} Q_0 & 0 & 0 & 0 \\ Q1 & Q_2 & -Q_4 & 0 \\ 0 & Q_3 & Q_5 & Q_6 \\ 0 & 0 & 0 & -\mu_4 \end{bmatrix} \tag{3.30}$$

where:

$Q_0 = \alpha_1 - (1-k)\lambda_1 E_1^*$

$Q_1 = (1-k)\lambda_1 E_1^*$

$Q_2 = d\alpha_2 - \mu_2 T_1^* - \gamma_2 M_1^* \mu_5$

$Q_3 = \frac{\mu_2^2 M_1^* \omega\rho - \gamma_3 M_1^* (\omega\mu_2 + d\alpha_2 - \gamma_2 M_1^* - \mu_5)^2}{(\omega\mu_2 + d\alpha_2 - \gamma_2 M_1^* - \mu_5)^2}$

$-Q_4 = -\gamma_2 T_1^*$

$Q_5 = \frac{T_1^*\rho)}{T_1^* + \omega} - \gamma_3 T_1^* - \mu_3 - \frac{(1-k)\lambda_3 E_1^*}{g + E_1^*}$

$$|J(P_d2)| = \begin{vmatrix} Q_0 - \delta & 0 & 0 & 0 \\ Q_1 & Q_2 - \delta & -Q_4 & 0 \\ 0 & Q_3 & Q_5 - \delta & Q_6 \\ 0 & 0 & 0 & -\mu_4 - \delta \end{vmatrix} \tag{3.31}$$

Clearly two eigenvalues of the system at P_{d2} are negative and real: $\delta_1 = -\mu_4$ However,the remaining can be analysed by simple calculation: $(Q_0 - \delta)(Q_2 - \delta)(Q_5 - \delta) = 0$ $\Rightarrow Q_5 = \delta_2$, $Q_2 = \delta_3$, $Q_0 = \delta_4$ where $A^* = (g\mu_4 - (1-k)\epsilon)$ and $C^* = (\omega\mu_2 + d\alpha_2 - \gamma_2 M_1^* - \mu_5)$ it follows the following conditions:

(a) $Q_0 < 0$ if $0 \leqslant k < 1$, $0 \leqslant k < 1$ and $\frac{(1-k)^2\lambda_1\epsilon}{\alpha_1\mu_4} > 1$

(b) $Q_5 < 0$ provided $A^* > 0$, $0 \leqslant k < 1$ and $\omega > \frac{A^*}{\mu_2}\frac{\mu_2 C^*\rho}{\gamma_3 A^* C^* + \mu_2\mu_3 C^* + (1-k)^2\lambda_3\epsilon} - 1)$

4. **Dead free type 3 equilibrium**

$P_{d3} = (0, \frac{d\alpha_2 - \gamma_2 M_2^* - \mu_5}{\mu_2}, M_2^*, \frac{(1-k)\epsilon}{\mu_4})$

P_d3 represent Type 3 dead equilibrium point which means immune system is weak and it cannot fight the tumor cells which eventually overpower normal cells and forced it to extinction.

Theorem 4

The Type 3 Dead equilibrium point P_{d3} of the system is locally asymptotically stable if $\frac{(1-k)^2\lambda_1\epsilon}{\alpha_1\mu_4} > 1$ and $\omega > \frac{A^*}{\mu_2}(\frac{\mu_2 C^*\rho}{\gamma_3 A^* C^* + \mu_2\mu_3 C^* + (1-k)^2\lambda_3\epsilon} - 1)$ otherwise unstable

Proof

Linearizing the system around Type 3 dead free equilibrium point P_{d3} we obtained the following Jacobian matrix $J(P_{d3})$

$$J(P_{d3}) = \begin{bmatrix} Z_0 & 0 & 0 & 0 \\ Z1 & Z_2 & -Z_4 & 0 \\ 0 & Z_3 & Z_5 & Z_6 \\ 0 & 0 & 0 & -\mu_4 \end{bmatrix} \tag{3.32}$$

where:

$Z_0 = \alpha_1 - (1-k)\lambda_1 E_2^*$

$Z_1 = (1-k)\lambda_1 E_2^*$

$Z_2 = d\alpha_2 - \mu_2 T_2^* - \gamma_2 M_2^* \mu_5$

$Z_3 = \frac{\mu_2^2 M_2^* \omega\rho - \gamma_3 M_2^*(\omega\mu_2 + d\alpha_2 - \gamma_2 M_2^* - \mu_5)^2}{(\omega\mu_2 + d\alpha_2 - \gamma_2 M_2^* - \mu_5)^2}$

$-Z_4 = -\gamma_2 T_2^*$

$Z_5 = \frac{T_2^*\rho)}{T_2^* + \omega} - \gamma_3 T_2^* - \mu_3 - \frac{(1-k)\lambda_3 E_2^*}{g + E_2^*}$

$$|J(P_d3)| = \begin{vmatrix} Z_0 - \nu & 0 & 0 & 0 \\ Z_1 & Z_2 - \nu & -Z_4 & 0 \\ 0 & Z_3 & Z_5 - \nu & Z_6 \\ 0 & 0 & 0 & -\mu_4 - \nu \end{vmatrix} \tag{3.33}$$

Clearly two eigenvalues of the system at P_{d2} are negative and real: $\nu_1 = -\mu_4$ However,the remaining can be analysed by simple calculation: $(Z_0 - \nu)(Z_2 - \nu)(Z_5 - \nu) = 0$ $\Rightarrow Z_5 = \nu_2$, $Z_2 = \nu_3$, $Z_0 = \nu_4$ where $A^* = (g\mu_4 - (1-k)\epsilon)$ and $C^* = (\omega\mu_2 + d\alpha_2 - \gamma_2 M_2^* - \mu_5)$ it follows the following conditions:

(a) $Z_0 < 0$ if $0 \leqslant k < 1$, and $\frac{(1-k)^2\lambda_1\epsilon}{\alpha_1\mu_4} > 1$

(b) $Z_5 < 0$ provided $A^* > 0$, $0 \leq k < 1$ and $\omega > \frac{A^*}{\mu_2}(\frac{\mu_2 C^* \rho}{\gamma_3 A^* C^* + \mu_2 \mu_3 C^* + (1-k)^2 \lambda_3 \epsilon} -$ 1)

5. **Dead free type 4 equilibrium**

$P_{d4} = (0, \frac{d\alpha_2 - \gamma_2 M_3^* - \mu_5}{\mu_2}, M_3^*, \frac{(1-k)\epsilon}{\mu_4})$

P_d4 show that Type 4 dead equilibrium point where ketogenic diet is not effective, immune booster is not active which lead to tumor cell over-compete normal cells as a result of infusion of excess estrogen to the body system.

Theorem 5 The Type 4 Dead equilibrium point P_{d4} of the system is locally asymptotically stable if $\frac{(1-k)^2 \lambda_1 \epsilon}{\alpha_1 \mu_4} > 1$ and $\omega > \frac{A^*}{\mu_2}(\frac{\mu_2 C^* \rho}{\gamma_3 A^* C^* + \mu_2 \mu_3 C^* + (1-k)^2 \lambda_3 \epsilon} - 1)$ otherwise unstable

Proof

Linearizing the system around Type 4 dead free equilibrium point P_{d4} we obtained the following Jacobian matrix $J(P_{d4})$

$$J(P_{d4}) = \begin{bmatrix} Y_0 & 0 & 0 & 0 \\ Y_1 & Y_2 & -Y_4 & 0 \\ 0 & Y_3 & Y_5 & Y_6 \\ 0 & 0 & 0 & -\mu_4 \end{bmatrix} \tag{3.34}$$

where:

$Y_0 = \alpha_1 - (1-k)\lambda_1 E_3^*$

$Y_1 = (1-k)\lambda_1 E_3^*$

$Y_2 = d\alpha_2 - \mu_2 T_3^* - \gamma_2 M_3^* \mu_5$

$Y_3 = \frac{\mu_2^2 M_3^* \omega \rho - \gamma_3 M_3^* (\omega \mu_2 + d\alpha_2 - \gamma_2 M_3^* - \mu_5)^2}{(\omega \mu_2 + d\alpha_2 - \gamma_2 M_3^* - \mu_5)^2}$

$-Y_4 = -\gamma_2 T_3^*$

$Y_5 = \frac{T_2^* \rho)}{\mu_2^* + \omega} - \gamma_3 T_3^* - \mu_3 - \frac{(1-k)\lambda_3 E_3^*}{g + E_3^*}$

$$|J(P_d4)| = \begin{vmatrix} Y_0 - \vartheta & 0 & 0 & 0 \\ Y_1 & Y_2 - \vartheta & -Y_4 & 0 \\ 0 & Y_3 & Y_5 - \vartheta & Y_6 \\ 0 & 0 & 0 & -\mu_4 - \vartheta \end{vmatrix} \tag{3.35}$$

Clearly two eigenvalues of the system at P_{d4} are negative and real: $\vartheta_1 = -\mu_4$ However,the remaining can be analysed by simple calculation: $(Y_0 - \vartheta)(Y_2 - \vartheta)(Y_5 - \vartheta) = 0$ $\Rightarrow Y_5 = \vartheta_2$, $Y_2 = \vartheta_3$, $Y_0 = \vartheta_4$ where $A^* = (g\mu_4 - (1-k)\epsilon)$ and $C^* = (\omega\mu_2 + d\alpha_2 - \gamma_2 M_3^* - \mu_5)$ it follows the following conditions:

(a) $Y_0 < 0$ if $0 \leqslant k < 1$, and $\dfrac{(1-k)^2\lambda_1\epsilon}{\alpha_1\mu_4} > 1$

(b) $Y_5 < 0$ provided $A^* > 0$, $0 \leqslant k < 1$ and $\omega > \frac{A^*}{\mu_2}(\dfrac{\mu_2 C^*\rho}{\gamma_3 A^* C^* + \mu_2\mu_3 C^* + (1-k)^2\lambda_3\epsilon} -$ 1)

6. **Co-existing equilibrium point**

$P_e = (N_4^*, T_4^*, M_4^*, E_4^*)$

P_e. A co-existing equilibrium state exists when all cells populations would have survived the competition.

Theorem 6

The Co-existing equilibrium point of the system is locally asymptotically stable if $Trace(J(P_e)) = (V_0 + V_3 + V_6 - \mu_4)$, $Det(J(P_e)) = (-\mu_4(V_0V_6V_3 + V_0V_4V_5 + V_1V_2V6)) > 0$ otherwise unstable.

Proof

We analyzed and linearized system around the co-existing equilibrium point P_e, we obtained the following Jacobian matrix $J(P_e)$ at $P_e = (N_4^*, T_4^*, M_4^*, E_4^*)$ where N_4^*, T_4^*, M_4^* and E_4^* represent the coexisting equilibrium values for normal cells, tumor cells, immune cells, and estrogen levels respectively.

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

$$T_4^* = \frac{\alpha_1^2\mu_1\mu_4^2 + 2\alpha_1\mu_1\mu_4^2\phi_1}{2\phi_1\alpha_1\mu_1^2\mu_4^3 - 2(1-k)^2\mu_1^2\mu_4^2\lambda_1\phi_1\epsilon}$$

$$M_4^* = \frac{(G^*)^2Z^*(1-k)^2\lambda_1\epsilon + (\alpha_1^2\alpha_2\mu_1\mu_4^3d + 2\alpha_1\alpha_2\mu_1\mu_4^3\phi_1d - \mu_4^3\mu_5\alpha_1^2 - 2\mu_4^3\mu_1\mu_5\alpha_1\phi_1)G^* - \mu_3\alpha_1^4\mu_1^2\mu_4^5 -}{(G^*)^2Q^*\mu_4}$$

$$E_4^* = \frac{(1-k)\epsilon}{\mu_4}$$

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

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

$$Q^* = \frac{\alpha_1^2\mu_1\mu_3^2\gamma_2 - 2\alpha_1\mu_1\mu_4^2\phi_1\gamma_2}{2\phi_1\alpha_1\mu_1\mu_4^2 - 2(1-k)^2\mu_1^2\mu_4^2\lambda_1\phi_1\epsilon}$$

$$J(P_e) = \begin{bmatrix} V_0 & -V_2 & 0 & -V_7 \\ V1 & V_3 & -V_5 & V_7 \\ 0 & V_4 & V_6 & V_8 \\ 0 & 0 & 0 & -\mu_4 \end{bmatrix} \tag{3.36}$$

where:

$$V_0 = \frac{\alpha_1\mu_4 - 2\mu_1\mu_4N_4^* - (1-k)^2\lambda_1\epsilon}{\mu_4}$$

$$V_1 = \frac{(1-k)^2\lambda_1\epsilon}{\mu_4}$$

$$V_2 = -\phi_1N - 4^*$$

$$V_3 = (d\alpha_2 - 2\mu_2T_4^* - \gamma_2M_4^* - \mu_5)$$

$$V_4 = \frac{M_4^*\omega\rho - \gamma_3M_4^*(\omega + T_4^*)^2}{(\omega + T_4^*)^2}$$

$$V_5 = -\gamma_2T_4^*$$

$$V_6 = \frac{T_4^*(g\mu_4 + (1-k)\epsilon)\rho - \gamma_3 T_4^*(\omega + T_4^*)(g\mu_4 + (1-k)\epsilon) - \mu_3(\omega + T_4^*)(g\mu_4 + (1-k)\epsilon) - (1-k)^2(\omega + T_4^*)\lambda}{(\omega + T_4^*)(g\mu_4 + (1-k)\epsilon)}$$

$$V_7 = -(1-k)\lambda_1 N_4^*$$

$$V_8 = \frac{\lambda_3 \mu_4^2 g M_4^*(1-k)}{(g\mu_4 + (1-k)^2}$$

$$|J(P_e)| = \begin{vmatrix} V_0 & -V_2 & 0 & -V_7 \\ V_1 & V_3 & -V_5 & V_7 \\ 0 & V_4 & V_6 & V_8 \\ 0 & 0 & 0 & -\mu_4 \end{vmatrix} = 0 \tag{3.37}$$

we need to show that: $Trace(J(P_e)) < 0$
that is :
$Tr(J(P_e)) = (V_0 + V_3 + V_6 - \mu_4) = \alpha_1(1 - A_0) - 2\mu_1 N_4^* + d\alpha_2(1 - \mu_5) - \mu_4 + \frac{T_4^*(-\gamma_3(\omega - T_4^*) + (\rho)}{\omega + T_4^*} - \mu_3 - \frac{(1-k)^4\lambda_3\epsilon}{g\mu_4 + (1-k)\epsilon}$

Thus, $Tr(J(P_e)) < 0$ if $A_0 > 1$, $\mu_5 > 1$,$\rho < \gamma_3(\omega + T4^*$ with $A_0 = \frac{(1-k)^2\lambda_3\epsilon}{\alpha_1\mu_4}$
to show that $|J(P_e)| = (-\mu_4(V_0V_3V_6 + V_0V_4V_5 + V_1V_2V_6)) > 0$ let
$\zeta_1 = -\mu_4 V_0 V_3 V_6$
$\zeta_2 = -\mu_4 V_0 V_4 V_5$
$\zeta_3 = -\mu_4 V_1 V_2 V_6$
$\zeta_1 = (\alpha_1(1 - A_0) - 2\mu_1 N_4^*)(d\alpha_2(1 - \mu_5) - 2\mu_2 T_4^* - \gamma_2 M_4^*)(\frac{T_4^*(-\gamma_3(\omega - T_4^*) + (\rho)}{\omega + T_4^*}) -$
$\mu_3 - \mu_3 - \frac{(1-k)^4\lambda_3\epsilon}{g\mu_4 + (1-k)\epsilon})$
this implies $\zeta_1 > 0$ is positive if $A_0 > 1$, $\mu_5 > 1$, $\omega\rho < \gamma_3(\omega + T_4^*)$ with $A_0 = \frac{(1-k)^2\lambda_3\epsilon}{\alpha_1\mu_4}$ $\zeta_2 = (\alpha_1(1 - A_0) - 2\mu_1 N_4^*)(\frac{M_4^*}{(\omega + T_4^*)^2})(\omega\rho < \gamma_3(\omega + T_4^*))(-\gamma_2 T_4^*)$
this implies that $\zeta_2 > 0$ is positive if $A_0 > 1$, $\mu_5 > 1$, $\omega\rho < \gamma_3((\omega + T_4^*)^2)$ with $A_0 = \frac{(1-k)^2\lambda_3\epsilon}{\alpha_1\mu_4}$
$\zeta_3 = \mu_4 A_0 \phi_1 N_4^*(\frac{T_4^*(-\gamma_3(\omega - T_4^*) + (\rho)}{\omega + T_4^*}) - \mu_3 - \mu_3 - \frac{(1-k)^4\lambda_3\epsilon}{g\mu_4 + (1-k)\epsilon})$ This implies that $\zeta_3 < 0$ is a negative and by Routh-Hurwitz criterion the system cannot be stable. Thus the co-existing equilibrium point is always unstable if the cells coexist.

Global stability Theorem 1

If the equilibrium point P_0 is locally asymptotically stable in the interior of a positive quadrant D then it will be globally asymptotically stable there.

Proof

Define Dulac function $H_1 = \frac{1}{NTME} N, T, M, E > 0$

Also we set:

$f(N,T,M,E) = N(t)\alpha_1 - \mu_1(N(t))^2$

$g = (N,T,M,E) = T\alpha_2 - \mu_2 T^2 - \mu_5 T + (1-k)\lambda_1 NE - \gamma_2 MT$

$h(N,T,M,E) = s\beta + \frac{MT\rho}{\omega} - \mu_3 M$

$j(N,T,M,E) = (1-k)\epsilon - \mu_4 E$

in D dedcribed above,which is positive invariant and calculate$div(H_1 f, H_1 g, H_1 h, H_1 j)$ and apply Dulac-Bendixson Theorem we have:

$div(H_1 f, H_1 g, H_1 h, H_1 j) = \frac{\partial H_1 f}{\partial N} + \frac{\partial H_1 g}{\partial T} + \frac{\partial H_1 h}{\partial M} + \frac{\partial H_1 j}{\partial E}$ and after calculations (see Appendix) $div(H_1 f, H_1 g, H_1 h, H_1 j) = -\frac{\mu_1}{TME} - (\mu_2 + \frac{(1-k)\lambda_1}{NT^2}) - \frac{s\beta}{NTM^2E} - (1-k)\frac{\epsilon}{NTME^2} < 0$

hence it does not change sign, which implies there is no limit cycle or homoclinic connection observed in D So $P_0, P_{d1}, P_{d2}, Pd3, P_{d4}, P_e$ which are locally asymptotic stable in positive invariant subset D then They will be globally asymptotic stable in the interior of D.

Global stability Theorem 2

If the equilibrium point P^* is locally asymptotically stable in the interior of the positive definite set then it will be globally asymptotically stable there.

Proof

Consider the following Lyapunov function $V(N,T,M,E)$ around $P^* = (N^*, T^*, M^*, E^*)$

$V(N,T,M,E) = (N - N^* - N^* ln(\frac{N}{N^*}) + (T - T^* - T^* ln(\frac{T}{T^*}) + (M - M^* - M^* ln(\frac{M}{M^*}) + (E - E^* - E^* ln(\frac{E}{E^*})$

Differentiating V with respect to t, we get:

$V' = (N - N^*)\frac{N'}{N} + (T - T^*)\frac{T'}{T} + (M - M^*)\frac{M'}{M} + (E - E^*)\frac{E'}{E}$ Substituting system's equations from 3.5 to 3.8 in the above we get:

$V' = \frac{(N\alpha_1 - \mu_1 N - \phi_1 T) - (1-k)\lambda_1 NE)(N - N^*)}{N} + \frac{(Td\alpha_2 - \mu_2 T^2 - \gamma_2 MT - \mu_5 T + (1-k)\lambda_1 NE)(T -$

$\frac{(s\beta + \frac{\rho MT}{\omega + T} - \gamma_3 MT - \mu_3 M - (1-k)\frac{\lambda_3 ME}{g+E}(M - M^*)}{M} + \frac{((1-k)\epsilon - \mu_4 E)(E - E^*)}{E}$ and after some factorizing in some terms

$V' = -[(N - N^*)^2 \frac{\alpha_1}{N - N^*}) + (T - T^*)^2 \frac{(-\mu_2 - \mu_5 + \alpha_2 d)}{T - T^*} + (M - M^*)^2 (\frac{\mu_3}{M - M^*}) + (E -$

$E^*)^2 (\frac{(1-k)\epsilon}{E(E - E^*)}) + (N - N^*)(T - T^*)(-\frac{\mu_1 N}{T - T^*} - \frac{\gamma_2 M}{N - N^*} + (N - N^*)(M - M^*)(-\frac{\phi_1 T}{M - M^*} -$

$\frac{\gamma_3 T + \frac{s\beta}{M} + \frac{T\rho}{\omega + T}}{N - N^*}) + (N - N^*)(E - E^*)(\frac{(1-k)\lambda_1 \epsilon}{E - E^*} - \frac{\mu_4 E}{N - N^*}) + (T - T^*)(M - M^*)(\frac{(1-k)\lambda_1 NE}{T(M - M^*)} -$

$\frac{(1-k)\lambda_3 E}{(g+E)(T - T^*)} + (E - E^*)(M - M^*)0 + (T - T^*)(E - E^*)0]$

Thus $V'(N,T,M,E)$ is a quadratic form which can be expressed as $V = -x^T Ax$ where $x^T = (N - N^*, T - T^*, M - M^*, E - E^*)$ and A is symmetric matrix given by

$$A = \begin{bmatrix} a_{11} & a_{12} & a_{13} & a_{14} \\ a_{21} & a_{22} & a_{23} & a_{24} \\ a_{31} & a_{32} & a_{33} & a_{34} \\ a_{41} & a_{42} & a_{43} & a_{44} \end{bmatrix} \tag{3.38}$$

$$a_{11} = \frac{-\alpha_1}{N - N^*}$$
$$a_{12} = \frac{\mu_1 N}{T - T^*} + \frac{\gamma_2 M}{N - N^*}$$
$$a_{13} = \frac{\phi_1 T}{M - M^*} + \frac{\gamma_3 T + \frac{s\beta}{M} + \frac{T\rho}{\omega + T}}{N - N^*}$$
$$a_{14} = -\frac{(1-k)\lambda_1 \epsilon}{E - E^*} + \frac{\mu_4 E}{N - N^*}$$
$$a_{21} = \frac{\mu_1 N}{T - T^*} + \frac{\gamma_2 M}{N - N^*}$$
$$a_{22} = \frac{(-\mu_2 - \mu_5 + \alpha_2 d)}{T - T^*}$$
$$a_{23} = -\frac{(1-k)\lambda_1 NE}{T(M - M^*)} + \frac{(1-k)\lambda_3 E}{(g+E)(T - T^*)}$$
$$a_{24} = 0 \; a_{31} = \frac{\phi_1 T}{M - M^*} + \frac{\gamma_3 T + \frac{s\beta}{M} + \frac{T\rho}{\omega + T}}{N - N^*}$$
$$a_{32} = -\frac{(1-k)\lambda_1 NE}{T(M - M^*)} + \frac{(1-k)\lambda_3 E}{(g+E)(T - T^*)}$$
$$a_{33} = -\frac{\mu_3}{M - M^*}$$
$$a_{34} = 0$$
$$a_{41} = -\frac{(1-k)\lambda_1 \epsilon}{E - E^*} + \frac{\mu_4 E}{N - N^*}$$
$$a_{42} = 0$$
$$a_{43} = 0$$
$$a_{44} = -\frac{(1-k)\epsilon}{E(E - E^*)}$$

$V^{\cdot}$ is negative definite if $D_i < 0$ for all odd $i = (1, 2, ..., n)$ and $D_i > 0$ for all even $i = (1, 2, ...n)$ where D_i is the determinant of A matrix.
Hence the V is a Lyapunov function with respect to P^*.

CHAPTER 4

Optimal controlled therapies

SECTION 4.1

Control methods Introduction

Definitions

Consider the m-input , n-state system:

$x \in \mathbb{R}^{\mathbb{N}}, u \in \mathbb{R}^{\mathbb{M}}$ $\dot{x} = A(t)x + B(t)u, x(0) = x_0$

find open loop u(r), $r \in [t_0, t_f]$ such that the following objective function is minimized $J(u, x_0, t_0, t_f) = \int_{t_0}^{t_f} [x^T Q(t)x + u^T R(t)u]dt + x_(t_f)^T Sx(t_f)^T$

where Q(t) and S are**symmetric, positive semi definite** nxn matrices, R(t) is a symmetric mxm matrix and x_0, t_0, t_f are fixed given data.
The control is to keep x(t) close to 0, at a final time t_f using little control effort u. This formulation can accommodate regulating an output $y(t) = C(t)x(t) \in \mathbb{R}^{\mathbb{R}}$ at near zero. In this case one choice for S and Q(t) are $C(t)^T W(t)C(t)$ where $W(t) \in \mathbb{R}^{\mathbb{R}\chi\mathbb{R}}$ is symmetic positive definite matrix.
Such problems are called **controlled problems**.
Now consider : $x' = f(x, u), x \in \mathbb{R}^n$ x(0) given , $u \in \Omega \subset \mathbb{R}^p$ where :
$f(x, u) = f_1(x, u), ..., f_n(x, u) : \mathbb{R}^n \times \mathbb{R}^p \to \mathbb{R}^n$ We wish to minimize a cost function J with terminal constraints $J = \int_0^T L(x, u)dt + V(x(T))$

In the optimal control theory it proves very useful to apply an auxiliary function H of four variables defined by :
$H(t, x, u, p) = f(t, x, u) + pg(t, x, u) = x^T Qx + u^T Ru + \lambda^T(Ax + Bu)$ which is called the **Hamilton function** (or **Hamiltonian**) of the given problem.
Pontryagin's Maximum principle gives conditions that are necessary for an admissible pair (x^*, u^*) to solve a given control problem.

The Maximum principle Theorem

Assume that $x^*(t), u*(t)$ is an optimal pair for the problem Then there exist a continuous function $p = p(t)$,such that $\forall t \in [t_0, t_f]$ the following conditions are satisfied:

1. $u^*(t)$ maximizes $H(t, x^*, u, p)$ $u \in \mathbb{R}$ that is :
   $H(t, x^*(t), u(t), p(t)) \leq H(t, x^*(t), u^*(t), p(t))$ for all $u \in \mathbb{R}$
2. The function p(t) called **the adjoint function** satisfies the differential equation $-\dot{p} = \frac{\partial H}{\partial x}(t, x^*, u^*, p) = Qx + A^T\lambda$, $\lambda(T) = Sx(T)$
3. $x' = (\frac{\partial H}{\partial T})^T = Ax + Bu, x(0) = x_0$
4. $\frac{\partial H}{\partial u} = Ru + \lambda^T B \Rightarrow u = -R^-1B^T\lambda$
5. $0 = PA + A^T P + PBR^{-1}B^T P + Q, P(T) = S$ which is called the algebraic **Riccati Equation**
6. The function p obeys the condition $p(t_1) = 0$ (transversality condition) hence, by the Maximum Principle, it is necessary that:
   $\dot{p} = -\frac{\partial H^*}{\partial x} = -\frac{\partial f^*}{\partial x}$

SECTION 4.2

Quadratic optimal control for cancer chemotherapy

Optimally controlling chemotherapy

In this section, we formulated a corresponding optimal control problem for the model in the system considering ketogenic diet and anti-cancer drugs as control interventions to minimize the breast cancer and tumor burden at final time. The units of cells were normalized in order for the carrying capacity of normal cells to be kept above threshold of $0 \leq t \leq t_f$. On the other hand,the aim is to reduce the tumor-size which indicates the degree of the disease in the body and and it requires the application of as much anti-cancer drugs as much as possible. However, it also minimized the systemic cost, which is based on the quantities of anti-cancer drugs, since large drug concentrations can be harmful and cause toxic side effects. In brief, the drug doses were minimized because the smaller the dose, the better. Then, we formulated the objective functional J_1

$J_1(u_1, u_2) = \int_0^{t_f}(A_1T(t) + A_2E(t) + \frac{1}{2}A_3u_1^2(t) + \frac{1}{2}A_4u_2^2(t))dt$
system equations is subject to:

$$\begin{cases} \frac{\partial N}{\partial t} & = N\alpha_1 - \mu_1N^2 - TN\phi_1 - (1-u_1(t))\lambda_1NE \\ \frac{\partial T}{\partial t} & = T(1-u_2(t))\alpha_2 - \mu_2T^2 - \gamma_2MT - \mu_3M + (1-u_1(t))\lambda_1NE \\ \frac{dM}{dt} & = s\beta + \frac{\rho MT}{\omega+T} - \gamma_3MT - \mu_3M - (1-u_1(t))\frac{\lambda_3ME}{g+E} \\ \frac{\partial E}{\partial t} & = (1-u_1(t))\epsilon - \mu_4E \end{cases}$$

J_1 involves a quadratic control. In , it was established that quadratic control in the treatment terms has the added benefit of keeping the tumor in check both when it is small or large in size. Quadratic control allows a weaker treatment to minimize the toxic side-effects while permitting the system to maintain a low tumor size. Furthermore, for us to address the tumor-to-therapy trade-off, we established the existence of an optimal control , which required an analysis of super-solutions (that is, the upper bounds on solutions) of the system . As soon as we were able to show that the system is bounded, we established the existence of an optimal control using a result from . In addition, we proved that there exists an optimal control that minimizes the objective functional using the established approach of . We use the fact that super-solutions $\bar{N(t)}, \bar{T(t)}, \bar{M(t)}, \bar{E(t)}$ of

$$\begin{cases} \frac{\partial \bar{N}}{\partial t} = N\alpha_1 \\ \frac{\partial \bar{T}}{\partial t} = T\alpha_2(1-u_2(t) \\ \frac{\partial \bar{M}}{\partial t} = s\beta + \frac{MT\rho}{\omega+T} \\ \frac{\partial \bar{E}}{\partial t} = 1 \end{cases}$$

are bounded on a finite time interval. Since the sub-solutions are zero, the result obtained shows that our system is bounded.

Existence of an Optimal control

Given the objective functional $J_1(u_1, u_2) = \int_0^{t_f}(A_1T(t) + A_2E(t) + \frac{1}{2}A_3u_1^2(t) + \frac{1}{2}A_4u_2^2(t))dt$ where $U = (u_i^*, Lebesguemeasure, 0 \leq u_i^* \leq 1, \forall t \in [0,t])$ subject to the system of equations with $N(0) = N_0, T(0) = T_0, M(0) = M_0, E(0) = E_0$ then there exist an optimal control $\bar{u_i^*}$ such that
$min_{\bar{u_i^*} \in [0,1]} J(\bar{u_i}^*) = J_1(u_i(t)^*)$ if the following conditions holds:

- f is not empty
- The admissible control set U is closed and convex
- 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 $u_i(t)^*$) with coefficients depending on time and the state.

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

Proof Since the system has bounded coefficients and the solutions are bounded on the finite time interval.Furthermore, we note that U is closed and convex by definition. For the third conditions, the right hand side of the system 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 $\vec{\phi}(t, \vec{X})$ be right hand side of the system except for the terms of $\bar{u_i^*}$ and define.

$$|\vec{f}(t, \vec{x}, u_i^*| = \vec{\phi}(t, \vec{X}) + \begin{bmatrix} 0 \\ \lambda_1 NE \\ 0 \\ u_1 \end{bmatrix} \text{ with } \vec{X} = \begin{bmatrix} N \\ T \\ M \\ E \end{bmatrix} \text{ thus using the boundedness conditions}$$

we get:

where c_1 depends on the coefficients of the system. For the forth equation we need to show: $J(t, T, E, (1 - P_i)u_i + P_iV_i) < (1 - P_i)J(t, T, E, u_i) + P_i(t, T, E, V_i)$
we analyse the difference of
$J(t, T, E, (1 - P_i)u_i + P_iV_i) - [(1 - P_i)J(t, T, E, u_i) + P_i(t, T, E, V_i)] = T(t) + E(t) + \frac{\epsilon}{2}u_i^2 - 2P_iu_i^2 + P_i^2u_i^2 + P_i^2V_i^2 - 2P_i^2V_i^2u_i^2 + 2P_iV_iu_i - (T(t) + E(t) + \frac{\epsilon}{2}u_i^2 - \frac{\epsilon}{2}P_iu_i^2 + \frac{\epsilon}{2}P_iV_i^2 = \frac{\epsilon}{2}(P_i^2 - P_i)(u_i - V_i)^2$
since $P_i \in [0, 1]$ this 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, $J(t, T, E, (1 - P_i)u_i + P_iV_i) \leq (1 - P_i)J(t, T, E, u_i) + P_i(t, T, E, V_i)$
Lastly, $T(t) + E(t) + \frac{\epsilon}{2}u_i^2(t) \geq \frac{\epsilon}{2}u_i^2(t) \geq -c + \frac{\epsilon}{2}u_i^2$ which gives $-c + \frac{\epsilon}{2}u_i^2$ as the lower bound.This completes the proof of the existence of optimal control.We now use Pontryagin's maximim principle. The constants A_1, A_2, A_3, A_4 are a measure of the relative cost of the interventions over $[0, T]$. The Optimal control problem is that of finding optimal functions (u_i^*, u_2^*) such that: $J_1(u_i^*, u_2^*) = min_{\Omega J_1(u_1(t), u_2(t))}$ where:
$\Omega = (u_1 \& u_2 : 0 \leq u_1(t) \leq u_1(t), 0 \leq u_2^*(t) \leq u_2(t), t \in [0, T_f]$

Therapy strategies
Three different control strategies are explored. This approach can be used to test various options. However, we only looked at the following three alternatives:

1. Anti-cancer drug treatment control on tumor cells (control $u_1(t)$ only)

2. Ketogenic diet control on excess estrogen and tumor cells (control $u_2(t)$ only)

3. Anti-cancer drug and ketogenic diet treatment combined control on tumor cells growth and excess estrogen (controls $u_1(t)$ and $u_2(t)$).

Thus, strategies 1-3 use the objective functional . We assumed that there are practical limitations on the maximum rate at which the anti-cancer treatment may be applied in a given time period. We defined the positive constant u_{max} accordingly. We also define the set Ω of admissible controls to be all Lebesgue measurable functions that take on values in the control set $u = [0, u_{max}]$ almost everywhere on [0,T]. We sought an optimal control $u^* \in \Omega$. In order $H = L(N, T, M, E, u_1, u_2) + \theta_1 N_0 + \theta_2 T_0 + \theta_3 M_0 + \theta_4 E_0$ where: where L is the Lagrangian function
$H = (A_1T(t) + A_2E(t) + \frac{1}{2}A_3u_1^2(t) + \frac{1}{2}A_4u_2^2(t)) + \theta_1(N\alpha_1 - \mu_1N^2 - \phi_1NT - (1 - u_1(t))\lambda_1NE) +$

$\theta_2(T(1-u_2(t))\alpha_2 - \mu_2 T^2 - \gamma_2 MT - \mu_3 M + (1-u_1(t))\lambda_1 NE) + \theta_3(s\beta + \frac{\rho MT}{\omega+T} - \gamma_3 MT - \mu_3 M - (1-u_1(t))\frac{\lambda_3 ME}{g+E}) + \theta_4((1-u_1(t))\epsilon - \mu_4 E)$
where $\theta_1, \theta_2, \theta_3, \theta_4$ are the adjoints variables for the states N, T, M, E. However, with the help of Pontryagin's Maximum Principle, we obtained a minimized Hamiltonian that minimizes the objective function or cost functional. We applied Pontryagin's Maximum Principle , to characterize the optimal control pair u_1^* and u_2^* in the following result

Theorem Given optimal control variables $u_1^* \& u_2^*$ and $N^*, T^*, M^* \& E^*$ are corresponding optimal state variables of the control system. Then there exists the adjoint variable $\theta_i = (\theta_1, \theta_2, \theta_3, \theta_4) \in \mathbb{R}_+^4$ that satisfies the following equations.

$$\begin{cases} \frac{\partial \theta_1}{\partial t} = 2\theta_1\mu_1 N + \theta_1 T\phi_1 + (\theta_1+\theta_2)(1-u_2(t))\lambda_1 E - \alpha_1\theta_1 \\ \frac{\partial \theta_2}{\partial t} = -A_1 + \theta_1 N\phi_1 + \theta_2(2T\mu_2 + \gamma_2 M + \mu_5 - \alpha_2(1-u_2(t)) + \theta_3(\gamma_3 M - \frac{\omega\rho M}{(\omega+T)^2} \\ \frac{\partial \theta_3}{\partial t} = \theta_2\gamma_2 T - \theta_3\rho T + \gamma_3\theta_3 T + \mu_3\theta_3 T + \theta_3((1-u_1)\frac{\lambda_3 Mg}{(g+E)^2}) \\ \frac{\partial \theta_4}{\partial t} = -A_2 + (\theta_1-\theta_2)(1-u_1)\lambda_1 N - \theta_3((1-u_1)\frac{\lambda_3 Mg}{(g+E)^2} - \theta_4\mu_4 \end{cases}$$

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:
$u_1^* = min(max(0, \frac{1}{A_3}(\theta_2\lambda_1 N^* E^* + \theta_3\epsilon - \theta_1\lambda_1 N^* E^* - \frac{\theta_3\lambda_3 M^* E^*}{g+E^*}), 1)$
and $u_2^* = min(max(0, \frac{1}{A_4}(\theta_2\alpha_2 T^*), 1))$

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 that minimize the cost functional or objective . Then by Pontryagin's maximum principle,there exists adjoint variables $\theta_1, \theta_2, \theta_3, \& \theta_4$ which satisfy the following equations:
$\frac{\partial \theta_1}{\partial t} = -\frac{\partial H}{\partial N}, \frac{\partial \theta_2}{\partial t} = -\frac{\partial H}{\partial T}, \frac{\partial \theta_3}{\partial t} = -\frac{\partial H}{\partial M}, \frac{\partial \theta_4}{\partial t} = -\frac{\partial H}{\partial E}$ □

with transversality conditions: $\theta_1(T_f) = \theta_2(T_f) = \theta_3(T_f) = \theta_4(T_f) = 0$ where H is the Hamiltonian and defined as: $H(N, T, M, E, u_1, u_2, \theta) = L(N, T, M, E, u_1, u_2) + \theta_1 N' + \theta_2 T' + \theta_3 M' + \theta_4 E^*$
so substituting we get:

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

from the optimality condition we have:
$\frac{\partial H}{\partial u_1} = 0$ at $u_1 = u_1^*$
and
$\frac{\partial H}{\partial u_2} = 0$ at $u_2 = u_2^*$
which implies that:
$\frac{\partial H}{\partial u_1} = A_3 u_1 + \theta_1\lambda_1 NE - \theta_2\lambda_1 NE + \theta_3\frac{\lambda_3 ME}{g+E} - \theta_4\epsilon = 0$

and

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

hence we obtain:

$u_1^* = \frac{\theta_2\lambda_1 NE + \theta_4\epsilon - \theta_1\lambda_1 NE - \theta_3\frac{\lambda_3 ME}{g+E}}{A_3}$
and
$u_2^* = \frac{1}{A_4}(\theta_2\alpha_2 T)$
By standar control arguments involving the bounds on the controls, we conclude that:

$$u_1^* = \begin{cases} 0 & if, \frac{\theta_2\lambda_1 NE + \theta_4\epsilon - \theta_1\lambda_1 NE - \theta_3\frac{\lambda_3 ME}{g+E}}{A_3} < 0 \\ \frac{\theta_2\lambda_1 NE + \theta_4\epsilon - \theta_1\lambda_1 NE - \theta_3\frac{\lambda_3 ME}{g+E}}{A_3} & if, 0 \leq \frac{\theta_2\lambda_1 NE + \theta_4\epsilon - \theta_1\lambda_1 NE - \theta_3\frac{\lambda_3 ME}{g+E}}{A_3} \leq 1 \\ 1 & if, \frac{1}{A_4}(\theta_2\alpha_2 T) > 1 \end{cases}$$

and

$$u_2^* = \begin{cases} 0 & if, \frac{1}{A_4}(\theta_2\alpha_2 T) < 0 \\ \frac{1}{A_4}(\theta_2\alpha_2 T) & if, 0 \leq \frac{1}{A_4}(\theta_2\alpha_2 T) \leq 1 \\ 1 & , if \frac{1}{A_4}(\theta_2\alpha_2 T) > 1 \end{cases}$$

SECTION 4.3

H_∞ methods

The phrase H_∞ control comes from the name of the mathematical space over which the optimization takes place: H_∞ is the Hardy space of matrix-valued functions that are analytic and bounded in the open right-half of the complex plane defined by $Re(s)$ The H_∞ norm is the maximum singular value of the function. There are methods being used in control theory to synthesize controllers to achieve stabilization with guaranteed performance. To use H_∞ methods, a control designer expresses the control problem as a mathematical optimization problem and then finds the controller that solves this optimization.

The "plant" is a given system with two inputs and two outputs. It is often referred to as the generalized system. The signal is an external input and represents driving signals that generate disturbances, measurement noise, and reference inputs. The signal is the control input. The output has the meaning of control error and ideally should be zero. The output finally, is the observed output and is available for feedback.

State Feedback problem

$X' = Ax + Bu + Gw$

$z = \begin{bmatrix} Hw \\ \\ u \end{bmatrix}$ u: input , w:disturbances

we seek a control law $u = Kx$ such that the control-loop system is stable and has $||H||_\infty < \gamma$ then system becomes:

$X' = (A + BK)x + Gw$

$z = \begin{bmatrix} Hw \\ \\ u \end{bmatrix}$ and must have:

$(A + BK)^T P + P(A + BK) + HH^T + KK^T + \frac{1}{\gamma^2} PGG^T P < 0$ and by choosing $K = -B^T P$,which is called **state-feedback gain**

$0 = A^T P + PA + HH^T + \frac{1}{\gamma^2} PGG^T P - PBB^T P$

Differential game

Consider $x' = Ax + Bu + Gw$

and $J = \int_O^\infty x^T H^T Hx + u^T u - \gamma^2 \omega^T \omega dt$

- u seeks to minimize J
- w seeks to maximize J

subject to both signal of finite energy

- Differential game has a Nash equilibrium
- the equilibrium involves both players employing a state feedback strategy, where $u(t) = Kx(t)$ is the **best control** and $K_d = -\frac{1}{\gamma^2} G^T P$ has the **worst disturbance** , $P \geq 0$ a stabilizing solution of $0 = A^T P + PA + HH^T + \frac{1}{\gamma^2} PGG^T P - PBB^T P$

Since the aim of this work is to design robust control for the system, deriving a linear model is necessary, as the H_∞ control design requires a linear nominal model. The linear model is acquired by working point linearization. We will linearize around steady state P_0 Let:

$$\vec{x_i'} = f(\vec{x_i}) \tag{4.1}$$

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

$$\vec{x'} = \begin{bmatrix} N' \\ T' \\ M' \\ E' \end{bmatrix} = \begin{bmatrix} f_1(N, T, M, E, u_1, u_2) \\ f_2(N, T, M, E, u_1, u_2) \\ f_3(N, T, M, E, u_1, u_2) \\ f_4(N, T, M, E, u_1, u_2) \end{bmatrix}$$

using Taylor's Expansion Series we get :

$f_i = f_i(N_0, T_0, M_0, E_0) + \frac{\partial f_i}{\partial N}\delta N + \frac{\partial f_i}{\partial T}\delta T + \frac{\partial f_i}{\partial M}\delta M + \frac{\partial f_i}{\partial E}\delta E$

calculated around P_0 for every $i = 1, 2, 3, 4$

The first term equals to 0 due to P_0 is a steady state point. Thus the system becomes: $x' = x_0' + \delta x'$

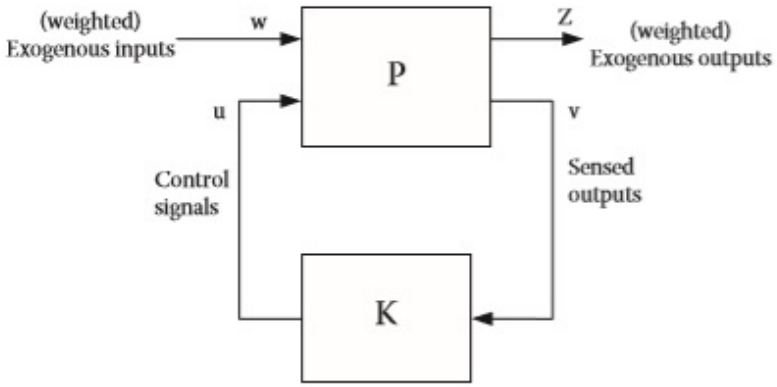
$$\delta x' = \begin{bmatrix} \frac{\partial f_1}{\partial N} & \frac{\partial f_1}{\partial T} & \frac{\partial f_1}{\partial M} & \frac{\partial f_1}{\partial E} \\ \frac{\partial f_2}{\partial N} & \frac{\partial f_2}{\partial T} & \frac{\partial f_2}{\partial M} & \frac{\partial f_2}{\partial E} \\ \frac{\partial f_3}{\partial N} & \frac{\partial f_3}{\partial T} & \frac{\partial f_3}{\partial M} & \frac{\partial f_3}{\partial E} \\ \frac{\partial f_4}{\partial N} & \frac{\partial f_4}{\partial T} & \frac{\partial f_4}{\partial M} & \frac{\partial f_4}{\partial E} \end{bmatrix} \begin{bmatrix} \delta N \\ \delta T \\ \delta M \\ \delta E \end{bmatrix} + \begin{bmatrix} \frac{\partial f_1}{\partial u_1} & \frac{\partial f_1}{\partial u_2} \\ \frac{\partial f_2}{\partial u_1} & \frac{\partial f_2}{\partial u_2} \\ \frac{\partial f_3}{\partial u_1} & \frac{\partial f_3}{\partial u_2} \\ \frac{\partial f_4}{\partial u_1} & \frac{\partial f_4}{\partial u_2} \end{bmatrix} \begin{bmatrix} \delta u_1 \\ \delta u_2 \end{bmatrix}$$

$\delta x' = A\delta x + B\delta u$

$\delta \vec{y} = \delta \vec{x}$ and $\vec{z} = H\vec{x} = \begin{bmatrix} 0 & A_1 & 0 & A_2 \end{bmatrix}$

Finally we get:

$$\begin{cases} x' = Ax + B_1 w + B_2 u \\ z = C_1 x + D_{11} w + D_{12} u \\ y = C_2 x + D_{21} w + D_{22} u \end{cases}$$



H infinity control setup

The objective of the problem is to design a linear, robust controller, which achieves good tracking property, takes into account the model uncertainties and limits the magnitude of the control input and the disturbance. The signals of the system are the following:

- r is the reference,
- u is the control input,
- y is the output,
- n is the measurement noise,
- z_p is the penalized control input, whereas
- z_n is the deviation of the output from the required one. The closed-loop system includes the feedback structure of the nominal model G_n and the two-degree controller
- $K = \begin{bmatrix} K_f & -K_y \end{bmatrix}$ which is portioned in two parts:

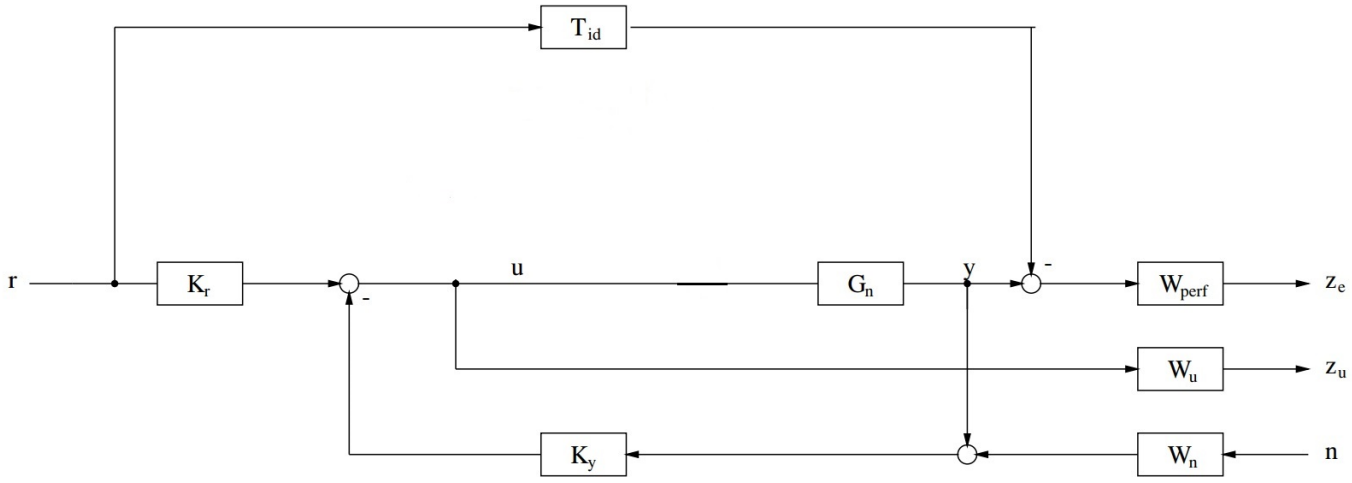
- K_y is the feedback part to meet the requirements of internal and robust stability, disturbance rejection, measurement noise attenuation, and sensitivity minimisation, while

- K_r is the prefilter part, which optimises the response of the overall system to the command input such that the output of the system would be near to that of the chosen ideal system.

The input multiplication uncertainty W_u takes into consideration the differences between the nominal model and the real plant. The weighting function W_n stands for the limitation of sensor noise. The limitation of the control input is achieved by the weighting function W_u which penalizes larger deflections. The model matching function T_{id} describes the ideal transfer function of the plant. Since the designed controller should effect tumor regression even in the worst case, the reference model, T_{id} describes fast regression from the maximal tumor volume predicted by the model. The weighting function W_p penalizes tracking.

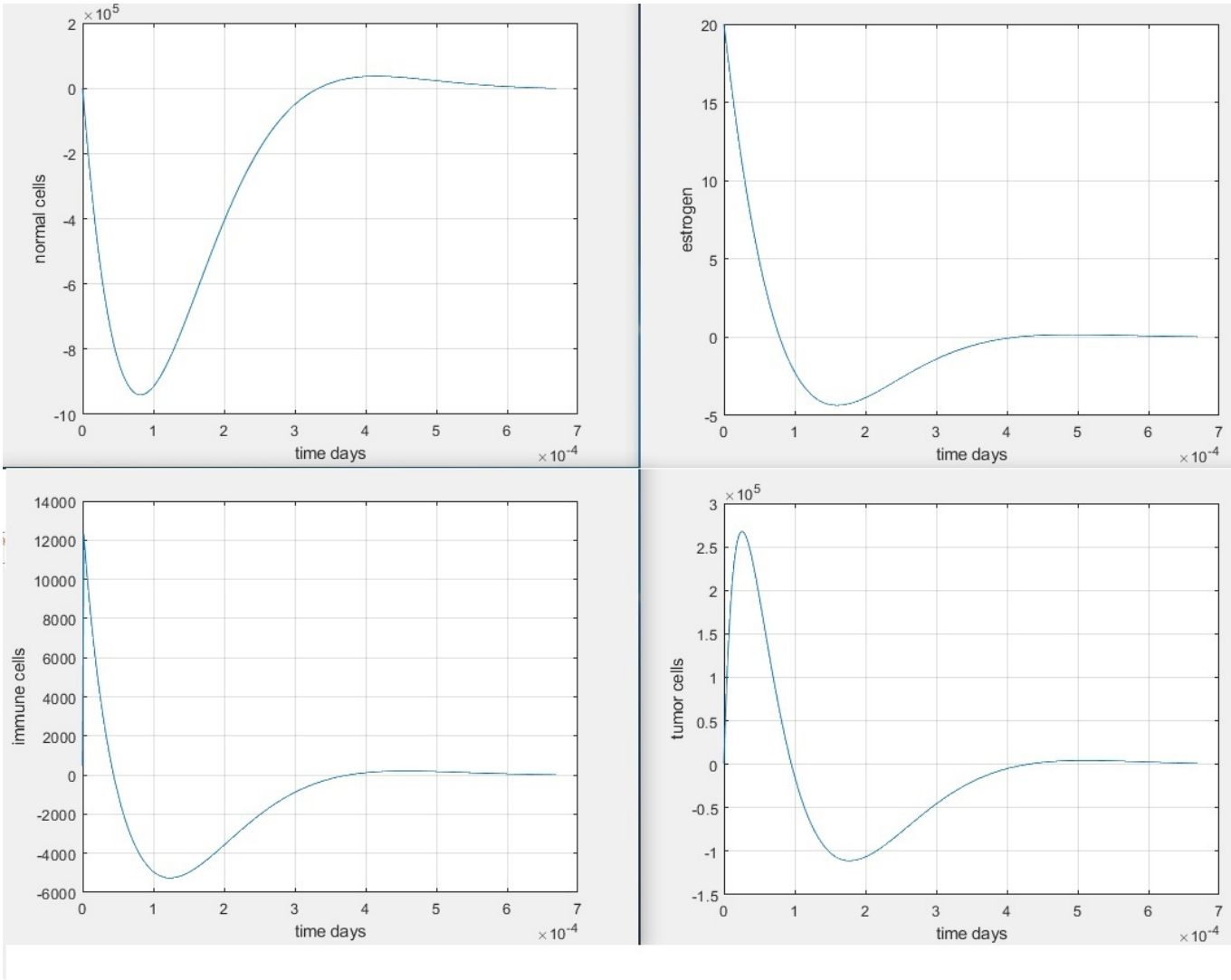
$$P = \begin{bmatrix} z_p \\ z_n \\ r \\ y \end{bmatrix} = \begin{bmatrix} -W_p T_{id} & 0 & W_p G \\ 0 & 0 & W_u \\ I & 0 & 0 \\ 0 & W_n G & 0 \end{bmatrix} = \begin{bmatrix} A & B_1 & B_2 \\ C_1 & D_{11} & D_{12} \\ C_2 & D_{21} & D_{22} \end{bmatrix}$$

where : $z_p = W_p[Gu - T_{id}r] = W_pGu - W_pT_{id}r$
$z_u = W_nu$
$y = Gu + W_nn$
$u = K_fr - K_y(Gu + W_nn)$



SECTION 4.4

Linearized system simulation



Conclusions

A new nonlinear control method has been developed for a mathematical model studying breast cancer,based on approximate linearization and stability theory. Above it has been shown that the proposed method enables the state vector elements to track all the reference points succesfully. The first stage of the proposed control method is the linearization of the dynamic model using first order Taylor series expansion and the computation of the associated Jacobian matrices. The errors due to the approximative linearization have been considered as disturbances that affect,along with external pertubation the cancer model. Feedback control scheme enabled accurate convergence,as diagrams show.

CHAPTER 5

Numerical Simulations

SECTION 5.1

System simulation

A picture of the dynamical behavior of breast cancer cells in the presence of normal cells, tumor cells, immune cells, and estrogen is given by the numerical simulations of the model. The optimal control is acquired by solving the optimality system of four ordinary differential equations from the state variables and the adjoint system. An iterative scheme is used to solve the optimality system.

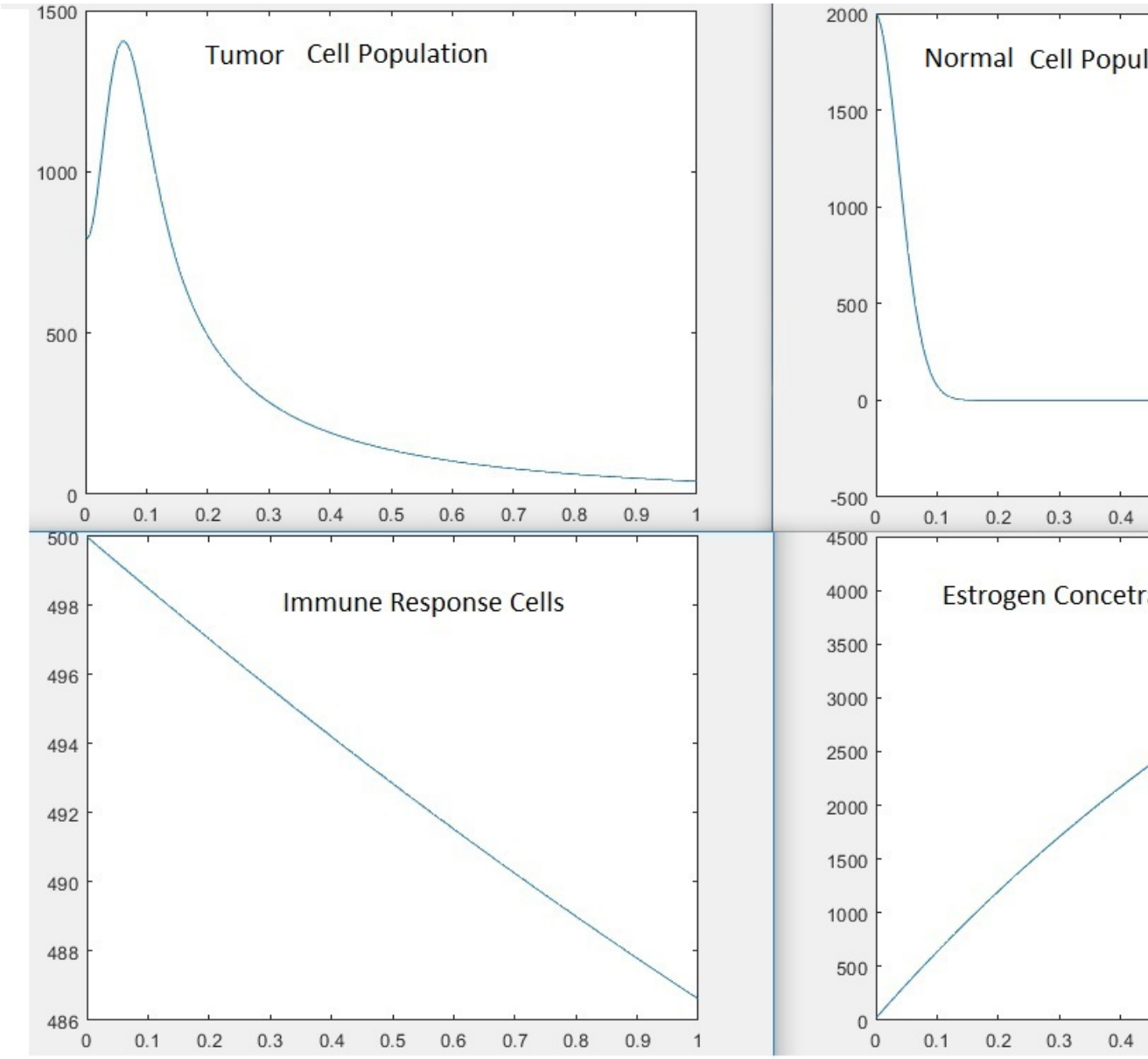
All the numerical simulations were executed in Matlab 2018Rb. We employed the forward-backward scheme method, beginning with an initial guess for optimal controls and solved the optimal state system forward in time and after that solved the adjoint state system backward in time. The aim of the therapy is to kill the tumor cells while minimizing the amount of drug application, which also reduces the possible detrimental toxicity effect, caused by the excess usage of the chemotherapy drugs. In the simulated cancer model, the healthy equilibrium point P_0 is locally stable, which means that the growth of cancer is controllable if a sufficient immune surveillance is guaranteed. In the absence of sufficient immune control, the tumor cells grow in number and kill the healthy tissue cells and reach the limit capacity, which is referred to as dead equilibrium point. In our simulations, in order to avoid selfcontrol of the immune system on the cancer cells, we choose a scenario where the initial immune cell population is very small and the tumor cell population is large, so that tumor growth is inevitable unless chemotherapy is applied. The initial states, i.e., the conditions when the chemotherapy treatment is started, are assumed to be : $N(0) = 2000, T(0) = 800, M(0) = 500, E(0) = 20$

While the initial values of variables are displayed in the chart below:

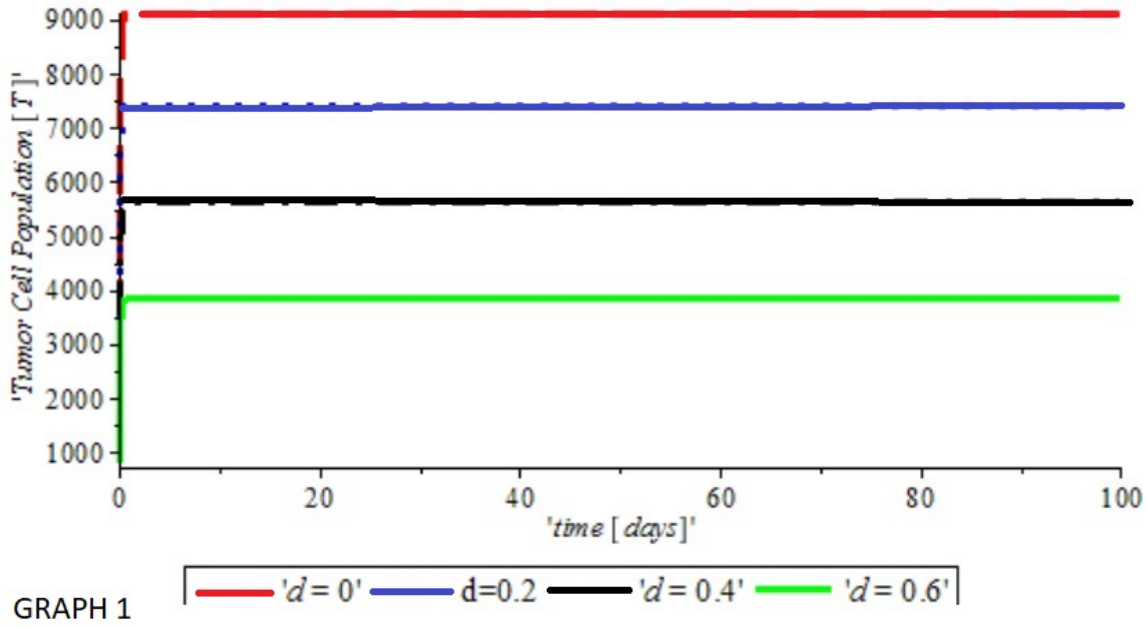
Parameter	Symbol	Value	Unit
Per capita growth rate of normal cells	α_1	0.70	day^{-1}
Per capita growth rate of tumor cells	α_2	0.514	day^{-1}
Natural death rate of normal cells	μ_1	0.00003	day^{-1}
Natural death rate of tumor cells	μ_2	0.01	day^{-1}
Rate of inhibition of normal cells	ϕ_1	6×10^{-8}	day^{-1}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

Data were imported to Matlab r2018a

Simulation of the system in Matlab gave us the populations of each cell type:



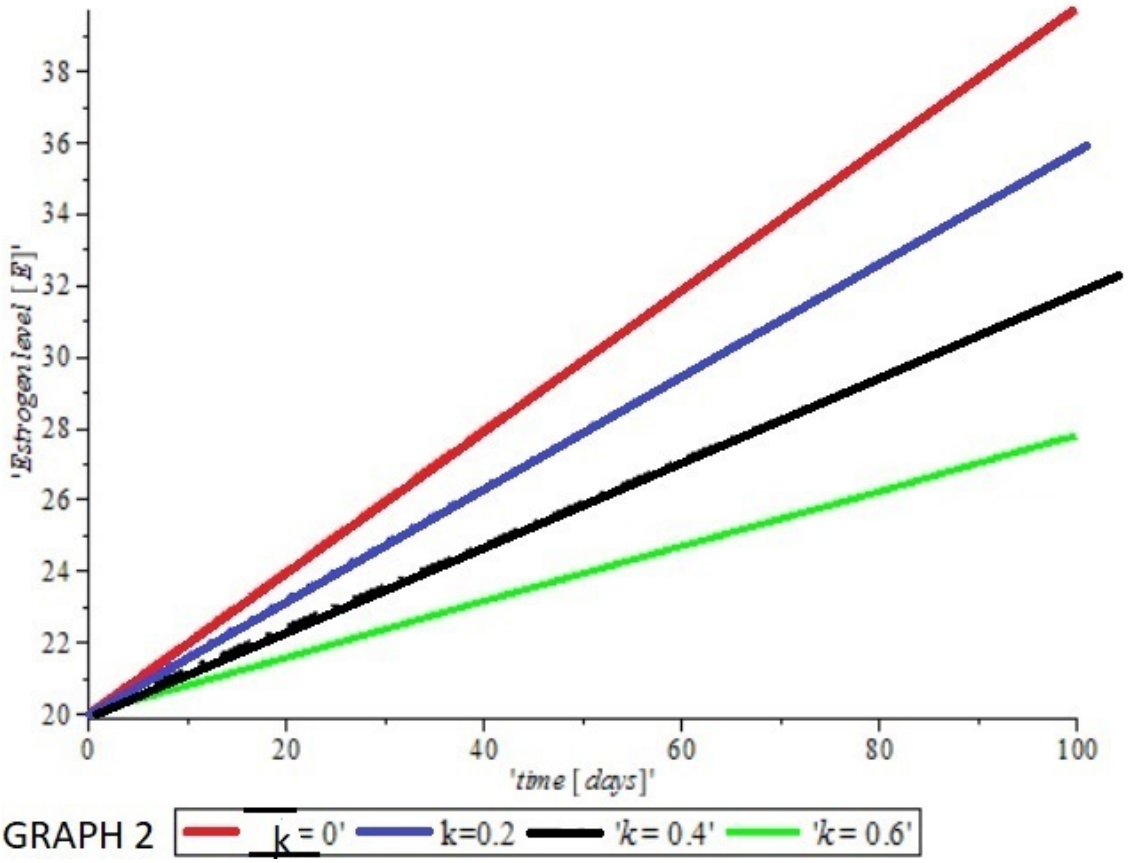
The variation of proportion of Tumor cell population for different values of d with other parameters fixed.



GRAPH 1

Graph 1 indicates that the introduction of a ketogenic diet results in a reduction of activities of cancer cells and we also note that too much of a ketogenic diet will result in ketoacidosis. **Ketoacidosis** is the combination of ketosis and acidosis. Ketosis is the accumulation of substances called ketone bodies and acidosis is the increased acidity of the blood which can cause frequent urination (Polyuria),poor appetite, and a loss of consciousness. Therefore, our ketogenic diet's parameter rate is best at d = 0.6 and it can complement the activity of the anti-cancer drug (Tamoxifen).

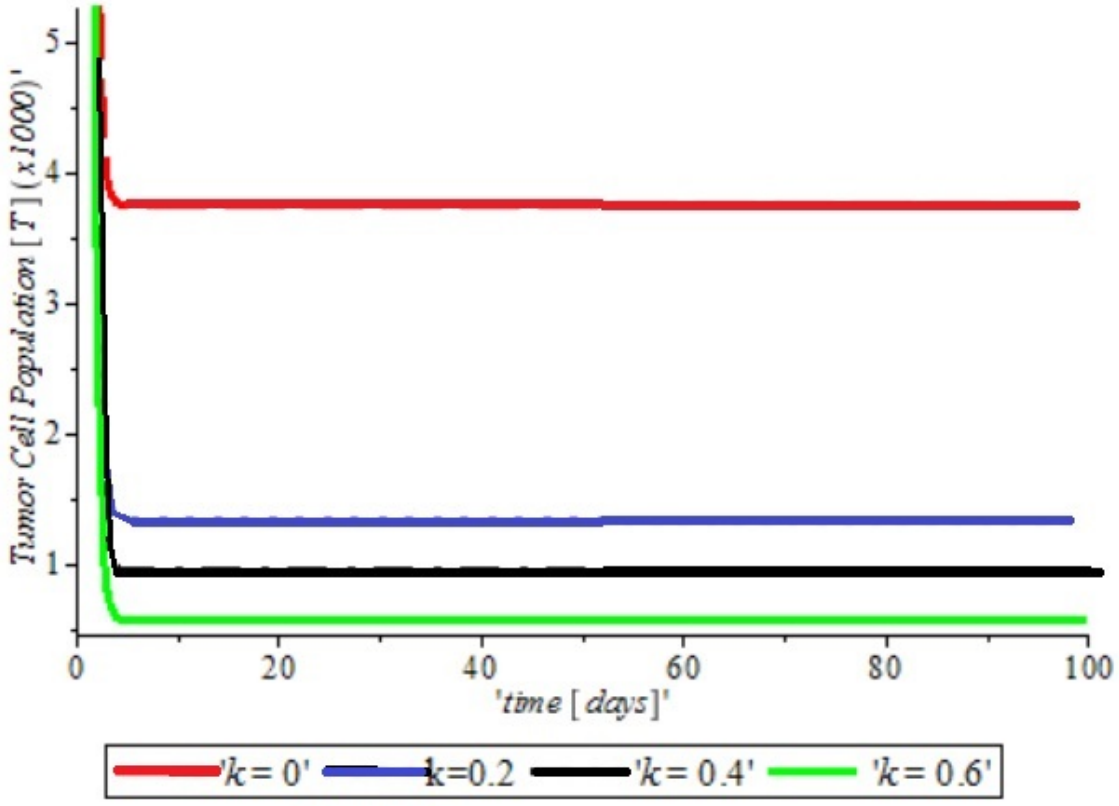
The variation of proportion of Estrogen level population for different values of k with other parapeters fixed



GRAPH 2

Graph 2 shows the impact of anti-cancer drugs in reducing the production of excess estrogen in the system, but when there is less production of estrogen there will not be a rapid activation of the growth factor that expresses breast normal cells. However, the rapid production of estrogen results in abnormal breast cells expression, which will lead to breast cancer.

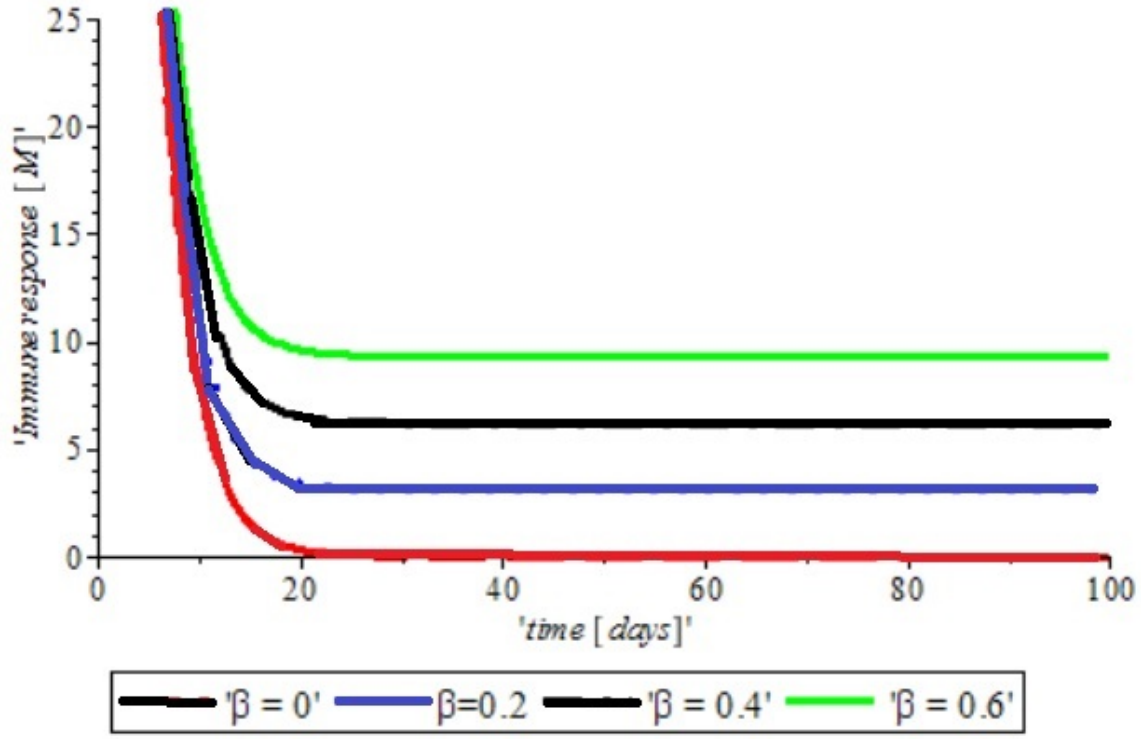
The variation of proportion of Tumor cell population for different values of k with other parameters fixed



Graph 3

Graph 3 shows the obvious effectiveness of anti-cancer drugs on tumor cells when there is no supply of nutrient or glucose to cancer cells.

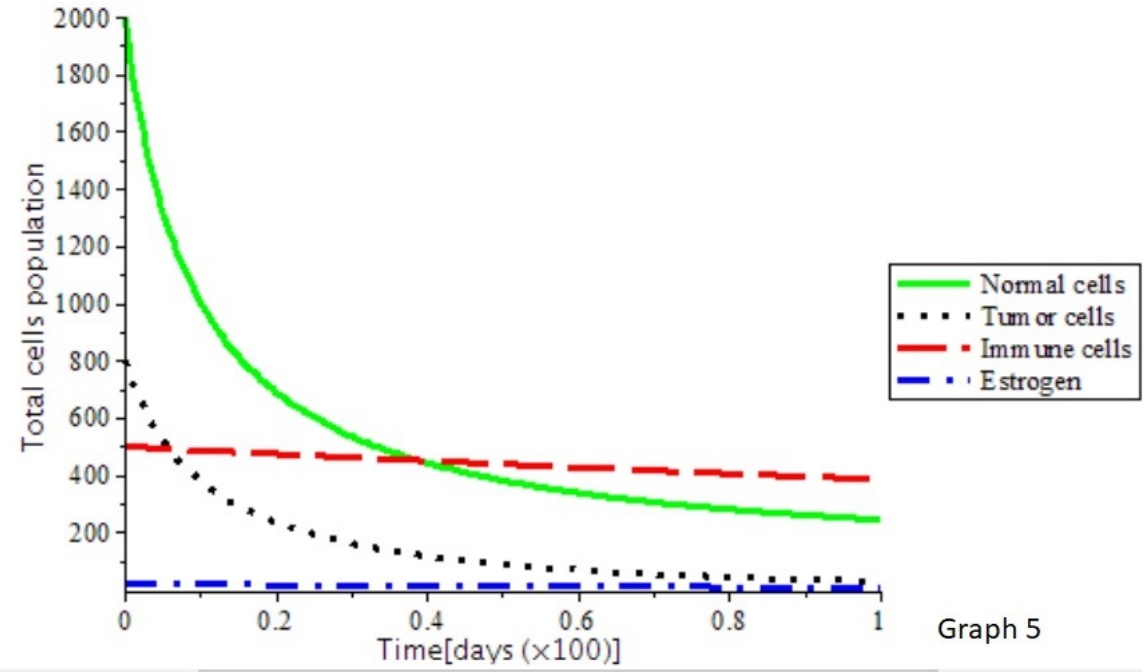
The variation of proportion of Immune booster population for different values of β with other parameters fixed.



Graph 4

Furthermore, Graph 4 illustrates that the red line $\beta = 0$ shows that during cancer formation the activities of both innate and adaptive reduces drastically, which is due to the expression of other proteins apart from those proteins that are responsible for the activation of the immune response, such as an immune booster introduced to the system, which reactivates the activities of the immune response towards the cancer cells.

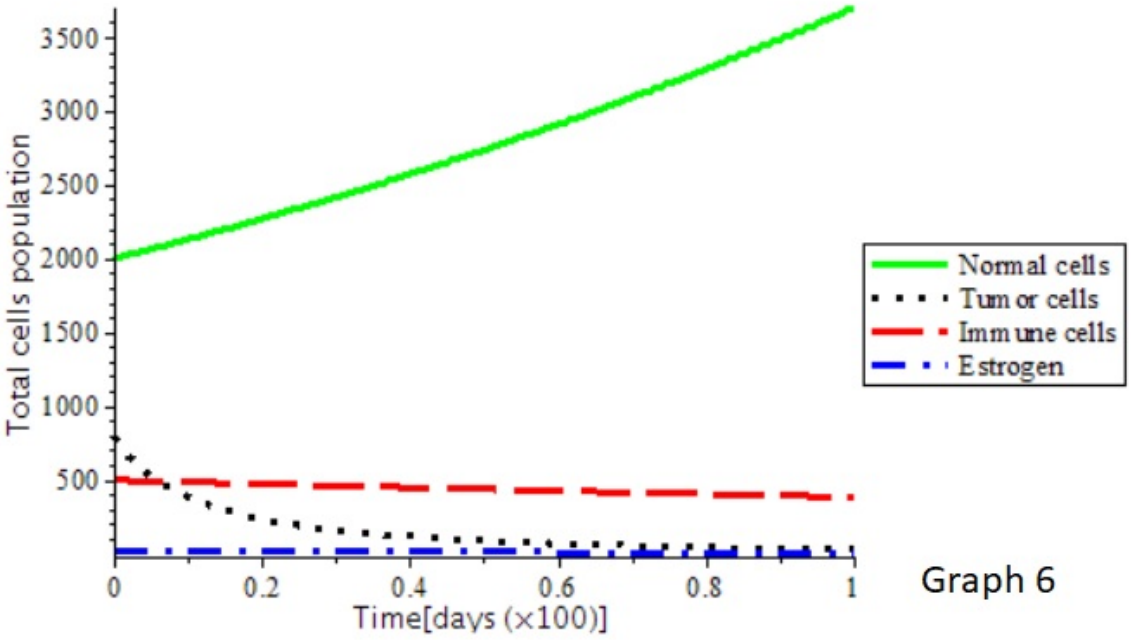
The variation of Total cells population depicted as locally asymptotically unstable.



Graph 5

The presence of abnormal estrogen level without anti-cancer drugs or a ketogenic diet will lead the system into critical condition and became unstable (Graph 5).

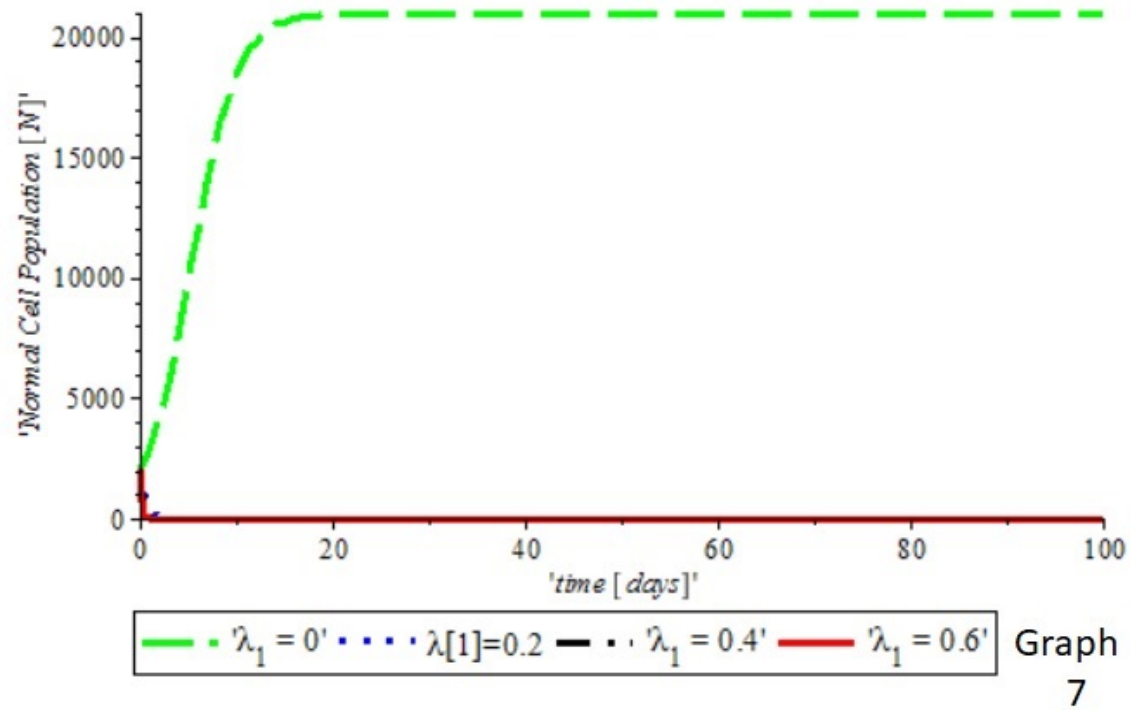
The variation of proportion of Normal cell population for different values of λ_1 with other parameters fixed



Graph 6

However, the system became stable as we introduced treatments, such as chemotherapy and the ketogenic diet as represented in Graph 6.

The variation of proportion of Normal cell population for different values of λ_1 with other parameters fixed



Graph 7

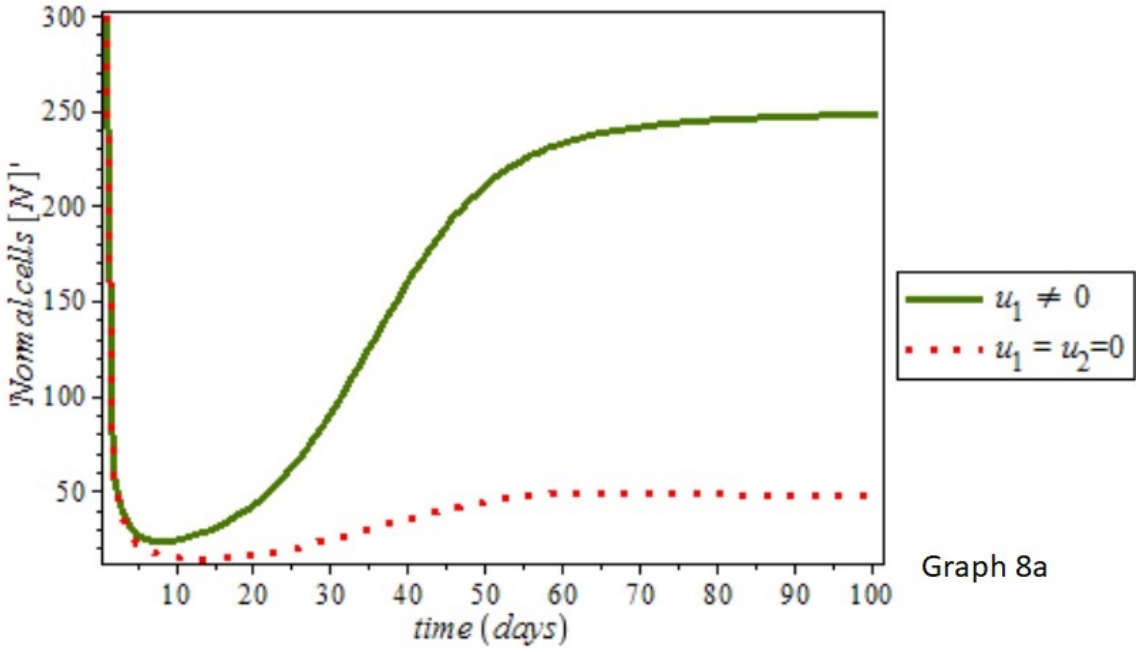
Graph 7, indicates that there is DNA damage at $\lambda_1 = 0$, which occurs naturally as a result of metabolic or hydrolytic processes. It is as a result of the Tumor Suppressor Gene

(TSG), which is able to control the activity of DNA gene repair successfully. On the other hand, at $\lambda_1 = 0.2, 0.4, 0.6$ showed that TSG (such as BRCA 1, BRCA 2, P53) compromised the pathway that leads cells to grow uncontrollably and later form a tumor or it leads to accelerated aging.

Control therapies on the system

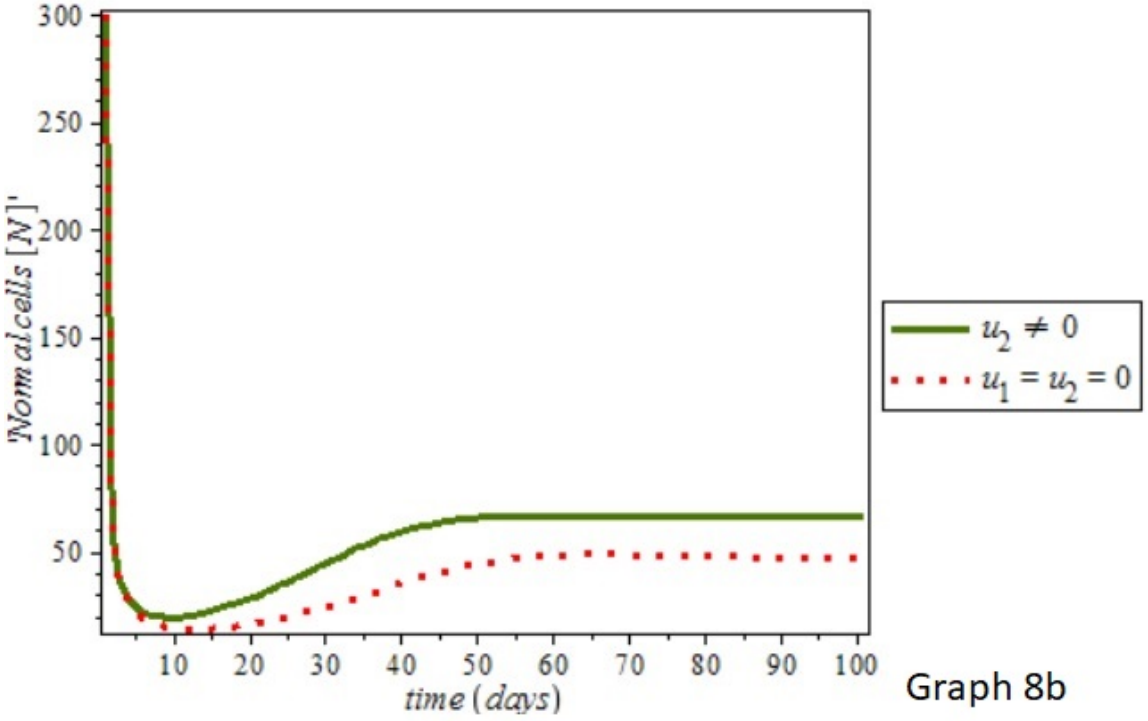
By numerical simulation, optimal single control of anti-cancer drugs measure u_1 and ketogenic-diet optimal control measure u_2 respectively. We set the time period in 100 days and we run the simulation with each,both and no therapies applied.

Simulation results showing population of normal cells against time, with and without control.



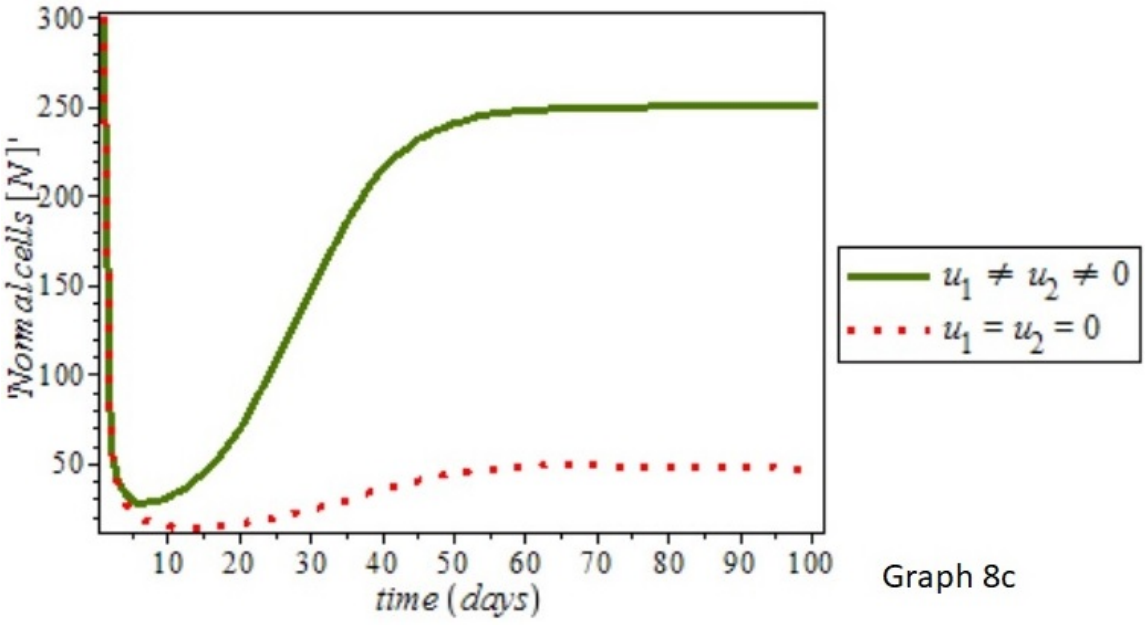
Graph 8a

Graph 8a shows the optimal single control of anti-cancer drugs



Graph 8b

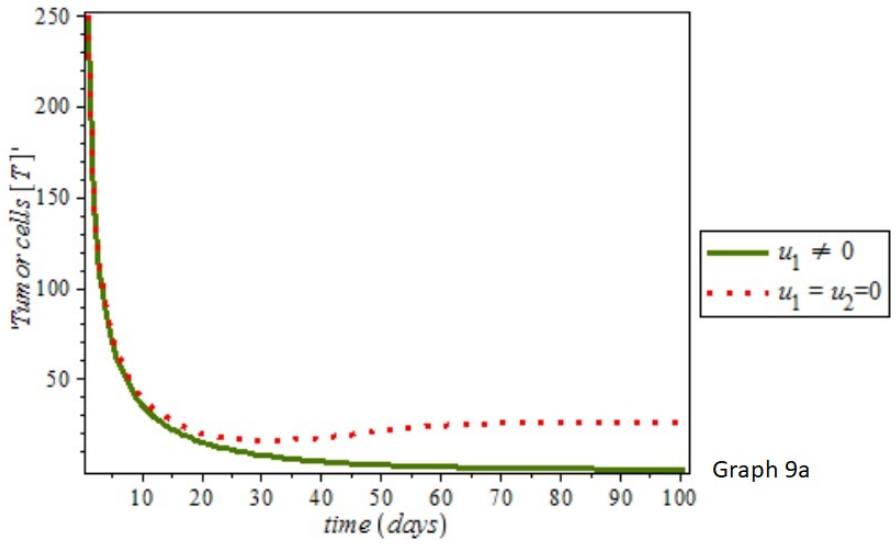
Graph 8b shows the optimal single control of ketogenic-diet



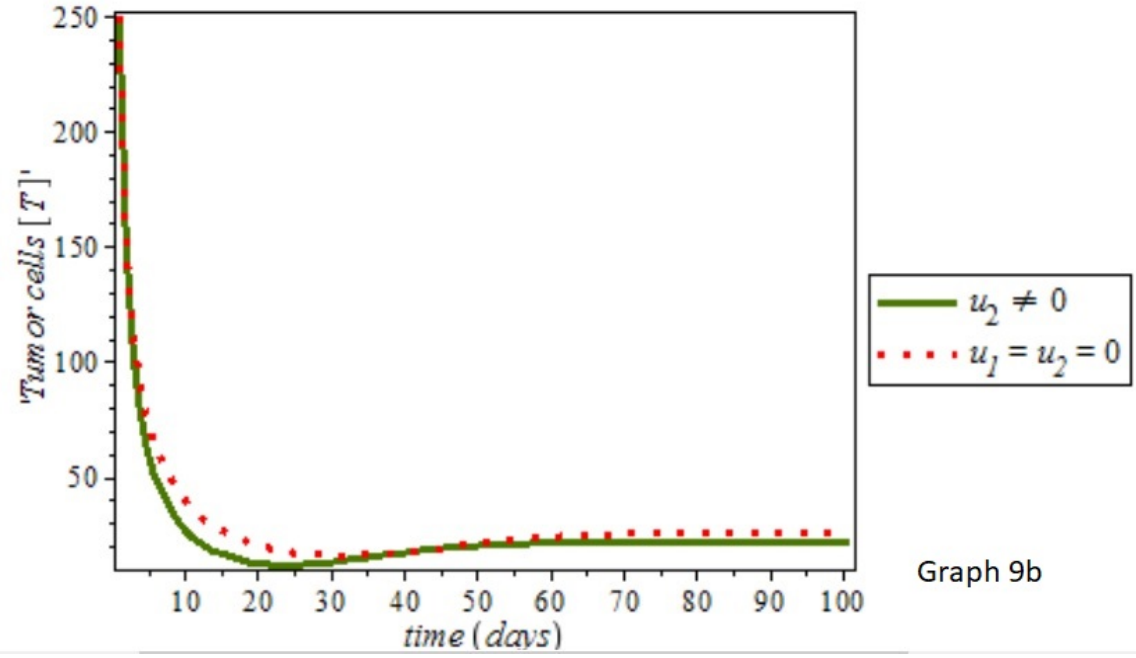
Graph 8c

Graph 8c is the use of combination of two control therapies which have significant impact on the increase of normal cells population against time. However, all the strategies are effectively restrain the tumor growth, they cannot totally eliminate a large tumor in 100 days.

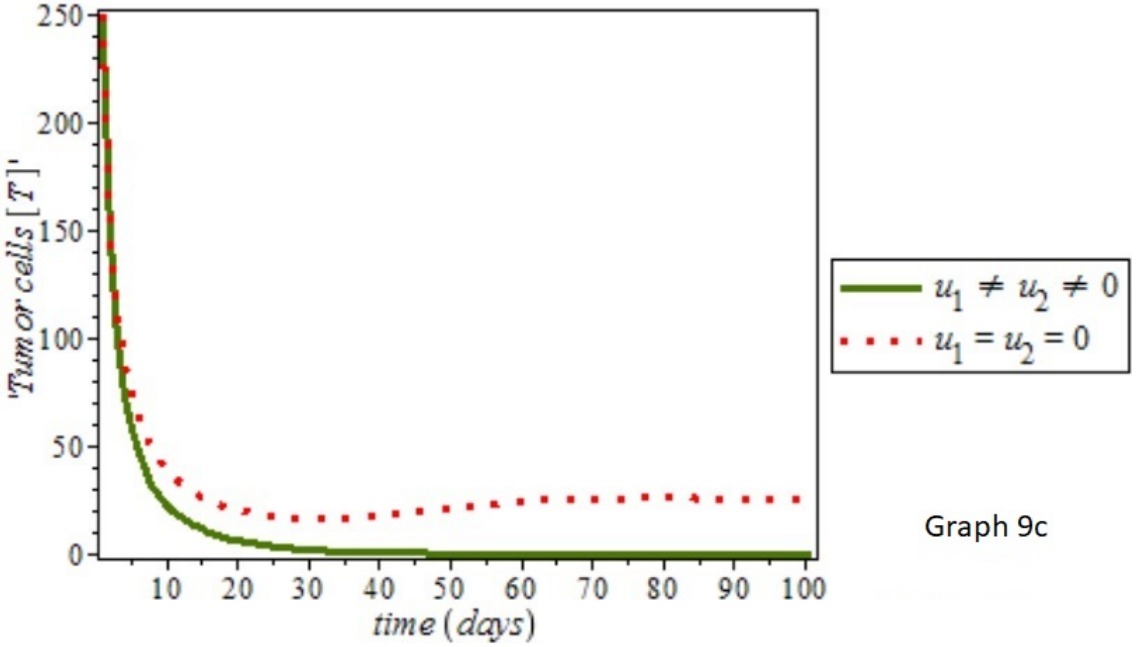
Simulation results showing population of tumor cells against time, with and without control.



Graph 9a



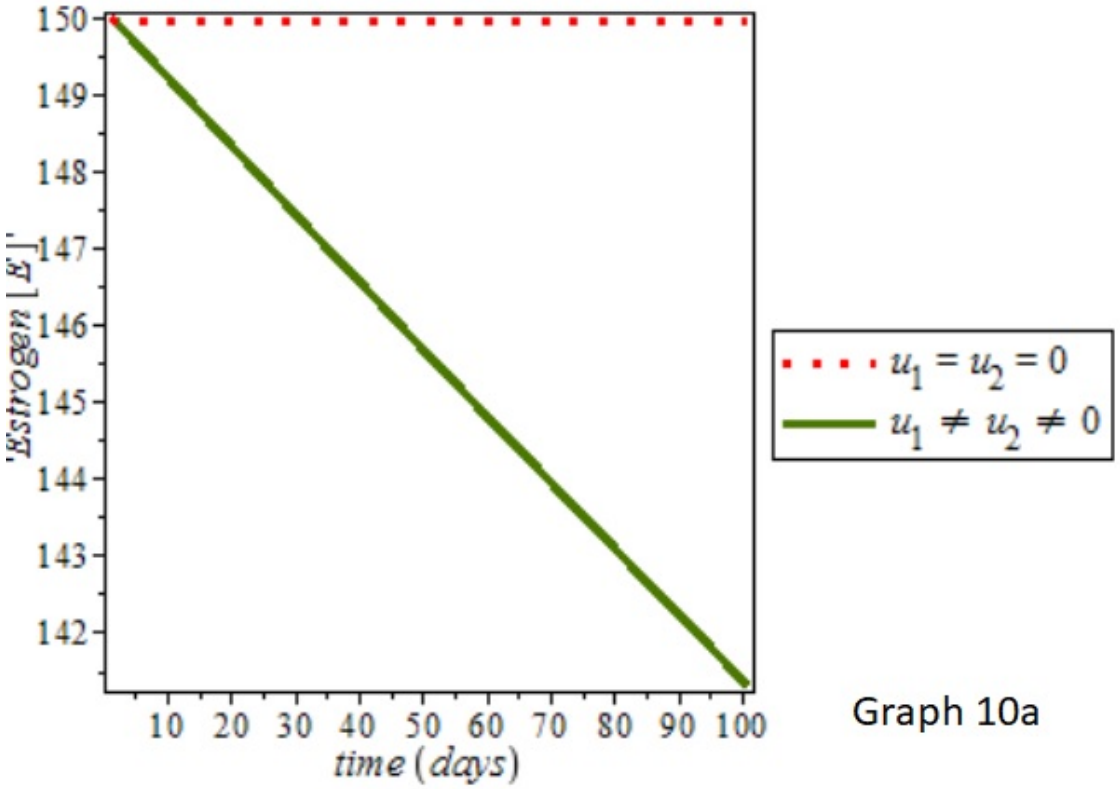
Graph 9b



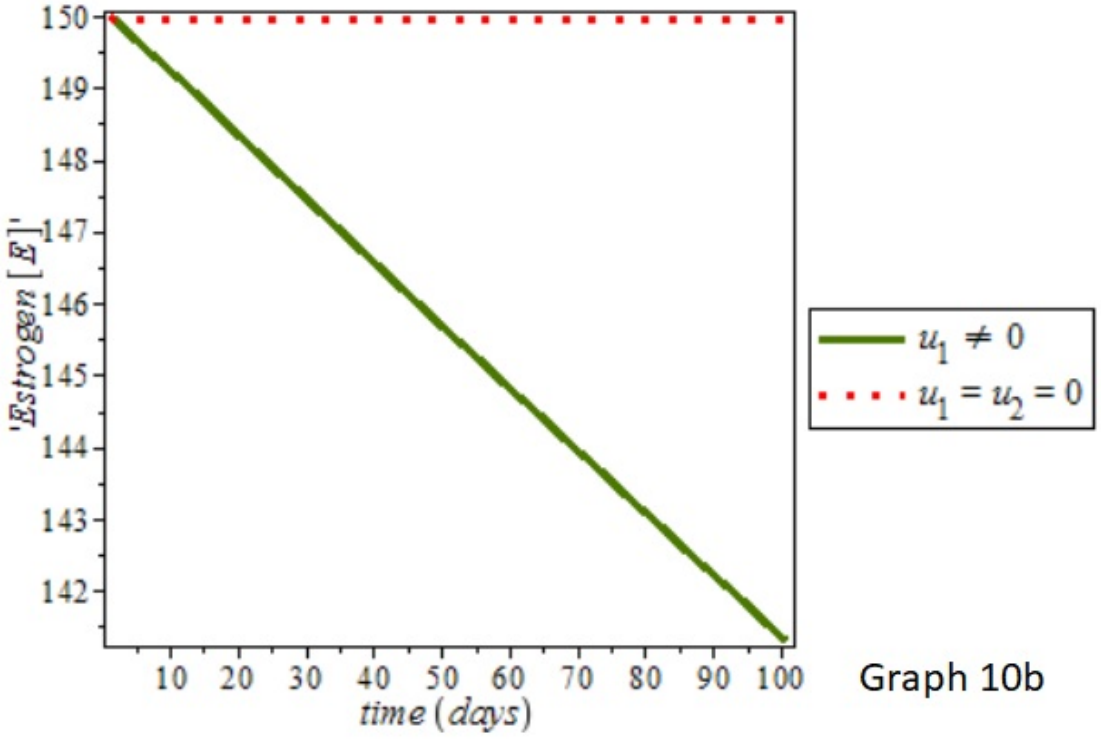
Graph 9c

It is observed that the combination of the two controls resulted in appreciable decreases in the number of tumor cells population in the presence of control (solid green line) while (dots red line)in the case of uncontrolled. However, tumor growth is driven to a very low but non-zero level.

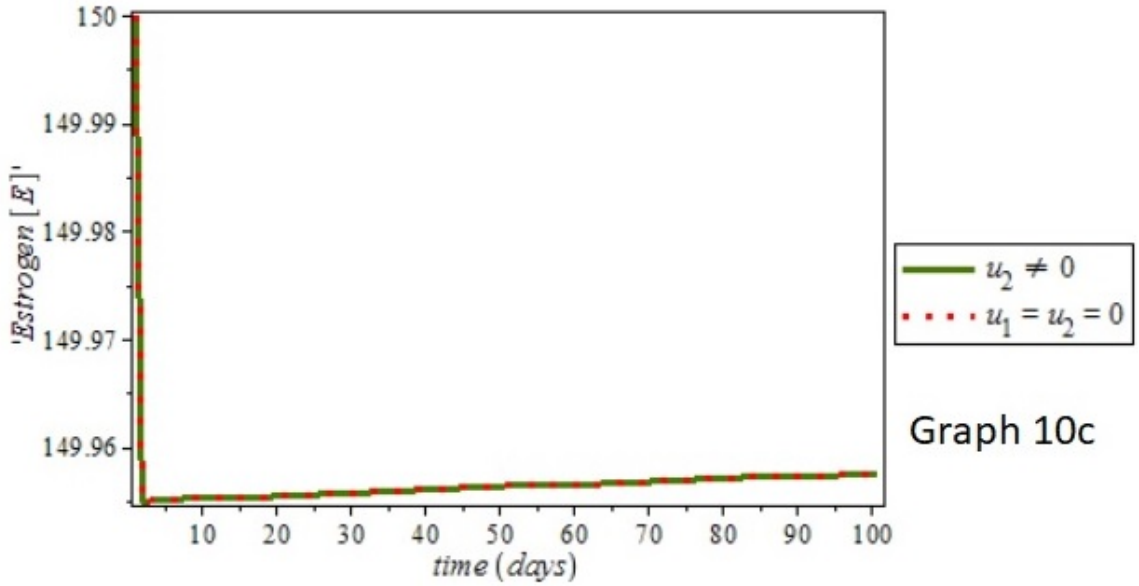
Simulation results showing estrogen level against time, with and without control.



Graph 10a



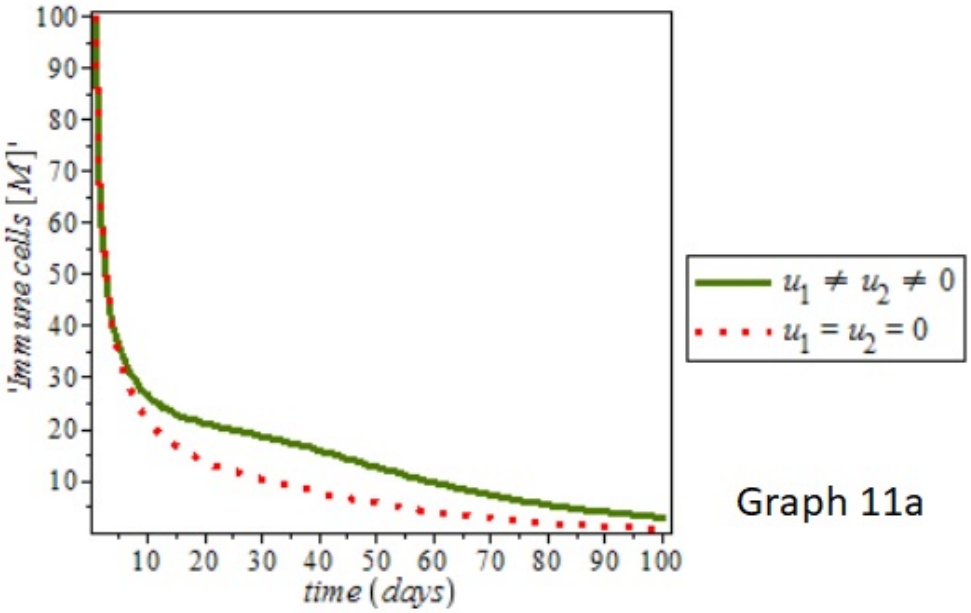
Graph 10b



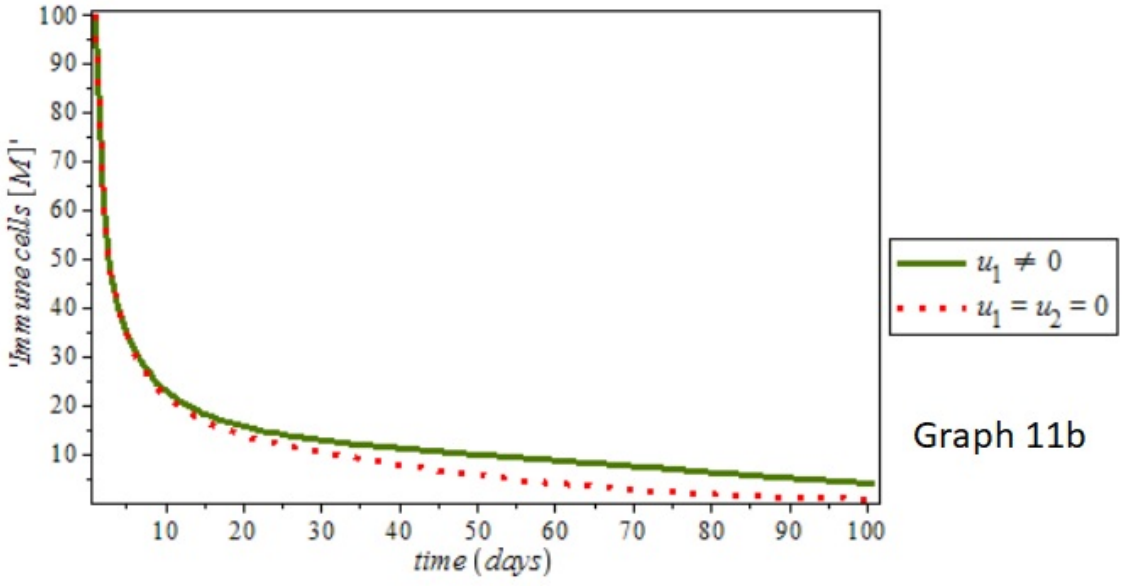
Graph 10c

Furthermore, it was noticed from Graphs 10, that the level of estrogen was reduced drastically in the presence of controls (solid green line) against the constant increase level of estrogen (dots red line) in uncontrolled cases. However, anti-cancer drugs (for example Tamoxifen) blocks estrogen receptors on breast cells, that is, it stops estrogen from connecting to the cancer cells while tamoxifen also acts like an anti-estrogen in breast cells; it acts like an estrogen in other tissues like the uterus and the bones . In addition, ketosis also regulating hormonal imbalance.

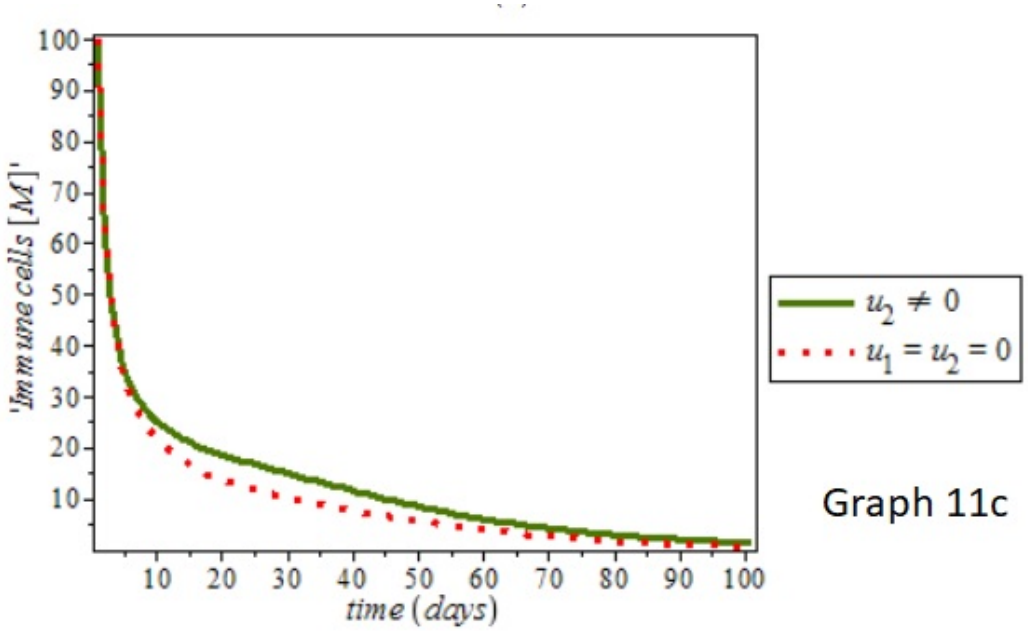
Simulation results showing immune response against time, with and without control.



Graph 11a



Graph 11b



Graph 11c

On the other hand, Graphs 11, shows that Immune response can help to fight cancer cells while immune system recognize cancer cells as abnormal and kill them. However,this may not be enough to eliminate cancer cells from the body.

Final conclusions

A four-dimensional compartmental deterministic model was designed and used to monitor the dynamics of breast cancer. The existing model was extended to incorporate treatments,ketogenic diet, and an immune booster. The system was rigorously analyzed to gain insight into their dynamical behaviors.

- The conditions of stability of the tumor-free equilibrium (TFE) was established and the system is only local asymptotically stable if a certain threshold quantity, known as the reproductive number, is less than unity ($R_0 < 1$). It implies that the number of tumor cells in the body will be brought to zero if proper treatments and a ketogenic diet that can force make the threshold to a value less than unity are monitored.

- An individual has the chance of developing breast cancer depending on the level of the immune system (s), the efficacy of the anti-cancer drug (k) and the rate at which the ketogenic diet (d) is being taken to fight tumor cells. We also found out that the presence of excess estrogen in system makes it unstable, as depicted in Graphs 10. This implies that any additional estrogen quantity introduced into the body through the birth control, and hormone replacement therapy enhances the rate of tumor formation. Thus, the development of breast cancer is certain.

- The transition from normal cells class to tumor cells class plays a crucial role in breast cancer dynamics. More tumor is formed if the DNA is damaged or altered as a result of excess estrogen, which reduces the number of normal cells being produced by red blood cells. Furthermore, the results show that tumor cell formation depend on the level of excess estrogen introduced into the body system. It must be noted that the ability to resist changes in structure and amount of estrogen released during natural biological processes is dependent on an individual's DNA.Such biological processes include: premenopausal and menopause stages. Other risk factors may also be incorporated in the model for future work, which might generate different results.

CHAPTER 6

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CHAPTER 7

Matlab algorithms

SECTION 7.1

LQR controller algorithm

The algorithm to compute LQR controller is the following:

```
alpha1=0.7;
alpha2=0.514;
mu1=0.00003;
mu2=0.01;
phi1=6e-8;
gamma2=3e-6;
gamma3=1e-7;
s=1.3e4;
eps1=1.3e4;
omega=3e5;
rho=0.2;
mu3=0.29;
kappa=0.5;
beta=0.01;
lam1=0.2;
lam3=0.002;
g=0.1;
mu4=0.97;
mu5=2;
d=0.6;
Ns=alpha1*mu4-(1-kappa)^2*lam1*eps1/mu1*mu4;
Ts=0;
Ms=s*beta*(g*mu4+(1-kappa)*eps1)/mu3*(g*mu4+(1-kappa)*eps1)+(1-kappa)^2*lam3*e
Es=(1-kappa)*eps1/mu4;
A=[alpha1-2*mu1*Ns-(1-kappa)*lam1*Es,-phi1*Es,0,(1-kappa)*lam1*Ns; (1-kappa)*l
B=[lam1*Es*Ns,0 ; -lam1*Ns*Es,-Ts*alpha2 ; lam3*Ms*Es/g+Es,0 ; 0,-eps1];
C=[1,1,1,1];
D=zeros(1,2);
Q=1e10*eye(4,4);
R=0.2*diag([1,1]);
%Q=C'*C;
K=lqr(A,B,Q,R);
%
Acl=A-B*K
sys_cl=ss(Acl,B,eye(4),zeros(4,2));
x0=[2000 800 500 20]';
```

```
[y,t,x] = initial(sys_cl,x0);
%
figure(1)
plot(t,x(:,1))
xlabel('time days')
ylabel('normal cells')
grid
%
figure(2)
plot(t,x(:,2))
xlabel('time days')
ylabel('tumor cells')
grid
%
figure(3)
plot(t,x(:,3))
xlabel('time days')
ylabel('immune cells')
grid
%
figure(4)
plot(t,x(:,4))
xlabel('time days')
ylabel('estrogen')
grid
```

SECTION 7.2

H_∞ controller algorithm

Using Matlab r2018a we were able to compute the Optimal h infinity controller under certain tolerance γ

```
%parameters
alpha1=0.7;
alpha2=0.514;
mu1=0.00003;
mu2=0.01;
phi1=6e-8;
gamma2=3e-6;
gamma3=1e-7;
s=1.3e4;
eps1=1.3e4;
omega=3e5;
rho=0.2;
mu3=0.29;
kappa=.5;
beta=0.01;
lam1=0.2;
lam3=0.002;
g=0.1;
mu4=0.97;
mu5=2;
d=0.6;
Ns=alpha1*mu4-(1-kappa)^2*lam1*eps1/mu1*mu4;
Ts=0;
Ms=s*beta*(g*mu4+(1-kappa)*eps1)/mu3*(g*mu4+(1-kappa)*eps1)+(1-kappa)^2*lam3*e
Es=(1-kappa)*eps1/mu4;
%Matrixes
A=[alpha1-2*mu1*Ns-(1-kappa)*lam1*Es,-phi1*Es,0,(1-kappa)*lam1*Ns; (1-kappa)*l
B=[lam1*Es*Ns,0 ; -lam1*Ns*Es,-Ts*alpha2 ; lam3*Ms*Es/g+Es,0 ; 0,-eps1];
C=[1,1,1,1];
D=zeros(1,2);
R=[10 0 ; 0 10];
%plant
[P,L,G]=care(A,B,C'*C,R);
%GAMMA
num = [ 0 0 1 ] ;
den = [ 1 0.8 1 ] ;
[A,B,C,D] = tf2ss(num,den) ;
tol = 1.0e-6 ;
[gama_toolbox] = normhinf(A,B,C,D,tol)

%Controller
s = zpk('s');
W1 =0.1*(s+100)/(100*s+1);
W2 = 0.1;
W3 = 0.1;
P = augw(G,W1,W2,W3);
[K,CL,GAMMA] = hinfsyn(P);
```

SECTION 7.3

Non-linear simulation

```
  function dy=fun1(t,y)
% function dy=fun1(t,y)
%-----------------------------------
% parameters
alpha1=0.7;
alpha2=0.514;
mu1=0.00003;
mu2=0.01;
phi1=6e-8;
gamma2=3e-6;
gamma3=1e-7;
s=1.3e4;
eps1=1.3e4;
omega=3e5;
rho=0.2;
mu3=0.29;
kappa=.5;
beta=0.01;
lam1=0.2;
lam3=0.002;
g=0.1;
mu4=0.97;
mu5=2;
d=0.6;
%-----------------------------------------------
n=y(1);
tc=y(2);
m=y(3);
e=y(4);
%
n_d=n*(alpha1-mu1*n-phi1*tc)-(1-kappa)*lam1*n*e;
tc_d=tc*(alpha2*d-mu2*tc)-gamma2*m*tc-mu5*tc+(1-kappa)*lam1*n*e;
m_d=s*beta+(rho*m*tc)/(omega+tc)-gamma3*m*tc-mu3*m-(1-kappa)*(lam3*m*e)/(g+e);
e_d=(1-kappa)*eps1-mu4*e;

dy=[n_d tc_d m_d e_d]';
end

% test ode45
%
n0=2000;
tc0=800;
m0=500;
e0=20;
%
[tout,yout] = ode45('fun1',[0 1],[n0 tc0 m0 e0]')


figure(1)
plot(tout,yout(:,1));

figure(2)
```

```
plot(tout,yout(:,2));

figure(3)
plot(tout,yout(:,3));

figure(4)
plot(tout,yout(:,4));
```