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Mathematical Modelling of the Efficacy and Toxicity of Cancer Chemotherapy

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093459

Submitted in partial fulfillment for the Degree of Master of Science in Biomathematics of Strathmore University

Institute of Mathematical Sciences

Strathmore University

Nairobi, Kenya

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John Indika Osotsi

June 12, 2017

Approval

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Abstract

From available literature, there is strong evidence that the growth of tumours is to a great extent influenced by the cellular response of the immune system in addition to the therapy administered. While chemotherapy treatment is very effective in killing cancer cells, the levels of toxicity associated with it affects other body cells negatively, the worst of which are cells with higher rate of multiplication and regeneration. A lot of research, with impressive results has been carried out in cancer for the past over four decades, yet there is still not a universally accepted effective mathematical model that provides a way of optimizing chemotherapy efficacy and toxicity.

The mathematical model developed in this research has provided a theoretical understanding of the interactions among cancer cells and body cells for cancer patients as well as laying the stage for future research work. Based on the findings from reviewed biological literature, a mathematical model comprising of six ODEs describing the growth of tumour cells while incorporating the immune system response and chemotherapy treatment was formulated and analyzed both analytically and numerically. Three scenarios are presented namely: no tumour with no treatment, tumour with no treatment and tumour with treatment. In the first case (no tumour and no treatment), the system was found to be stable. The tumour with no treatment equilibrium was on the other hand was found be unstable implying that the immune system can not eliminate cancer cells on their own. Lastly, the case of tumour with treatment was found to be stable hence longer survival times for the patients receiving chemotherapy treatment. When however, the concentration of chemotherapy was increased, the system goes back to instability due to the decline of the number of NK and $CD8^+$ T-cells as a result of chemotherapeutic toxicity.

According to the results of the formulated mathematical model, treatment regimens consisting of right concentrations of chemotherapy is effective in eliminating the tumour cell population. Further research should therefore focus on developing models that quantify the optimal drug concentration for maximum efficacy on tumour cells with minimal toxicity to immune cells.

Acknowledgment

First and foremost, I thank The Almighty God, the gracious giver of life, knowledge and strength.

To my principal supervisor, Prof. Livingstone S. Luboobi and associate supervisor, Dr. Rachel W. Mbogo, I remain greatly indebted to the most valuable guidance, suggestion and encouragement that they made from the very beginning to the final stage of the production of this research. I am extremely grateful because they read the document from page to page and didn't miss a comment that lead to the improvements of the contents.

I further extend my warmest gratitude to staff of IMS, both lecturers and post-graduate students for the knowledge imparted and shared, and classmates for being there to set a completive environment as well as sharing of skills, knowledge and information. In particularly, I thank Dr. Andrew Cole for his medical insight that was very critical to the understanding of the biological phenomena presented herein. Without his contribution from a medical perspective, the application of mathematical and computational principles would not have achieved the desired goal.

Lastly, I would like to thank my family, friends and colleagues and everyone else for their diverse support, encouragement and understanding whenever this task seemed overwhelming.

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List of abbreviations

Acronyms	Meaning
IMS	Institute of Mathematical Sciences
NK	Natural Killer cells
WHO	World Health Organization
MOH	Ministry of Health, Government of Kenya.
ODEs	Ordinary Differential Equations
PDEs	Partial Differential Equations
SPDEs	Stochastic Partial Differential Equations

Chapter One

1 Introduction

1.1 Overview

Cancer is an uncontrollable multiplication of cells (Figure 1.1) caused by multiple changes in gene expression leading to the dysregulated balance of cell proliferation and cell death and ultimately evolving into a population of cells that can invade tissue and metastasize to distant sites (Ruddon, 2007). These physiological changes in the genetic behaviour of cells lead to a progressive loss and the consequent malfunction of body cells. In the absence of effective treatment, death by cancer is caused by the relentless increase in the population of these abnormally dividing cells, otherwise referred to as cancerous cells (Ruddon, 2007).

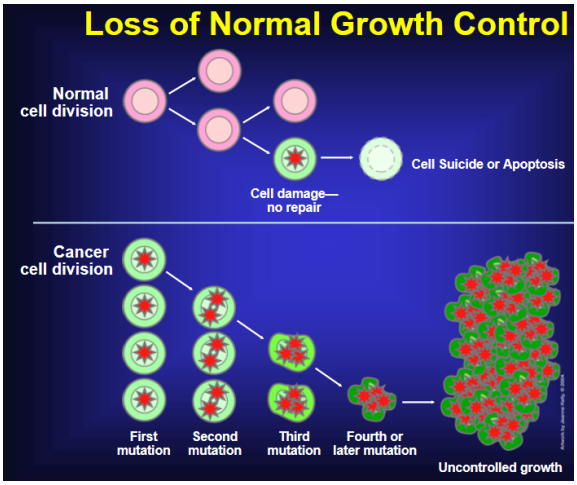

Figure 1.1: Comparison between cell division in normal body cells and cancerous cells (AACR, 2016)

The World Health Organization, ranks cancer as the second leading cause of death in the world accounting for 8.8 million (13%) deaths in the year 2015. This number of new cases is expected to rise by approximately 70% within the next two decades. Essentially, what

this means is that there will be an estimated number of 24 million new cases of cancer annually in the year 2032 (WHO, 2016). In Kenya, cancer is ranked as the third leading cause of death accounting for 7 per cent of the total annual mortality behind infectious and cardiovascular diseases (MOH-Kenya, 2011). Although data about population is not available in the country, the annual incidence of cancer is about 28,000 cases with an annual mortality of over 22,000 (MOH-Kenya, 2011).

It is clear from this statistics that cancer posses a great burden to the population, and the fight against it has become of create concern for public health officials not only nationally but also globally. A greater understanding of the dynamics of cancer indeed has a great potential of providing solutions to the cancer problem. There can not be a better way to clearly understand cancer dynamics other than the application of mathematical models. It is with this understanding that scientists have, for the past over four decades, been developing mathematical models that mainly study and explain the dynamics of tumour growth. Evidently, a breakthrough in this determination has a great potential to save the many lives that are currently at risk.

1.2 Biological background of cancer

1.2.1 Cancer

As already defined, cancer is an abnormal growth of cells caused by multiple changes in gene expression leading to the dysregulated balance of cell proliferation, death and ultimately evolving into a population of cells that can invade tissue and metastasize to distant sites (Ruddon, 2007). Cancer occurs when there are genetic mutations which can be as a result of many causes, among them, physical carcinogens (ultraviolet and ionizing radiation), chemical carcinogens (asbestos, components of tobacco smoke, aflatoxin and arsenic) and biological carcinogens (viral, bacterial and parasite infections) (WHO, 2016).

Tumour formation is the result of passing of these mutations through the generations of the cell's progeny (Fechheimer and Karp, 2000). A population of cells is said to be cancerous

if the mutations result in the uncontrolled proliferation and intrusion into nearby tissues, thus interfering with normal functioning of normal body cells. In the absence of effective treatment, these interference bears negative effects to the ultimate survival of the organism, and in some cases, leads to death (Hanahan and Weinberg, 2000).

1.2.2 The biology of tumours

Under normal circumstances, cells grow, divide in a manner that is orderly and the formation of tissues and organism is done to achieve a specified function in the body. In some instances however, some cells, after developing a random genetic mutation divide uncontrollably forming a mass referred to as tumour or neoplasm (Melicow, 1982). These tumours give the cells all or any combination of the following capabilities.

i.) Apoptosis avoidance: Cells avoid the trigger that causes them to die naturally whenever they begin to behave abnormally.

ii.) Self-sufficient growth signaling: Increased production of pro-growth factors or heightened sensitivity to them.

iii.) Anti-growth signal insensitivity: Avoidance of differentiation or the quiescent state.

iv.) Angiogenesis promotion: upregulation of proangiogenic factors and insensitivity to angiogiogenic factors, leading to tumour vasculature.

v.) Senescence prevention: Unlimited replicative potential.

vi.) Invasion: Ability to move to surrounding tissues.

vii.) Metastasis: Ability to travel and colonize distant regions of the organism.

1.2.3 Benign and malignant tumours

There are two groups of tumours namely benign and malignant. Benign tumours are non-invasive and non-metastasis and are generally non-life threatening. They can however

sometimes be fatal in two ways namely: if they develop in some parts of the body e.g. the brain and if they acquire some additional mutations. On the other hand, malignant tumours are characterized by their great ability to grow and divide uncontrollably, invade nearby tissues what is referred to as invasion and to spread to other parts of the body by a process called metastasis. Malignant tumours are potentially fatal.

Metastasis, the spreading of tumour cells to other parts of the body is achieved through the bloodstream and the lymphatic system in which case, the cells are carried and lodged some distance away from the initial point as shown in Figure 1.2. where they begin to invade and colonize the surrounding tissue. While some tumours grow, invade and metastasize quickly leading to death in a short period of time, there are others that stay in the body for several years without showing any symptoms (Hanahan and Weinberg, 2000).

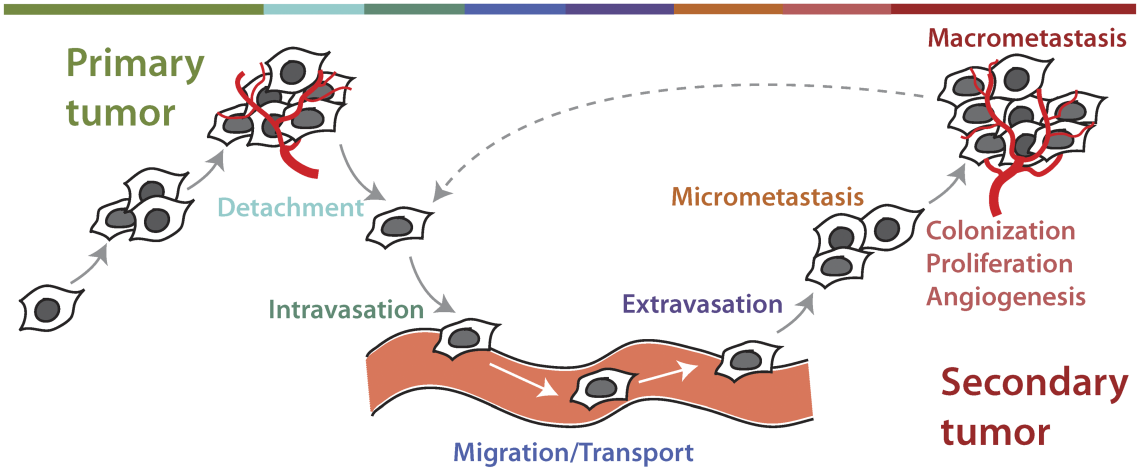

Figure 1.2: Tumour angiogenesis and metastasis in cancerous cells (Divoli et al., 2011)

1.2.4 Tumour angiogenesis

Just like any other cells of a living organism, the growth of tumours is very much dependent on the supply of oxygen and nutrients. In the initial stages, this supply of oxygen and nutrients is not a big problem since they (oxygen and nutrients) diffuse from the surrounding cells into the tumour quite easily. However, as the tumour continues to increase in volume, usually from 2-3millimeters in diameter, diffusion becomes limited. As an

adaptation, tumour cells begin to release hypoxia-induced factors (HIFs), which trigger the release of proangiogenic factors in nearby cells among them being the vascular endothelial growth factor (VEGF). This causes blood vessels to sprout from nearby existing vasculature in a manner that is unregulated with the aim of supplying oxygen and nutrients to the growing tumour (Phipps, 2009). This is represented by the red branches as appears in Figure 1.2.

1.3 Tumour and immune cells interaction

The immune system is a collection of mechanisms and processes inside the body of an organism with the purpose of providing protection to the organism against foreign material. The immune system achieves its functions by recognizing and eliminating foreign matter that include viral particles, parasites, and, in this particular case tumour cells (Chang et al., 2003). The two main types of immune cells that respond to the presence of tumour cells in the body are non-specific immune cells (innate immune system) and specific immune cells (adaptive immune system). The non-specific immune cells e.g. natural killer (NK) cells travel throughout the body and attack any foreign matter they come across. Specific immune cells on the other hand only attack foreign material after being primed by some mechanisms Melicow (1982). $CD8^+$ T-cells is an example of cells that are categorized under the adaptive immune system.

1.3.1 Natural Killer (NK) cells

These are a type of non-specific white blood cells that forms the body's first line of defence against infection and diseases. They are always present in the body of a healthy organism traveling through the bloodstream and the lymphatic system to the extracellular fluid and destroy any foreign matter that they come across (Cabrera et al., 1996). There are two ways that NK cells are adapted to recognizing tumour cells. In the first case, they are attracted to tumour cells by certain tumour antigens and once there, they kill the tumour

cells. In the second case, the NK cells destroy abnormal cancer cells before they replicate and grow (van der Merwe and Davis, 2002). Their recruitment of has been defined as a function of both tumour cell population $T(t)$ and the available NK cell population $N(t)$. Algebraically, their recruitment takes the form presented in Equation (1.1).

$$F(T, N) = \rho \left(\frac{TN}{\theta + T} \right) \tag{1.1}$$

Equation (1.1) is the Michaelis-Menten term which is commonly used in tumour growth models to describe cell-cell interactions (de Pillis et al., 2005). The term, in addition to others, was included in the model of equations developed as part of this research to account for the increase in the NK cells as a result of their interaction with tumour cells.

1.3.2 CD8$^+$ T-cells

Unlike the NK cells, CD8$^+$ T-cells first need to be activated before they can move to and attack the tumour cells. The activation of the CD8$^+$ T-cells is dependent on the following:

- Population of tumour cells that have been killed by other CD8$^+$ T-cells.
- Debris from tumour cells killed by NK cells.
- Presense of tumour cells in the blood stream which causes the other circulating lymphocytes to signal their activation.

The above were considered as part of the factors that describe the dynamics of the CD8$^+$ T-cells populations under Section 3.2.

Activation of CD8$^+$ T-cells takes place in the lymph nodes where they are presented with antigens specific to the tumour cells. Two types of tumour antigens have been identified on tumour cells: tumour-specific transplantation antigens (TSTAs) that are unique to tumour cells and do not occur in normal body cells. The second type are the tumour-associated

transplantation antigens (TATAs) which are not unique to tumour cells and are expressed on normal body cells during fetal development (Jackson, 2003).

Once primed a majority of these cells, the cytotoxic T-cells, multiply, and leave the lymph node to find the source of the tumour antigens presented to them. Though the process by which the movement of these cells to the sources is not well understand, a number of researchers agree that one possible mechanism is chemostatic gradient, a process by which the $CD8^+$ T-cells travel up to get to the tumour cells by following chemical gradients. Once at the target site, the $CD8^+$ T-cells kill tumour cells either by inserting signals that causes apoptosis in the tumour cells or binding to the Fas ligand (FasL or CD95L) on the outside of the tumour cells then using it to induce apoptosis (Delves and Roitt, 2000). Fas ligand is a type-II trans-membrane protein that belongs to the tumor necrosis factor (TNF) and the Fas ligand/receptor interactions play an important role in the regulation of the immune system and the progression of cancer.

1.3.3 Inactivation of immune cells

In the presence of tumour cells, there may occur several interactions between the immune cells (NK and $CD8^+$ T-cells) the result of which is a failure by these cells to effectively destroy more foreign cells that may be present in the body. In addition, the NK cells can cause the inactivation of $CD8^+$ T-cells which occurs mainly when there are high levels of $CD8^+$ T-cells without responsiveness to the cytokines (Gett et al., 2003). While the exact cause of these is scientifically unknown, there is evidence from experimental data that in the absence of the NK cells, the $CD8^+$ T-cells proliferate at a higher rate. Rosenberg and Lotze (1986) noted that the inactivation of immune cells happens even when there are tumour cells in the body.

1.4 Mathematical background of tumour modeling

The first mathematical models of tumour growth were formulated and analysed with the aim of reproducing and providing mathematical explanations to experimentally observed tumour growth curves (Billy et al., 2013). According to surveys done by Friberg and Mattson (1997) and Rodriguez-Brenes et al. (2013), the most common laws that have been used in tumour modelling over the past decades include: power law, power law with linear death, Gompertz model, generalized logistic model, logistic model (when $\beta = 1$ in the generalized logistic model) and exponential model (when $\beta = \infty$ in the generalized logistic model). Table 1.1 presents the equations and the respective solutions of each of the mentioned models. For comparison purposes of the exponential, Gompertz and logistic models, see Figure 1.3.

Table 1.1: Most commonly used models and laws for modelling the growth of tumours.

Model	Equation	Solution
Power law	$\frac{\mathrm{d}N}{\mathrm{d}t} = r(N(t))^{\alpha}$	$N = (N_0 + (1-\alpha)rt)^{1-\alpha}$ when $\alpha < 1$
Gompertz model	$\frac{\mathrm{d}N}{\mathrm{d}t} = rN(t)\ln\left(\frac{K}{N(t)}\right)$	$N(t) = N_0 \mathrm{e}^{\mathrm{A}(1-\mathrm{e}^{-\mathrm{rt}})}$ where $A = \ln\left(\frac{N_\infty}{N_0}\right)$
Generalized logistic	$\frac{\mathrm{d}N}{\mathrm{d}t} = rN(t)\left(1-\left(\frac{N(t)}{K}\right)^{\beta}\right)$	$N = K\left(1+Q\mathrm{e}^{-\beta rt}\right)^{-1/\beta}$ where $Q = \left(\left(\frac{K}{N_0}\right)^{\beta} - 1\right)$
Logistic model	$\frac{\mathrm{d}N}{\mathrm{d}t} = rN(t)\left(1-\frac{N(t)}{K}\right)$	$N(t) = \frac{KN_0\mathrm{e}^{\mathrm{rt}}}{K + N_0\left(\mathrm{e}^{rt}-1\right)}$
Exponential growth	$\frac{\mathrm{d}N}{\mathrm{d}t} = rN$	$N(t) = N_0\mathrm{e}^{\mathrm{rt}}$

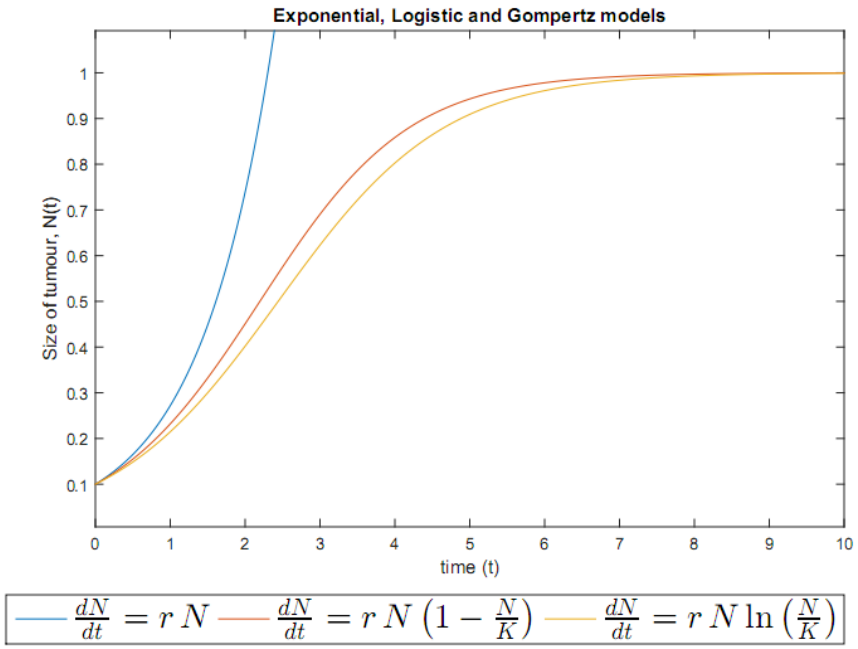

Figure 1.3: Comparison graphs for the Exponential, Logistic and Gompertz models for tumour growth.

1.5 Cancer treatment by chemotherapy

Treatment of cancer by chemotherapy involves the administration of one or more drugs with the aim of killing tumour cells, that exhibit rapid and uncontrollable division and growth. Most chemotherapy drugs that are administered to cancer patients specifically target cells that are actively dividing (Chabner and Longo, 2011). Chemotherapy drugs causes the cell to die either by attaching to the cell during the S phase eventually interfering with its DNA replication, or during the M phase, in which case it disrupts the actual division of the cell.

Once delivered to the blood stream, chemotherapy drugs begin to decay at a rate which some researchers have modelled using the term $F(M) = 1 - e^{-M}$. Rosenberg and Lotze (1986) in his work suggested a drug response of the form

$$F_{M\phi_i} = M_{\phi_i}\left(1 - e^{-M}\right)\phi_i$$

where ϕ_i are the different cell populations included in the model of equations. This thesis

will adopt the above function to describe the loss of cell populations $T(t), N(t), L(t), C(t)$ and $R(t)$ by subtracting it from the mentioned cell populations.

1.5.1 Pharmacodynamics - Efficacy

Anti-cancer drugs target tumour cells, which are characterized by uncontrolled division and growth. As noted earlier, these drugs kill cells in certain phases of their cell cycle which therefore means that only a fraction of them can be killed. This fractional kill rate can modelled using the log-kill law presented in Equation (1.2).

$$\frac{dN}{dt} = \alpha \tag{1.2}$$

At some point, the fractional kill rate reaches a saturation level and no more tumour cells can be killed by the drug. Further, Peters and Dansey (1997) in their work showed that the growth of tumours with targeted chemotherapy treatment can be modeled using the Gompertz growth equation shown in Equation (1.3).

$$\frac{dN(t)}{dt} = rN(t)\ln\left(\frac{K}{N(t)}\right) - \lambda N(t) \tag{1.3}$$

where $N(t)$ denotes the number of tumour cells at any time t. K and λ are the growth parameters of the Gompertz growth equation and $\lambda N(t)$ defines the total number of tumour cell that are lost which depends on the concentration of the drug. This term as appears in equation (1.3) has been simplified to keep both the equation and discussion simple.

1.5.2 Pharmacodynamics - Toxicity

When cancer drugs are introduced into the body, not only do they kill the tumour cells but also normal body cells. This consequently leads to chemotherapy related side effects that include:

- A reduction in the production of leukocytes, erythrocytes and thrombocytes.
- Pain and inflammation of the body's mucous membrane.

- Hair loss that is the result of hair follicle cells begin attacked by the drugs.

In general, the release of bone marrow cells to proliferation, maturation and to the blood is severely disturbed by chemotherapy leading to a fall in the cell levels of the patient. There is therefore a need to ensure that the fall in the cell count as a result of chemotherapy administration does not become extensively large for cancer patients.

1.6 Problem statement

Despite the impressive amount of research work that has been carried out in cancer, there has not been a universally accepted effective model that provides the optimum drug concentration level which maximizes efficacy while at the same time keeping the toxicity levels as low as is possible. By combining knowledge from different fields, precisely, mathematics, computation and medicine, this research has formulated and analyzed a mathematical model for tumour growth with the aim of addressing the above limitation.

1.7 Research objectives

This research investigated one main objective and two specific objectives which are as outlined below:

Main objective

To mathematically determine the level of chemotherapeutic drug concentration administered which maximizes efficacy on malignant tumour cells while keeping the toxicity levels to normal body cells as minimal as is possible.

Specific objectives

1. Formulate and analyze a mathematical model describing the interaction of tumour cells, normal body cells under targeted chemotherapy treatment.

2. Determine the impact of chemotherapy treatment on both tumour and normal body cell population over time.

1.8 Summary of chapters

The remainder of this thesis consists of three chapters. In chapter 2, a review of relevant literature is presented with particular focus on the tumour growth models that set the foundation for the formulation of the model developed in this research as well as the original models that were modified to come up with the new mathematical model.

In chapter 3, a mathematical model for the interaction between tumour cells, immune cells (NK and $CD8^+$ T-cells) and chemotherapy is presented. In this description, a series of six coupled ordinary differential equations is formulated and three cases considered namely: no tomour and no treatment, tumour with no drug and finally, tumour with treatment. The stability of each of these cases is analyzed with the aim of determining the oscillatory behaviour of the system.

Chapter 4 summaries the results of the research as presented in Chapter 3. The chapter also includes conclusions and recommendations that could be undertaken in future research to further improve on this work.

Chapter Two

2 Literature review

2.1 Introduction

Mathematical modelling to study and explain the dynamics of tumour growth, their interaction with immune cells, other body cells, drugs among others has been an area of great interest and exploitation by a majority of mathematical modelling scientists since the mid 60s (Mallet and De Pillis, 2006). The earliest models were developed by Burton (1966) and Greenspan (1972) at which time, their models only focused on simple chemical diffusion and differential equations.

Currently however, modelling of tumours and their interactions has been expanded to incorporate the use of advanced mathematical techniques that include ordinary differential equations (Enderling and Chaplain, 2014), partial differential equations (Hillen et al., 2015), stochastic differential equations (Lisei and Julitz, 2008) and cellular automata (Poleszczuk and Enderling, 2014). In addition, developed models are being tested and validated using *in vitro* tumour growth data (Li et al., 2010) which is indisputably an important aspect of modelling as it verifies that developed models predict the real phenomena, and that the treatments proposed are biologically significant.

2.2 Early tumour growth models

There have been several explanations for the underlying mechanism in tumour growth retardation as exhibited in exponential growth models. While Laird (1964) argues that according to the available data, the retardation is due at least in part to an actual increase in the mean generation time during tumour growth, Mayneord (1932) in his earlier work had showed that such a retardation is as a result of the formation of a necrotic region in

the centre of a tumour, which has the effect of gradually reducing the region of active tumour cell growth to a thin shell at the tuomour surface. The findings by Mayneord were considered favourable by Burton (1966) who formulated a model that examined both the distribution of oxygen in spherical tumours and relative radius of the central zone to the total radius. In this model, Burton studied the effect of diminishing growth fraction while keeping the rate of mitotic activities constant. In this way, he was able to overcome the limitation of the Gompertzian relation by showing that the growth of tumours can be explained by a linear model, a fact that has overtime been proved to be true experimentally.

Greenspan developed a mathematical model of tumour growth by diffusion with the aim of investigating the evolution of solid carcinoma Greenspan (1972). Greenspan's work was an extension of the model developed by Burton (1966) and that of Thomlinson and Gray (1955) which he achieved by introducing a surface tension among the living tumour cells in order to maintain a compact, solid mass and by assuming that necrotic cellular debris continually disintegrate into simpler chemical compounds that are freely permeable through cell membranes. He thus was able to explain the existence of a steady-state tumour size by showing that the inward motion of cells from the outer region due to adhesion and surface tension replace the tissues that are lost due to necrosis. In this paper, Greenspan describes, the shape of a growing tumour as a sphere with three layers namely: a central necrotic core, quiescent layer of non-proliferating cells and the proliferating zone where all mitosis occur. These three layers are illustrated in Figure 2.1

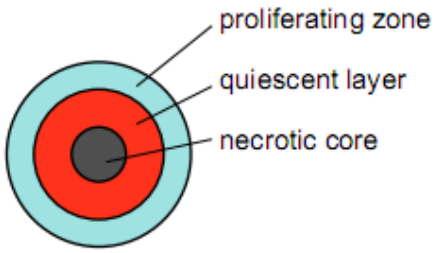

Figure 2.1: Layers of a growing tumour

In this paper also, Greenspan made the assumption that a chemical is produced somewhere within the tumour volume which has an inhibiting effect on the mitosis of cancer

cells without necessarily resulting into their death. To study these effects, he developed a model by applying the conservation of mass principle, which after a series of mathematical derivations led to an integro-differential equation given in Equation (2.1), which relates the tumour radius to the volume production and loss as a result of mitosis and necrosis respectively.

$$R_0^2 \frac{\mathrm{d}R_0}{\mathrm{d}t} = \int_{max(R_1, R_g)}^{R_0} S(\alpha, \beta)\, r^2\, \mathrm{d}r - \lambda\, R_i^3 \tag{2.1}$$

where $R_0(t)$ is the radius of tumour at any time t, $R_i(t)$ is the radius of necrotic core, $R_g(t)$ is the radius at which cell proliferation ceases, $S(\alpha, \beta)$ is the proliferation rate of cells, α, β and λ represent concentration of nutrients, concentration of inhibitors and proliferation constant at which the necrotic core loses cell volume respectively. From this model, he concluded that the development of tumour spheroids was characterized by three distinct phases namely: an initial exponential phase, followed by some degree of retardation in growth which then culminated into a final phase of dormancy as a result of both mitotic inhibition and tumour cell death. It was however shown from the model that there were different growth patterns prior to arriving at a steady state, an outcome that Greenspan himself was not able to explain but proposed it for future experiments. Unfortunately, no such experiment seems to have been successfully undertaken.

Greenspan also extended his earlier work Greenspan (1972) in which he considered the stability to asymmetric perturbations of the spherical shape of an equilibrium sized tumour (Greenspan, 1976). While doing this work, he paid attention to the experiments done by Sutherland et al. (1971) in which the authors had found that some cell aggregates disintegrated at a certain stage of development. In this paper, Greenspan explained the distribution of nutrients to the growth of cell cultures and solid tumours by investigating the unstable development of tumours when surface tension and adhesion are overcome by internal pressure. The model he developed described the relationship between nutrient concentration, pressure on the surface and surface tension forces. He concluded that if the tumour reaches a critical size beyond which surface tension is overcome by pressure forces, then the tumour becomes unstable.

The work by both Burton (1966), Greenspan (1972) and Greenspan (1976) were based on the assumption that oxygen consumption per unit volume per unit time by the cells was constant. However in his paper, Deakin (1975) made the argument that this assumption contradicted the experimental results as had been presented by Sutherland et al. (1971) in which they had shown that viable rim thickness decreases relatively slowly following the onset of necrosis. He therefore extended their models by incorporating an oxygen consumption that was proportional to the oxygen concentration within critical limits. By varying the model parameters, Deakin was able to show that the results of the model agreed with the available experimental evidence.

Whereas the model by Deakin was restricted to the effect of non-uniformity of the amounts of oxygen consumed on the viable rim thickness, the model developed by McElwain and Ponzo (1977) investigated the effect of this non-uniformity on the rate of growth of a tumour. This model, just as was the case with Greenspan (1972), exhibited three phases that were distinct. In the first phase, the model showed that oxygen concentration was above the critical value everywhere, resulting in a uniform consumption of oxygen by all cells which consequently gave raise to an exponential growth of the tumour. This was followed by a decreased growth rate in the second phase due to a reduction of oxygen in the central region which caused a decrease in the effective proliferation rate. The final stage was characterized by viable dormancy with reduced proliferation. Evidently, this model results are significantly different from those found by Greenspan (1972) discussed earlier.

The above early models were discussed for they provided a clear understanding into the growth of tumour cells and further formed a framework for the ODE-based model that was developed and analysed as part of this research.

2.3 Tumour, immune system and drug interaction models

A good understanding of the interaction between drug, immune system and tumour cells is critical to the formulation of ODE based models in this study. The study of the interaction between tumour, immune system and drug has attracted an abundance of mathematical models over the past few decades. de Pillis et al. (2005) presented a mathematical model describing tumour-immune interactions focusing on the role of natural killer cells (NK) and $CD8^+$ T cells in tumour surveillance. To construct the model, the authors considered three cell populations namely: tumour cell population, total level of NK cells effectiveness and total level of tumour-specific $CD8^+$ T cells effectiveness. They found that the traditional power law of tumour growth representation did not fit well to the available experimental results which led them to formulate a new law presented in Equation (2.2)

$$D = d\frac{(L/T)^\lambda}{s + (L/T)^\lambda}T \tag{2.2}$$

where L and T is the tumour-specific $CD8^+$ cell effectiveness and tumour cell population respectively; d and s is the saturation level of fractional tumour cell kill by $CD8^+$ T cells and the steepness coefficient of tumour $CD8^+$ T cell competition term respectively. Further, they established a clear distinction between the NK and $CD8^+$ T cells dynamics in tumour surveillance. In an earlier paper de Pillis and Radunskaya (2001), the two populations NK and $CD8^+$ T cells had both been considered as single population — the immune cells. Another notable finding from the numerical analysis was that the activation of $CD8^+$ T cells was important in cancer therapy. In the model formulated in this research, the NK and $CD8^+$ T cells were considered as separate populations thanks to the findings by this authors, and that each of them had different interaction and recruitment rates.

de Pillis et al. (2007) while investigating tumour-immune interaction developed a mathematical with four four populations including drug therapy. Their model described the growth, death and interaction of these populations with targeted chemotherapy treatment. Whereas in their earlier model they had used the population of normal body cells $N(t)$, in this new model, they decided to consider the circulating lymphocyte population which they denoted by $C(t)$. In such a setting, they aimed at keeping the normal cells above

some threshold level required for minimal level of patient health. They extended the analysis to an optimal control problem whose solution they obtained by using the collocation method Biegler (2007) over a simulated time period of 150 days. From the results of their simulations, the authors showed that the traditional therapy fails to bring the system to the zero-tumour burden state when the immune system of the host is weak. With the application of the drug therapy solution however, the authors found that the population of tumour cells goes to zero but the normal cells population remain above the constraint level.

In their subsequent paper de Pillis et al. (2009), which was an extension of their previous work de Pillis et al. (2006), the authors noted that the understanding of the immune system is critical to the understanding of tumour growth and that if immunotherapy and chemotherapy are to be administered simultaneously in a clinical setting, then their interaction (immuno and chemo) and their interaction with the host cells must be properly understood. In this model, they formulated a system of six differential equations where they again used the ratio form for the $CD8^+$ T-cell kill rate of tumour cells given in Equation (2.2), a law they had formulated in their earlier work de Pillis et al. (2005). They updated this work by removing the term $\frac{gT^2N}{h+T^2}$ which they thought would be insignificant in addition to introducing complexity to the model. Further, they included the term $IL-2$ (induced NK cell proliferation) and $\frac{P_N NI}{g_N+I}$ in this new model.

From their simulation results with no therapy and for large initial tumour size, the immune system is not able to destroy the tumour which causes its population to grow to the high tumour equilibrium. Introducing chemotherapy was however found to eliminate the tumour population rapidly. Similarly, combined therapy (chemo and immuno) destroys the tumour cells but leads to a slight drop in the population of NK and $CD8^+$ T cells to a level that was still consistent with the results found by Jurisic et al. (2007). Their model indicated that if the $CD8^+$ T cell kill tumour cells more effectively than immunotherapy, it may be more useful to administer immunotherapy and chemotherapy simultaneously. With the availability of individual data for $CD8^+$ T cell effectiveness in killing tumour cells, the authors suggested that the feasibility of using immunotherapy in combating growing tumours could be determined. Regrettably, from the available literature, no research to

determine this has been undertaken to date. We relied heavily on this work by de Pillis et al. (2009) to formulate the model presented and analyzed in this research by making a few modifications and improvements as illustrated in Section 3.1.

2.4 Models developed in this project

This literature review has demonstrated that so far, there has been a significant progress in tumour growth modelling with particular interest in the interactions that occur within the host tissue as a result of the presence of tumour cells in the body. Despite all this, the review suggests that the dynamics of tumour growth and normal body cell count under targeted chemotherapy treatment has not been fully studied, and as a result, research in this area is still open. The new model developed as part of this research expanded upon existing models to provide a more complete picture of the interaction between growing tumours and the host immune system, especially with regard to individual level cell interactions. In particular, the model by de Pillis et al. (2009) was considered and modified as described in Section 3.1.

Chapter Three

3 Models for Chemotherapeutic Efficacy and Toxicity

3.1 Introduction

Mathematical models of the interaction between tumour, immune and normal body cells populations provided an excellent frame work for addressing specific questions about tumour-immune interaction dynamics in addition to the response of tumour cells to treatment, and in particular, treatment by chemotherapeutic drugs. The new model developed as part of this research is a modification of the work done by de Pillis et al. (2009) in which the authors formulated and analyzed a system of six ordinary differential equations presented equations (3.1).

$$\left.\begin{aligned}
\frac{dT}{dt} &= aT(1-bT) - cNT - DT - K_T\left(1-e^{-\delta_T M}\right)T \\
\frac{dN}{dt} &= f\left(\frac{e}{f}C - N\right) - pNT + \frac{\rho_N NT}{g_N + I} - K_N\left(1-e^{-\delta_N M}\right)N \\
\frac{dL}{dt} &= \frac{\theta m L}{\theta + L} + j\frac{T}{k+T}L - qLT + (r_1 N + r_2 C)T - \frac{uL^2CI}{\lambda + I} \\
&\quad - K_L\left(1-e^{-\delta_L L}\right)L - \frac{p_I LT}{g_I + I} + \nu_L(t) \\
\frac{dC}{dt} &= \beta(\frac{\alpha}{\beta} - C) - K_C\left(1-e^{-\delta_C M}\right)C \\
\frac{dM}{dt} &= -\gamma M + \nu_M(t) \\
\frac{dI}{dt} &= -\mu_I + \phi C + \frac{\omega LI}{\xi + I} + \nu_I(t)
\end{aligned}\right\} \tag{3.1}$$

where

$$D = \frac{d(L/T)^l}{s + (L/T)^l}$$

In this model, the authors used $T(t)$, $N(t)$, $L(t)$, $C(t)$, $M(t)$ and $I(t)$ to denote tumour cells, natural killer cells, $CD8^+$ T cells, circulating lymphocytes, chemo and immunotherapeutic drug concentrations respectively.

In the new model formulated in this research, the following modifications were made to the model by de Pillis et al. (2009), as presented in equations (3.1).

i.) In the first equation, the decay of tumour cells is denoted by the term $-\delta_d LT$ instead of $-DT$ where $D = d\dfrac{(C/T)^\lambda}{s + (C/T)^\lambda}T$ as used in the de Pillis et al. (2009) model.

ii.) Excluded the term $-pNT$ and replaced the term $\dfrac{\rho_N NT}{g_N + I}$ by $\dfrac{pNT}{q + T}$ in the second equation because the new model did not investigate the role of immuno-therapy in the activation of CD8$^+$ T-cells.

iii.) Excluded the terms $\dfrac{\theta_m L}{\theta + L}$, $-\dfrac{uL^2CI}{\lambda + I}$ and $-\dfrac{p_I NT}{g_I + I}$ and $\nu_L(t)$ because they are related to treatment by immuno-therapy.

iv.) Added the red blood cell populations (erythrocytes) to the new model.

v.) The new model did not include the last equation of the original model since its an equation that describes the dynamics of immuno-therapy drug, something that was not studied in the new model.

3.2 Model formulation

The mathematical tumour growth model formulated as part of this research considers five cell populations with their interaction dynamics under treatment by chemotherapeutic drugs. These cell populations and drug concentration at any time t are given below:

- $T(t)-$ Total population of tumour cells.
- $N(t)-$ Concentration of NK cells per litre of blood (cells/litre).
- $L(t)-$ Concentration of CD8$^+$ T cells per litre of blood (cells/litre).
- $C(t)-$ Concentration of other circulating white blood cells (lymphocytes) not including the NK and cells CD8$^+$ T cells per litre of blood (cells/litre).

- $R(t)-$ Concentration of red blood cells (erythrocytes) per litre of blood (cells/litre).
- $M(t)-$ Concentration of chemotherapy drug per litre of blood (mg/litre).

To formulate the model equations, the following key assumptions were made:

i.) The tumour cell populations, in the absence of immune response and drug therapy is governed by the logistic growth equation.

ii.) All cell populations are homogeneous (i.e. the cells exhibit similar growth dynamics for all parts of the population).

iii.) The negative interaction between tumour cells with the body cell populations is accounted for in the respective natural death terms of these populations.

iv.) Tumour and immune cells exhibit a *Lokta-Voltera* predator-prey type of competition, in which case the immune cells prey on the tumour cells. Further, it is assumed that both NK and $CD8^+$ T cells have the capacity to kill tumour cells.

v.) The delivery of chemotherapy drugs at the tumour site is almost immediately after administration.

Table 3.1 presents the model parameters for the model alongside their respective descriptions.

Table 3.1: Description of parameters used in the model.

Parameter	Description
β_t	Intrinsic tumour growth rate.
α_t	Inverse of the carrying capacity of tumour cells.
δ_t	Decay of tumour cells due to attack by NK cells.
δ_d	Decay of tumour cells due to attack by $CD8^+$ T-cells.
ν_t	Chemotherapy induced death rate.
λ_t	Chemotherapeutic efficacy coefficient for tumour cells.
β_n	Rate of recruitment of NK cells from circulating lymphocytes.
p	Rate of tumour induced proliferation in NK cells.
q	Saturation level of NK cells.
δ_n	Natural death rate of NK cells.
ν_n	Chemotherapy induced death rate.
λ_n	Chemotherapeutic toxicity coefficient for NK cells.
j	Rate of tumour induced proliferation in $CD8^+$ T-cells.
k	Saturation level of $CD8^+$ T-cells.
ω_l	Rate of stimulation of $CD8^+$ T-cells by NK-lysed tumour cell debris.
σ_l	Activation of $CD8^+$ T-cells by other lymphocytes.
δ_l	Natural death rate of lymphocytes.
ν_l	Chemotherapy induced death rate.
λ_l	Chemotherapeutic toxicity coefficient for $CD8^+$ T-cells cells.
β_c	Rate of production of lymphocytes from the bone marrow.
δ_c	Natural death rate of lymphocytes
ν_c	Chemotherapy induced death rate.
λ_c	Chemotherapeutic toxicity coefficient for lymphocytes.
β_r	Rate of production of erythrocytes from the bone marrow.
δ_r	Natural death rate of erythrocytes.
ν_r	Chemotherapy induced death rate.
λ_r	Chemotherapeutic toxicity coefficient for erythrocytes.
$\gamma(t)$	Increase in drug concentration by infusion.
φ_m	Rate of elimination of chemotherapy drug from the system.

3.2.1 Model terms

This section describes the terms included in the formulated mathematical model and the relevant literature for their source. From here henceforth, the short hand derivative notation $\dot{\phi(t)}$ will be used in the place of $\frac{d\phi}{dt}$ for convenience purposes ($\phi = T(t)$, $N(t)$, $L(t)$, $C(t)$, $R(t)$ and $M(t)$).

Drug intervention: $\dot{M(t)}$

According to de Pillis and Radunskaya (2001), drug kinetics for chemotherapy treatment is modelled using an exponential function of the form presented in equation (3.2).

$$\Gamma(u) = \nu_\phi(1 - e^{-\lambda_\phi M})\phi \tag{3.2}$$

Equation (3.2) represents the fractional cell kill for a particular amount of drug at the site of tumour where ν_ϕ and λ_ϕ denote the medicinal kill rate and chemotherapeutic efficacy/toxicity for a particular cell population ($\phi = \mathrm{T},\ \mathrm{N},\ \mathrm{L},\ \mathrm{C}\ \mathrm{and}\ \mathrm{R}$) in the system. This equation is subtracted from all the five cell populations to represent the effect of treatment by chemotherapy both to the tumour cells (efficacy) and normal body cells (toxicity). The concentration of the chemotherapeutic drug is increased in the system by infusion, a term that is denoted by $\gamma(t)$. On the other hand, the drug decays at a rate proportional to φ through metabolic activities such as excretion[1] and elimination

Tumour cells dynamics: $\dot{T(t)}$

Numerous studies in cancer modelling have shown that in the absence of immune response and drug therapy, the growth of tumour cells follows a logistic growth model. This research, just as was the case with de Pillis et al. (2009), adopts the logistic growth term with an intrinsic tumour growth rate of β_t and carrying capacity $\alpha_t = \frac{1}{\alpha}$ to describe the

[1]It is understood that excretion as a biological process is also determined by protein and tissue binding capacity

recruitment of tumour cells. This population is reduced through its interaction with both NK and CD8$^+$ T-cells, dynamics that are denoted by $(-\delta_t TN)$ and $(-\delta_d TL)$ respectively. Further, the tumour cells decay at a rate proportional to ν_T as a result of the chemotherapeutic drug. This decay is accounted for by subtracting the term in equation (3.2) from this population.

NK cells dynamics: $\dot{N(t)}$

According to the paper by de Pillis et al. (2009), it is assumed that in the presence of tumour cells, NK cells are recruited at a rate proportional to β_n which depends on the populations of circulating lymphocytes, hence the term $\beta_n C$. In addition, the cell-cell interaction between NK and tumour cells causes NK cells to be recruited to the site of tumour which is accounted for by the term $\dfrac{pTN}{q+T}$. This expression represents the Michaelis-Menten term widely used in tumour growth models to govern cell-cell interactions (Kirschner and Panetta, 1998). The term was chosen in favour of $\dfrac{pT^2N}{q+T^2}$ because the later has been criticized for possible oversimplification of the steady state assumption without necessary conditions (Lefever et al., 1992). NK cells are reduced by natural death $(-\delta_n N)$ and chemotherapeutic drug effect with kill rate parameter ν_n and toxicity coefficient of λ_t which lead to the term $-\nu_n(1-e^{-\lambda_n M})N$.

CD8$^+$ T cells dynamics: $\dot{L(t)}$

In the absence of tumour cells, there are no $CD8^+$ T-cells present in the system though they are present in the bone marrow and lymph nodes (Chabner and Longo, 2011). In the presence of tumour cells however, these cells are activated as a result of a number of factors. This research considers three of these factors namely: the interaction between CD8$^+$ T and tumour cells $\left(\dfrac{jLT}{k+T}\right)$, the interaction between NK and tumour cells $(-\omega_l NT)$ and that between lymphocytes and tumour cells $(-\sigma_l CT)$. CD8$^+$ T-cells are, on the other hand decreased by natural death $(-\delta_l L)$ and toxic chemotherapy effect $(-\nu_n(1-e^{-\lambda_n M})N)$.

Other lymphocytes dynamics: $\dot{C(t)}$

White blood cells (lymphocytes) are recruited at a constant rate of β_c, decrease both as a result of natural death at a rate proportional to δ_c and from the effect of chemotherapy drug with a cell kill rate of ν_c and toxicity rate of λ_c These dynamics result in the three terms namely: β_c, $-\delta_c C$ and $-\nu_c(1 - e^{-\lambda_c M})C$ respectively.

Erythrocytes dynamics: $\dot{R(t)}$

The dynamics of red blood cells are defined by a constant recruitment term of β_r, natural death term denoted by $-\delta_r R$ and chemotherapeutic drug toxicity induced death represented by $-\nu_r(1 - e^{-\lambda_r M})C$.

The above cell population dynamics are summarized in the compartmental diagram presented in Figure 3.1. The continuous lines with arrows represent the recruitment (inward arrows) and decrease (outward arrows) for each of each of the model variables. Dashed black lines with arrows on the other hand are used to denote the interaction between the various populations. The dotted lines without arrows indicate that the interaction between two populations (with no arrows) leads to the signaling/activation of a third population ($CD8^+$ T-cells in this case). While it deviates from the norm, the use of arrows for dashed lines has been used to show the direction of effect among the different interacting populations for purposes of clarity.

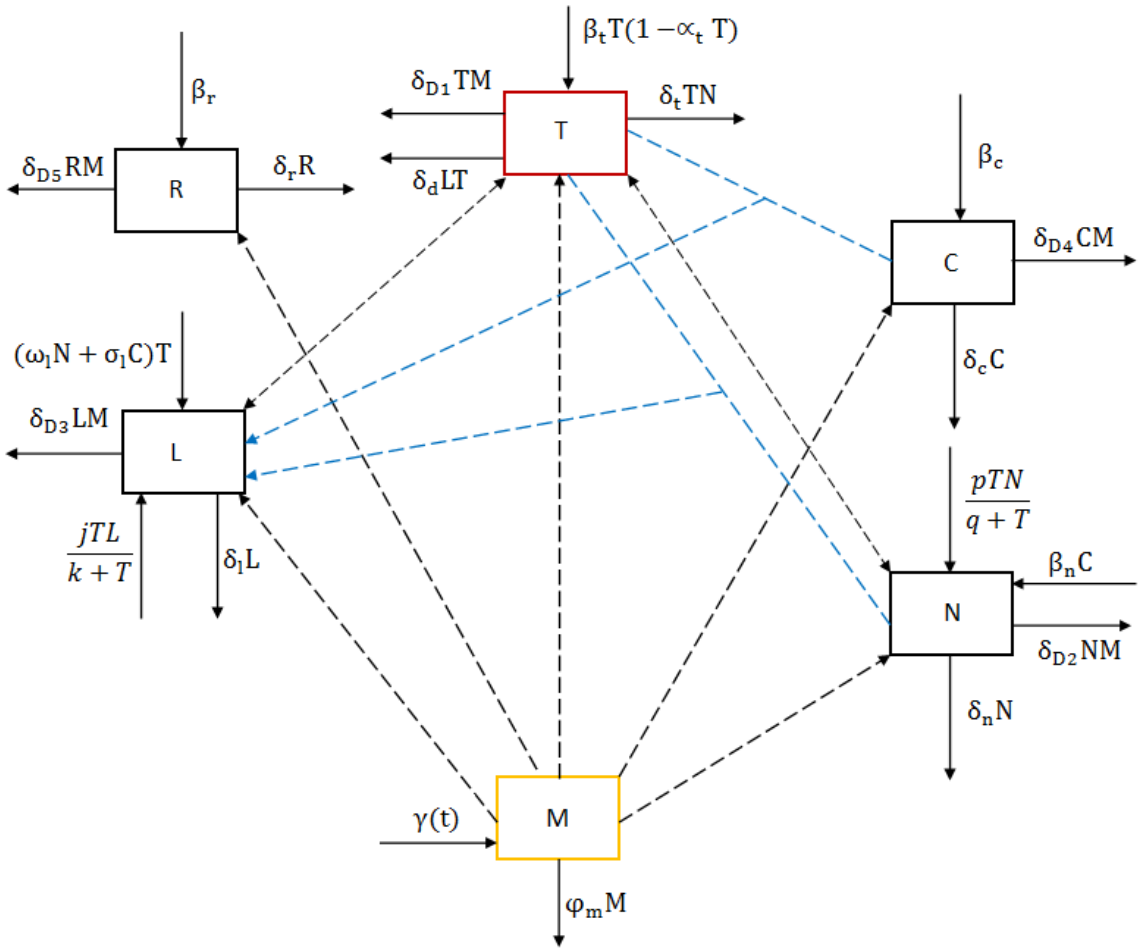

Figure 3.1: A compartmental diagram for the tumour-immune interactions with chemotherapy treatment. The term $\delta_{Di}\phi\ M(i = 1, 2, 3, 4, 5)$ for each of the cell cell population compartments was used to denoted the decrease in the cell populations as a result of chemotherapy effect denoted in equation (3.3) by: $\nu_\phi(1 - e^{-\lambda_\phi M})\phi$ where $(\phi = \mathrm{T},\ \mathrm{N},\ \mathrm{L},\ \mathrm{C}\ \text{and}\ \mathrm{R})$

3.2.2 Model equations

From the compartmental diagram in Figure 3.1, a series of six coupled ordinary differential equations representing the five cell populations and chemotherapy drug is given by

equation (3.3).

$$\left.\begin{aligned}
\dot{T(t)} &= \beta_t T\left(1-\alpha_t T\right) - \left(\delta_t N + \delta_d L\right) T - \nu_t(1-e^{-\lambda_t M})T \\
\dot{N(t)} &= \beta_n C + \frac{pTN}{q+T} - \delta_n N - \nu_n(1-e^{-\lambda_n M})N \\
\dot{L(t)} &= \frac{jTL}{k+T} + (\omega_l N + \sigma_l C)T - \delta_l L - \nu_l(1-e^{-\lambda_l M})L \\
\dot{C(t)} &= \beta_c - \delta_c C - \nu_c(1-e^{-\lambda_c M})C \\
\dot{R(t)} &= \beta_r - \delta_r R - \nu_r(1-e^{-\lambda_r M})R \\
\dot{M(t)} &= \gamma(t) - \varphi_m M
\end{aligned}\right\} \tag{3.3}$$

In the model, it is assumed that all the parameters (as presented in Table 3.1) together with their initial conditions are non-negative. That is:

$T(0) = T_0 \geq 0$, $N(0) = N_0 > 0$, $L(0) = L_0 \geq 0$, $C(0) = C_0 > 0$ and $R(0) = R_0 > 0$

3.3 Model analysis

The aim of this section is to discover and help understand the mathematical behaviour of tumour growth, particularly how the presence of the immune cells affects the stability of a growing tumour both with and without targeted chemotherapy treatment.

3.3.1 Linearization and stability analysis

We first begin by linearizing the system of non-linear equations presented in equation (3.3) using the Jacobian method. We first present two definitions and one theorem that will be critical in determining the nature of stability of the equilibrium points for the system of equations.

Definition 3.1 *Equilibria points for a system of equations (also called critical points) are points $X \in \Re^2$ where*

$$F_1(X) = F_2(X) = \cdots = 0$$

If $X \in \Re^2$ is an equilibrium solution, of a system of equations, then the constant function $x_1(t) = X_1, x_2 = X_2$ define a solution $x(t) = (X_1, X_2)$ to the system of equations.

Definition 3.2 *Let $X \in \Re^2$ be a critical point of a system of ordinary differential equations of the form $x^{'} = F(x)$, then*

1. *The critical point X is stable if for any $\varepsilon > 0$, there exists $\delta > 0$ such that if a solution $x = \phi(t)$ satisfies $||\phi(0) - x|| < \delta$, then*

$$||\phi(t) - X|| < \varepsilon$$

   for all $t > 0$. Here $||X|| = \sqrt{x_1^2 + x_2^2}$ denotes the Euclidean norm on $\Re^2$.

2. *The critical point X is unstable if it is not stable as defined above.*

3. *The critical point X is asymptotically stable if there exists a $\delta > 0$ such that if a solution $x = \phi(t)$ satisfies $||\phi(0) - X|| < \delta$ then*

$$\lim_{x \to 0} \phi(t) = X$$

Theorem 3.1 *(Liapunov's Theorem). Let $f : \Re \to Re$ be $C^{'}$ and $x_0 \in \Re$ be a fixed point of $x = f(x)$. Let $A = Df(x_0)$ be the linearization of f, $\left(so\ A_{ij} = \dfrac{\partial f_i}{\partial x_i} \right)$ be the Jacobian matrix and $\lambda_1, \lambda_2, \cdots, \lambda_i$ is its eigenvalues. Then x_0 is;*

1. *Asymptotically stable if $\Re\lambda_i < 0$ for all $i = 1, 2, \cdots, n$*

2. *Unstable if $\Re\lambda_i > 0$ for some i.*

If the eigenvalues all have real parts all equal to zero, then further analysis is necessary.

3.3.2 Steady states and equilibrium points

No tumour no treatment

In the absence of tumour cells and therefore no treatment, the variables T and M are set to zero ($T = 0, M = 0$). Further, the dynamics for tumour cell population and that of the drug reduce to zero, that is, $\dot{T(t)} = 0$ and $\dot{M(t)} = 0$. The new system of equations is then given by equation (3.4).

$$\left.\begin{aligned} \dot{T(t)} &= 0 \\ \dot{N(t)} &= \beta_n C - \delta_n N \\ \dot{L(t)} &= -\delta_l L \\ \dot{C(t)} &= \beta_c - \delta_c C \\ \dot{R(t)} &= \beta_r - \delta_r R \\ \dot{M(t)} &= 0 \end{aligned}\right\} \tag{3.4}$$

Next we describe how each of the initial values to be used later were arrived at. The value of C was found by assuming a lymphocyte count of 3.333×10^9 cells per litre of blood (Abbas and Lichtman, 2005). NK and CD8$^+$ T-cells count were assumed to form 10% and 1% of the lymphocytes per litre of blood respectively (Abbas and Lichtman, 2005). L was taken from de Pillis et al. (2009) whose estimation was based on mathematical calculations using pharmaceutical information. Lastly, R was estimated from the fact that erythrocytes form 45% of the blood. Therefore, at the tumour-drug free point, we have the following initial conditions.

$$T = 0, \qquad N = 3.333 \times 10^8, \qquad L = 2.526 \times 10^4,$$

$$C = 3.000 \times 10^9, \qquad R = 1.350 \times 10^{10}, \qquad M = 0$$

The Jacobian matrix of the of the system in equation (3.4) is evaluated as:

$$\begin{pmatrix} -\delta_n & 0 & \beta_n & 0 \\ 0 & -\delta_l & 0 & 0 \\ 0 & 0 & -\delta_c & 0 \\ 0 & 0 & 0 & -\delta_r \end{pmatrix}$$

Since the above matrix is lower triangular, its eigenvalues are the elements on the major diagonal. That is;

$$\begin{pmatrix} \lambda_1 & \lambda_2 & \lambda_3 & \lambda_4 \end{pmatrix} = \begin{pmatrix} -\delta_n & -\delta_l & -\delta_c & -\delta_r \end{pmatrix}$$

Using Theorem 3.1, we conclude that the tumour-drug-free equilibrium is stable since all the eigenvalues are negative. That is, $\lambda_i < 0$ $(i = 1, 2, 3, 4, 5)$.

Large tumour with no treatment

In order to investigate how the cell populations interact, the system of equations is examined without chemotherapy treatment, that is, the variable M is set to zero ($M = 0$). The system in equation (3.5) thus simplifies to

$$\left.\begin{aligned} \dot{T}(t) &= \beta_t T\left(1 - \alpha_t T\right) - \left(\delta_t N + \delta_d L\right) T \\ \dot{N}(t) &= \beta_n C - \delta_n N + \frac{pTN}{q+T} \\ \dot{L}(t) &= \frac{jTL}{k+T} + (\omega_l N + \sigma_l C)T - \delta_l L \\ \dot{C}(t) &= \beta_c - \delta_c C \\ \dot{R}(t) &= \beta_r - \delta_r R \\ \dot{M}(t) &= 0 \end{aligned}\right\} \tag{3.5}$$

We thus aim to analyze the system to discover how close to the tumour free equilibrium a patients needs to get to in order to be considered completely cured without the threat of re-occurrence of the tumour cells. To achieve this we set each of the above equations to zero and then solve for each of he model variables.

$$\dot{T(t)} = 0 \qquad \dot{N(t)} = 0 \qquad \dot{L(t)} = 0 \qquad \dot{C(t)} = 0 \qquad \dot{R(t)} = 0$$

Solving for each of the above equations results in the following steady states.

$$R^* = \frac{\beta_r}{\delta_r} \qquad C^* = \frac{\beta_c}{\delta_c} \qquad N^* = -\frac{\beta_n \beta_c \left(q + T\right)}{\delta_c \left(Tp - T\delta_n - q\delta_n\right)}$$

$$N^* = -\frac{\beta_c \left(Tp\sigma_l - T\beta_n\omega_l - T\delta_n\sigma_l - q\beta_n\omega_l - q\delta_n\sigma_l\right) T \left(k + T\right)}{\delta_c \left(Tp - T\delta_n - q\delta_n\right) \left(Tj - T\delta_l - k\delta_l\right)}$$

$$T^*_{1,2} = 0, -\frac{L\delta_d + N\delta_t - \beta_t}{\alpha_t \beta_t}$$

When equation (3.5) is solved simultaneously, a set of two solutions is returned one of which is given below (the other solution is a complex analytic expression which we choose not to include). This solutions indeed agrees with experimental findings that CD8$^+$ T-cells are absent in the system $(L = 0)$ when there are no tumour cells $(T = 0)$. That is:

$$C = \frac{\beta_c}{\delta_c}, \quad L = 0, \quad N = \frac{\beta_c \beta_n}{\delta_c \delta_n}, \quad R = \frac{\beta_r}{\delta_r}, \quad T = 0$$

Evaluating the Jacobian of equation (3.5) results in a Jacobian matrix of order five as is presented below.

$$\begin{pmatrix} \beta_t \left(-T\alpha_t + 1\right) - \beta_t T\alpha_t - L\delta_d - N\delta_t & -\delta_t T & -\delta_d T & 0 & 0 \\ \dfrac{pN}{q+T} - \dfrac{pTN}{\left(q+T\right)^2} & -\delta_n + \dfrac{Tp}{q+T} & 0 & \beta_n & 0 \\ \dfrac{jL}{k+T} - \dfrac{jTL}{\left(k+T\right)^2} + C\sigma_l + N\omega_l & \omega_l T & \dfrac{Tj}{k+T} - \delta_l & \sigma_l T & 0 \\ 0 & 0 & 0 & -\delta_c & 0 \\ 0 & 0 & 0 & 0 & -\delta_r \end{pmatrix}$$

Further calculations involving the above matrix result in complex analytic expressions which we do not present here, instead we turn to the numerical calculations to obtain the eigenvalues of this matrix. We first calculate the initial conditions for a patient with a large tumour population who is not on chemotherapy treatment $(T = 0, M = 0)$. Since the presence of tumour cells causes the immune system to activate CD8+ T-cells, we increase the value from $L = 2.526 \times 10^4$ to 5.268×10^5, a value that was derived by de Pillis et al. (2009). We use an initial value of $T = 4.65928 \times 10^9$, which is slightly lower than the

theoretical value of $T = 4.66 \times 10^9$ due to the fact that the response by the immune system prevents the tumour from attaining its carrying capacity. The values of N, R and C are left unchanged. These initial conditions are summarized below.

$$T = 4.65928 \times 10^9, \qquad N = 3.333 \times 10^8, \qquad L = 5.268 \times 10^5,$$

$$C = 3.000 \times 10^9, \qquad R = 1.350 \times 10^{10}, \qquad M = 0$$

At this point, we use the above initial conditions together with the parameter values presented in Table 3.2 to first evaluate the Jacobian matrix numerically. These step results in the following matrix

$$\begin{pmatrix} -3.665723 & -0.001355 & -0.001355 & 0 & 0 \\ 0.00000026 & 0.054296 & 0 & 8.889 & 0 \\ 0.011446 & 0.135492 & 0.007396 & 0.002724 & 0 \\ 0 & 0 & 0 & -0.0063 & 0 \\ 0 & 0 & 0 & 0 & -0.00315 \end{pmatrix} \tag{3.6}$$

from which we define a characteristic equation presented in equation (3.7) below.

$$| A - \lambda I | = 0 \tag{3.7}$$

where A is the matrix in equation (3.6), I is an identity matrix of order equal in magnitude to the order of A and λ is an arbitrary constant. That is;

$$\begin{vmatrix} -3.665722 - \lambda & -0.001355 & -0.001355 & 0 & 0 \\ 0.00000026 & 0.054296 - \lambda & 0 & 8.889 & 0 \\ 0.011446 & 0.135492 & 0.007396 - \lambda & 0.002724 & 0 \\ 0 & 0 & 0 & -0.0063 - \lambda & 0 \\ 0 & 0 & 0 & 0 & -0.00315 - \lambda \end{vmatrix} = 0$$

Evaluating the above determinant and equating the result to zero results in a 5^{th} order polynomial in λ which is factored and presented below.

$$-(1.0\,\lambda + 3.6657)(\lambda + 0.0063000)(\lambda + 0.0031500)(\lambda - 0.0073921)(\lambda - 0.054296) = 0$$

When the above polynomial is solved for its roots, five values are obtained which are the eigenvalues of the Jacobian matrix in equation (3.6) and are given below.

$$\begin{pmatrix} \lambda_1 \\ \lambda_2 \\ \lambda_3 \\ \lambda_4 \\ \lambda_5 \end{pmatrix} = \begin{pmatrix} -3.665718065 \\ -0.006299999998 \\ -0.003149999999 \\ 0.05429640986 \\ 0.007392061304 \end{pmatrix}$$

By theorem 3.1, the large tumour equilibrium with no treatment is unstable since

$$\lambda_1 = 0.007392061304 > 0, \lambda_2 = 0.05429640986 > 0$$

This result shows that for a large tumour population, the response by immune cells may not sufficiently eliminate tumour cells. Due to the failure of the immune system to contain this uncontrollable growth of the tumour, it is expected that its (tumour) population will continue to grow without bound.

Large tumour with chemotherapy treatment

For the case where a patients has tumour cells and chemotherapy is administered, the steady states for equation (3.3) is evaluated as follows. The expressions for N^*, L^* and T^* have been left in terms of other variables due to the complexity of the resulting expressions when further substitution is attempted.

$$R^* = -\frac{\beta_r}{\nu_r \mathrm{e}^{-\lambda_r M} - \delta_r - \nu_r}, \qquad C^* = -\frac{\beta_c}{\nu_c \mathrm{e}^{-\lambda_c M} - \delta_c - \nu_c}$$

$$N^* = \frac{\beta_n \beta_c (q+T)}{(\nu_c \mathrm{e}^{-\lambda_c M} - \delta_c - \nu_c)(\mathrm{e}^{-\lambda_n M} T\nu_n + \mathrm{e}^{-\lambda_n M} q\nu_n + pT - T\delta_n - T\nu_n - q\delta_n - q\nu_n)}$$

$$L^* = -\frac{T(CT\sigma_l + Ck\sigma_l + NT\omega_l + Nk\omega_l)}{\mathrm{e}^{-\lambda_l M} T\nu_l + \mathrm{e}^{-\lambda_l M} k\nu_l + jT - \delta_l T - T\nu_l - \delta_l k - k\nu_l}$$

$$T^*_{1,2} = 0, -\frac{L\delta_d + N\delta_t - \nu_t \mathrm{e}^{-\lambda_t M} - \beta_t + \nu_t}{\alpha_t \beta_t}$$

For the steady state $T^*_{1,2}$, there were two solutions. Since we are dealing with a large tumour equilibrium, it suffices to assume that $T = 0$ is not a solutions of the system. Now

the Jacobian matrix of the model including the chemotherapeutic drug is evaluated to give the the matrix in equation (3.8).

$$\begin{pmatrix} j_{11} & -\delta_t T & -\delta_d T & 0 & 0 & -\nu_t \lambda_t \mathrm{e}^{-\lambda_t M} T \\ j_{21} & j_{22} & 0 & \beta_n & 0 & -\nu_n \lambda_n \mathrm{e}^{-\lambda_n M} N \\ j_{22} & \omega_l T & j_{33} & \sigma_l T & 0 & -\nu_l \lambda_l \mathrm{e}^{-\lambda_l M} L \\ 0 & 0 & 0 & j_{44} & 0 & -\nu_c \lambda_c \mathrm{e}^{-\lambda_c M} C \\ 0 & 0 & 0 & 0 & j_{55} & -\nu_r \lambda_r \mathrm{e}^{-\lambda_r M} R \\ 0 & 0 & 0 & 0 & 0 & -\varphi_m \end{pmatrix} \tag{3.8}$$

where

$$j_{11} = \beta_t \left(-T\alpha_t + 1\right) - \beta_t T \alpha_t - L\delta_d - N\delta_t - \nu_t \left(1 - \mathrm{e}^{-\lambda_t M}\right)$$

$$j_{21} = \frac{pN}{q+T} - \frac{pTN}{(q+T)^2}$$

$$j_{31} = \frac{jL}{k+T} - \frac{jTL}{(k+T)^2} + C\sigma_l + N\omega_l$$

$$j_{22} = -\delta_n + \frac{pT}{q+T} - \nu_n \left(1 - \mathrm{e}^{-\lambda_n M}\right)$$

$$j_{33} = \frac{jT}{k+T} - \delta_l - \nu_l \left(1 - \mathrm{e}^{-\lambda_l M}\right)$$

$$j_{44} = -\delta_c - \nu_c \left(1 - \mathrm{e}^{-\lambda_c M}\right)$$

$$j_{55} = -\delta_r - \nu_r \left(1 - \mathrm{e}^{-\lambda_r M}\right)$$

Using the parameters in Table 3.2 and the initial conditions stated in section 3.3.2, we find

the following matrix.

$$\begin{pmatrix} -4.69 \times 10^{-1} & -5.82 \times 10^{-9} & -5.82 \times 10^{-9} & 0 & 0 \\ 6.86 \times 10^{-1} & -7.51 \times 10^{-2} & 0 & 8.89 \times 10^{0} & 0 \\ 1.32 \times 10^{-3} & 5.82 \times 10^{-7} & -4.86 \times 10^{0} & 1.17 \times 10^{-8} & 0 \\ 0 & 0 & 0 & -4.03 \times 10^{-2} & 0 \\ 0 & 0 & 0 & 0 & -3.72 \times 10^{-2} \end{pmatrix}$$

We again form and solve the characteristic equation given by

$$| A - \lambda I | = 0 \tag{3.9}$$

where A is the above matrix. Equation (3.9) is a polynomial of order five whose factors are given by:

$$f(\lambda) = (\lambda + 4.8650)(\lambda + 0.46902)(\lambda + 0.075059)(\lambda + 0.040300)(\lambda + 0.037150) = 0$$

The roots of this 5^{th} order polynomial are thus given by the solutions of the function $f(\lambda) = 0$. That is

$$\lambda_1 = -0.075059, \lambda_2 = -0.46902, \lambda_3 = -4.8650, \lambda_4 = -0.03715 \text{ and } \lambda_5 = -0.04030$$

It can be seen that all the $\lambda_i^{'}s$ $(i = 1, 2, 3, 4, 5)$ are less than zero. Therefore the large tumour equilibrium which we found to be unstable when there was no treatment is now stable. This results therefore show that tumour cells can be eliminated by both the response of immune cells and the efficacy of the chemotherapeutic drugs.

3.4 Numerical analysis and simulation

To carry the numerical simulation, relevant literatures were reviewed and came up with the parameters presented in Table 3.2. These parameters were used to numerically evaluate the results over an interval of 714 days (about two years). Figure 3.2 shows the results of the numerical simulation plotted on the same figure. In the subsequent pages, these plots are presented separately for easy of visualization.

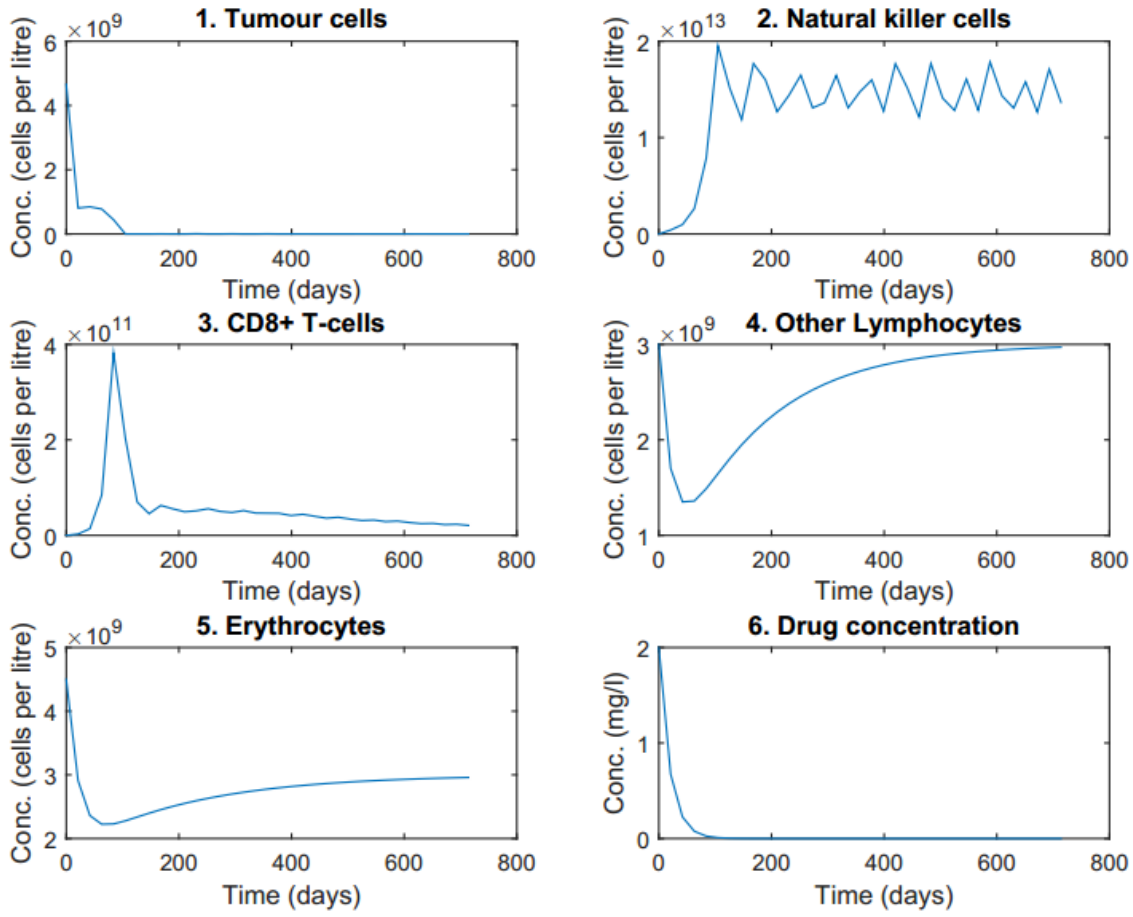

Figure 3.2: Interaction dynamics among tumour, NK, $CD8^{+}$, other lymphocytes red blood cells under targeted chemotherapy treatment.

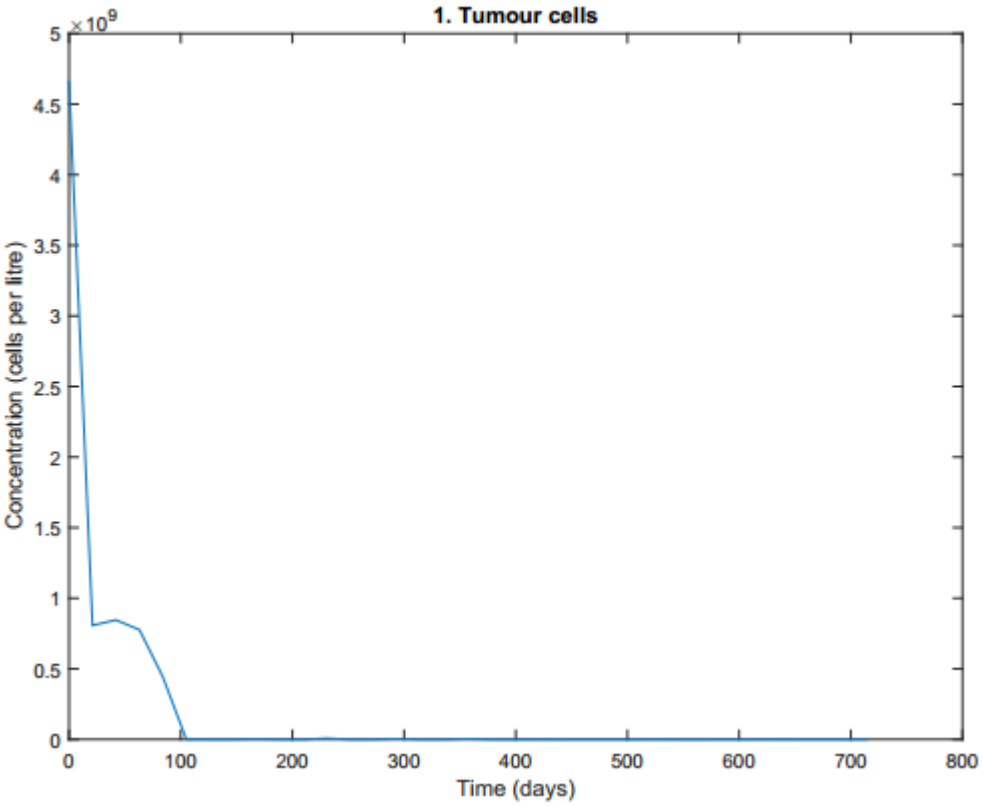

Figure 3.3: Total population of tumour (cells/litre) against time (in days)

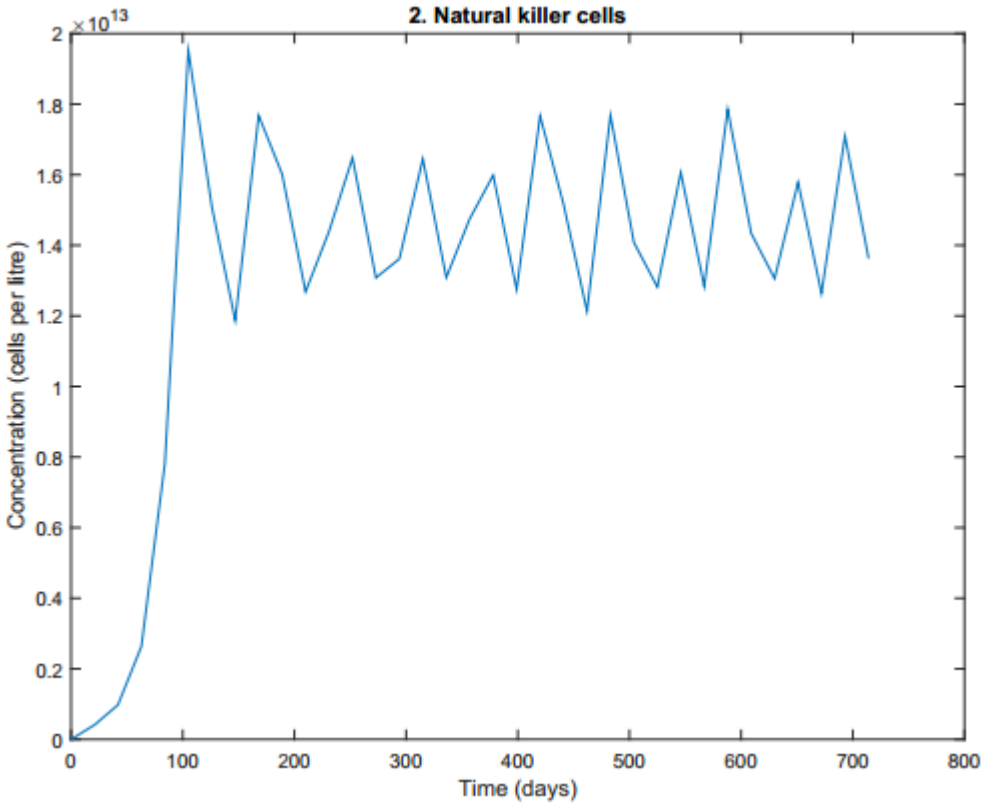

Figure 3.4: Concentration of Natural killers (cells/litre) against time (in days)

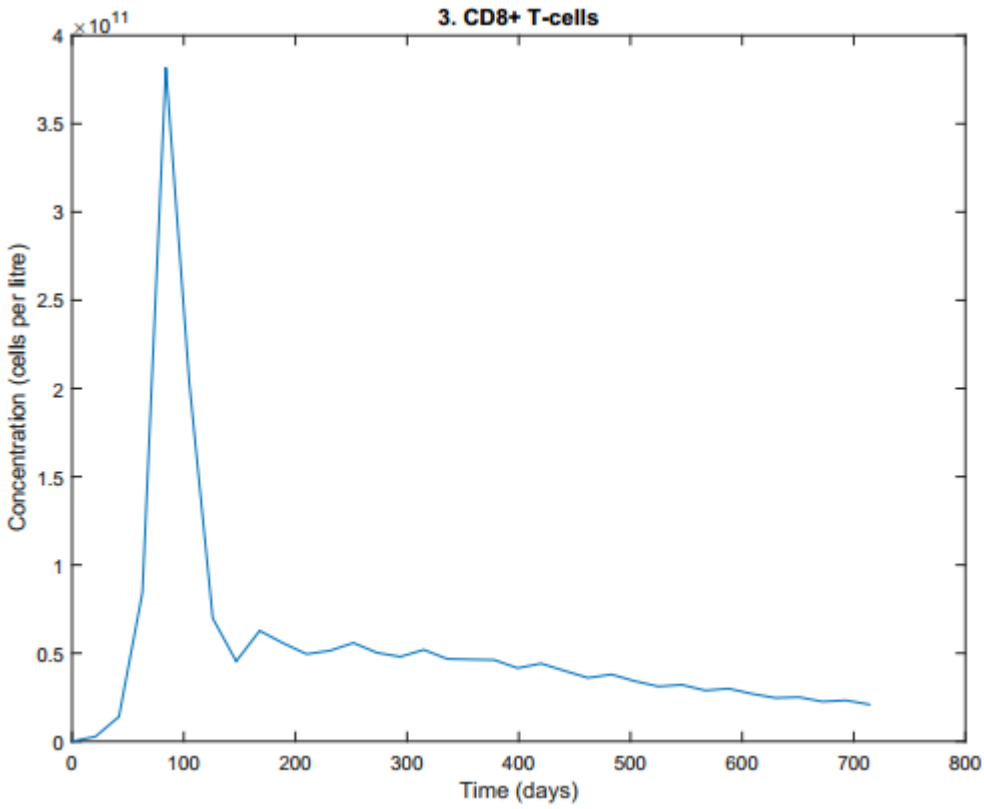

Figure 3.5: Concentration of $CD8^+$ (cells/litre) against time (in days)

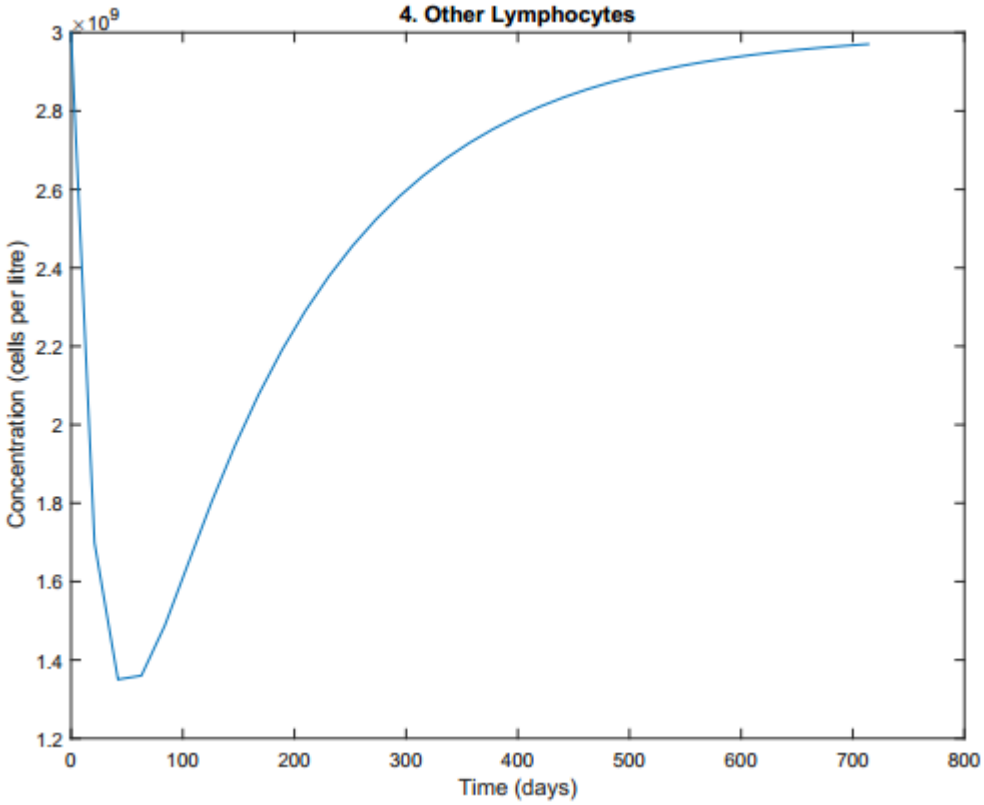

Figure 3.6: Concentration of other lymphocytes (cells/litre) against time (in days)

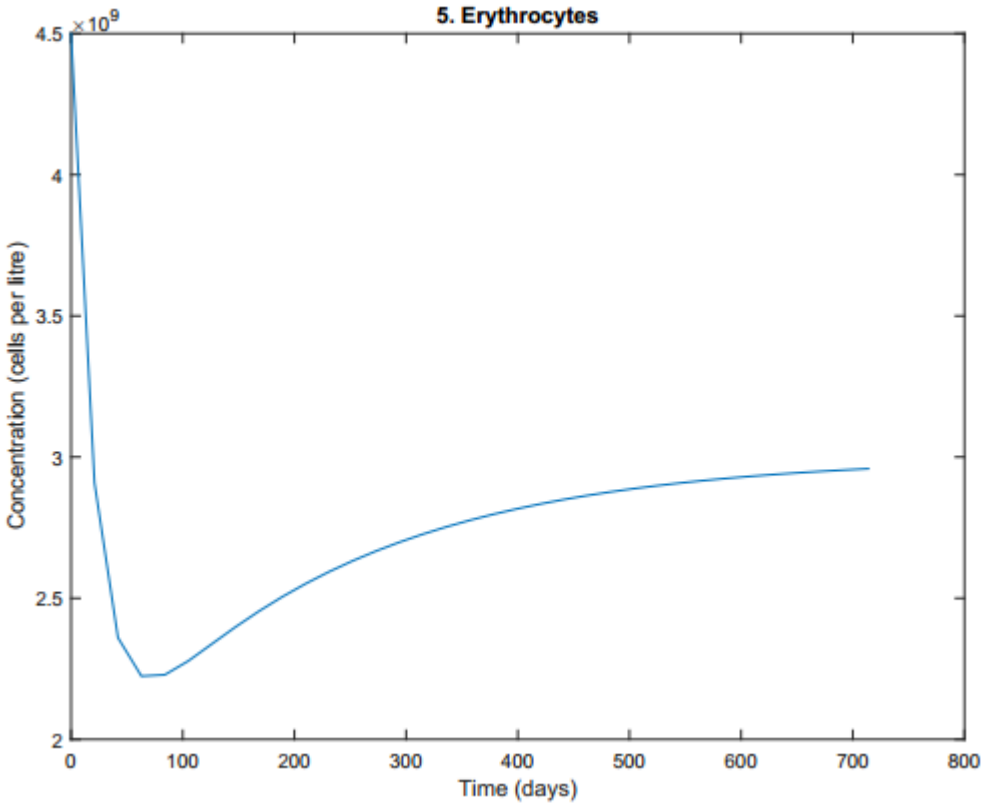

Figure 3.7: Concentration of erythrocytes (cells/litre) against time (in days)

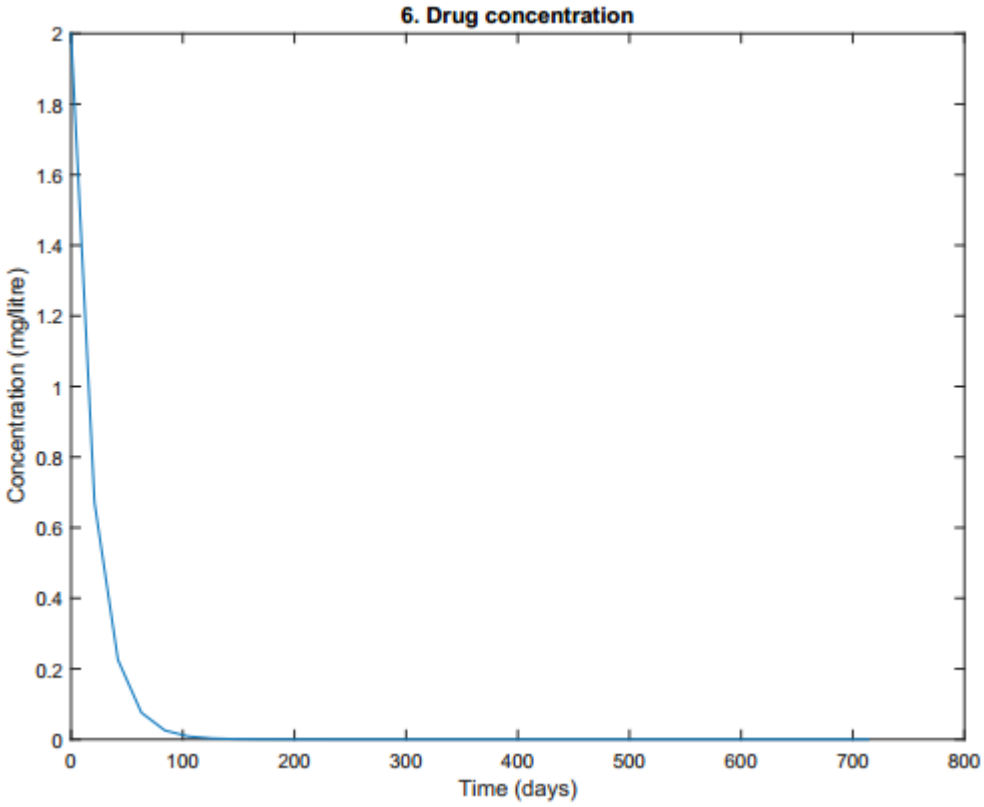

Figure 3.8: Concentration of chemotherapy drug in mg/l against time (in days)

Table 3.2: Parameters values used for numerical computations and simulation.

Parameter	Value	Units	Source
β_t	4.310×10^{-1}	Day^{-1}	de Pillis et al. (2009)
α_t	1.020×10^{-9}	Cells^{-1}	de Pillis et al. (2009)
δ_t	2.908×10^{-13}	l cells^{-1} per day^{-1}	de Pillis et al. (2009)
δ_d	2.908×10^{-13}	l cells^{-1} per day^{-1}	Estimated
ν_t	9.000×10^{-1}	Day^{-1}	de Pillis et al. (2009)
$\lambda_t, \lambda_n, \lambda_l, \lambda_c, \lambda_r$	1.833×10^{0}	l/mg^{-1}	de Pillis et al. (2009)
β_n	8.889×10^{0}	-	de Pillis et al. (2009)
δ_n	1.250×10^{-2}	-	de Pillis et al. (2009)
p	6.680×10^{-2}	Day^{-1}	de Pillis et al. (2009)
q	2.504×10^{5}	Day^{-1}	de Pillis et al. (2009)
ν_n	6.750×10^{-2}	Day^{-1}	Catimel (1985)
j	1.245×10^{-2}	Day^{-1}	de Pillis et al. (2009)
k	2.019×10^{7}	Cells	de Pillis et al. (2009)
ω_l	2.908×10^{-11}	Cells^{-1} per Day^{-1}	de Pillis et al. (2009)
σ_l	5.847×10^{-13}	Cells^{-1} per Day^{-1}	de Pillis et al. (2009)
δ_l	5.000×10^{-3}	Day^{1}	Estimated
ν_l	4.860×10^{0}	Day^{-1}	de Pillis et al. (2009)
β_c	1.890×10^{7}	Day^{-1}	de Pillis et al. (2009)
δ_c	6.300×10^{-3}	Day^{-1}	de Pillis et al. (2009)
ν_c	3.400×10^{-2}	Day^{-1}	Catimel (1985)
β_r	1.890×10^{7}	Day^{-1}	Estimated
δ_r	6.300×10^{-3}	Day^{-1}	Estimated
ν_r	3.400×10^{-2}	Day^{-1}	Estimated
φ_m	5.199×10^{-2}	day^{-1}	Estimated from Catimel (1985)

Chapter Four

4 Conclusion and Recommendations

We have modified the model developed by de Pillis et al. (2009) and have, by estimating and/or using available parameter values analysed three equilibrium states namely: *no tumour no treatment, tumour with no treatment and tumour with chemotherapy treatment*. The first equilibrium point *no tumour no treatment*, was found to be stable. The second equilibrium point, *tumour with no treatment* was found to be unstable — the immune system on its own is incapable of completely driving the tumour population to zero. At this equilibrium, the tumour population will as a result continue to grow resulting in a high tumour burden for the patient. The large tumour equilibrium with treatment was found to be stable. With the right administration of chemotherapy and a strong immune system for a cancer patient, the tumour cell population could thus be eliminated completely. It was also found that presence of chemotherapy drug in the system weakens the immune cells ability to effectively fight the tumour cells.

From the numerical simulation results, we noted a very sharp drop in the level of white blood cells with the introduction of the drug in the system. The levels began to rise only after the drug was completely eliminated from the body, and as depicted from Figure 3.6 it took almost one and a half years for the cells to get back to their initial levels. While the simulated results did not clearly show a sharp decline in the number of NK and $CD8^+$ T-cells as would have been expected, there was a bit of retardation in their recruitment as a result of severe toxicity of the drug to born marrow cells where they (NK and $CD8^+$ T-cells) are produced. A lot of precaution should therefore be taken so that the patients is not bombarded with too much of the chemotherapeutic drug for this is likely going to weaken the immune cells and therefore drive the system to instability causing the tumour population to re-grow.

We also edited the model to include red blood cells with the aim of investigating the effect

of chemotherapy drug to these cells. It was found, as can be seen from Figure 3.7 that the red blood cell population suffered severely from the toxic levels of the drug. Consequently, their number dropped significantly with the introduction of the drug, but again began to rise when the drug was completely eliminated from the body. Unlike the case of the white blood cells, which got back to their initial cell count, we found that red blood cells are unable to get back to their original levels even after almost two years. Such a situation cause patients on chemotherapy treatment to exhibit a much lower red blood count which ultimately may lead to cases of anemia and further worsen the situation.

Evidently, while chemotherapy drugs are guaranteed to effectively eliminate tumour cells, the cost of their toxicity to other body cells is quite high and their administration in cancer management should be taken with a lot of precaution. In future research, we put forth a number of recommendations that could be done to improve on the model developed herein, in order to realize better and promising scientific results in the fight against cancer and chemotherapy related side effects. These recommendations include:

i.) Extending the model to include an optimal control strategy by using objective functions with different combination of constraints. By doing this, it could be possible to come up with a mathematical model that quantifies the exact chemotherapy drug concentration that maximizes efficacy on tumour cells but at the same time minimizing the levels of toxicity to other normal body cells.

ii.) Including additional cell populations to the model. In particular, it would shade more light if the model was modified by including additional immune cell populations, and particularly those that are involved in the signaling and activation of the $CD8^+$ T-cells whenever tumour cells are present in the body, good examples being the CD4 and CD3 cells.

iii.) More equations could be added to the developed model to capture additional details for example the patients well being — social, financial and health in order to predict secure and effective chemotherapy treatment strategies.

iv.) For purposes of justifying the validity of the model and in order to obtain more re-

cent and relevant model parameters, we recommend that various sets of experiments be fitted to the model developed in this research. Experimental data from clinical trials on humans need to be carried out in order to limit the over-reliance on mouse experiments for model parameters.

v.) The ordinary differential equations could be extended to partial differential equations. In this case, it will be possible to capture and investigate the spatial characteristics of tumour cells for example, their ability to metastasize quickly to other parts of the body.

vi.) The aspect of resistance to drugs by chemotherapy drugs, in addition to combination therapy could also be investigated in future models.

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APPENDICES

Appendix A: Maple codes

Listing 1: **Equation (3.3) entered in Maple.**

```
#########################################################
# Run this file before running syntax in Listing 2 & 3 #
#########################################################

# clear the Maple workspace
restart:
# Enter the system of differential equations

# Tumour cells
dotT := beta[t]*T*(-T*alpha[t]+1)-delta[t]*N*T-delta[d]*L*T
   -nu[t]*(1-e^(-lambda[t]*M))*T:

# Natural killers
dotN := delta[n]*(beta[n]*C/delta[n]-N)+m*T*N/(n+T)-nu[n
   ]*(1-e^(-lambda[n]*M))*N:

# CD8+ T-cells
dotL := j*T*L/(k+T)+(C*sigma[l]+N*omega[l])*T-delta[l]*L-nu
   [l]*(1-e^(-lambda[l]*M))*L:

# Lymphocytes
dotC := delta[c]*(beta[c]/delta[c]-C)-nu[c]*(1-e^(-lambda[c
   ]*M))*C:

# Red blood cells
dotR := delta[r]*(beta[r]/delta[r]-R)-nu[r]*(1-e^(-lambda[r
   ]*M))*R:

# Chemotherapy drug
dotM := gamma(t)-varphi[m]*M:
```

Listing 2: **Model Analysis with no tumour and no treatment (T = 0 & M = 0) for Equation (3.3).**

```
#########################################################
# Run the file in Listing 1 before running this file #
#########################################################

T := 0: # No tumour
M := 0: # No treatment

# Steady states

Rs := solve(dotR,R)
Cs := solve(dotC,C)
Ns := subs({C = Cs}, solve(dotN,N))
Ls := simplify(subs({C = Cs,N = Ns}, solve(dotL,L)))
Ts := solve(dotT,T)

# solve all equations simultaneously and extracting the
   first set of solutions

solve({dotT,dotN,dotL,dotC,dotR},{T,N,L,C,R})[1]

# Load packages with functions in vector calculus and
   linear algebra.

with(VectorCalculus):
with(LinearAlgebra):

# Calculate the Jacobian of the system

JE := Jacobian([dotT,dotN,dotL,dotC,dotR],[T,N,L,C,R])
JE0 := subs({T = 0}, JE)

# form the matrix I_lambda used in the characteristic
   equation find eigen values

I_lambda := lambda*IdentityMatrix(5): # create an identity
   matrix of order 5
Char_Eqtn := JE0-I_lambda;
```

```
det_Char_Eqtn := Determinant(Char_Eqtn) # Eigen values
   using the determint
eigen_JE0 := Eigenvalues(JE0) # Eigenvalues using the Maple
    function

# Numerical calculations

JE1 := subs({T = 1,N = 1}, JE)

JE1C := CharacteristicPolynomial(JE1, lambda):
JEE := Eigenvalues(JE1):
```

Listing 3: **Model Analysis with no treatment (M = 0) for Equation (3.3).**

```
#######################################################
# Run the file in Listing 1 before running this file #
#######################################################

M := 0: # No treatment

# Steady states

Rs := solve(dotR,R)
Cs := solve(dotC,C)
Ns := subs({C = Cs}, solve(dotN,N))
Ls := simplify(subs({C = Cs,N = Ns}, solve(dotL,L)))
Ts := solve(dotT,T)

# solve all equations simultaneously and extracting the
   first set of solutions

solve({dotT,dotN,dotL,dotC,dotR},{T,N,L,C,R})[1]

# Load packages with functions in vector calculus and
   linear algebra.

with(VectorCalculus):
with(LinearAlgebra):

# Calculate the Jacobian of the system
```

```
25
26 JE := Jacobian([dotT,dotN,dotL,dotC,dotR],[T,N,L,C,R])
27 JE0 := subs({T = 0}, JE)
28
29 # form the matrix I_lambda used in the characteristic
      equation find eigen values
30
31 I_lambda := lambda*IdentityMatrix(5): # create an identity
      matrix of order 5
32 Char_Eqtn := JE0-I_lambda;
33 det_Char_Eqtn := Determinant(Char_Eqtn) # Eigen values
      using the determint
34 eigen_JE0 := Eigenvalues(JE0) # Eigenvalues using the Maple
       function
35
36 # Numerical calculations
37
38 JE1 := subs({T = 1,N = 1}, JE)
39
40 JE1C := CharacteristicPolynomial(JE1, lambda):
41 JEE := Eigenvalues(JE1):
```

Listing 4: **Model Analysis with treatment for Equation (3.3).**

```
#########################################################
# Run the file in Listing 1 before running this file #
#########################################################

# Steady states

Rs := solve(dotR,R)
Cs := solve(dotC,C)
Ns := subs({C = Cs}, solve(dotN,N))
Ls := simplify(subs({C = Cs}, solve(dotL, L))):
Ls := subs({lambda[c]+lambda[l] = b, lambda[c]+lambda[l]+
   lambda[n] = a}, Ls)
Ts := solve(dotT,T)

# solve all equations simultaneously and extracting the
   first set of solutions

solve({dotT,dotN,dotL,dotC,dotR},{T,N,L,C,R})[1]

# Load packages with functions in vector calculus and
   linear algebra.

with(VectorCalculus):
with(LinearAlgebra):

# Calculate the Jacobian of the system

JE := Jacobian([dotT,dotN,dotL,dotC,dotR],[T,N,L,C,R])

# form the matrix I_lambda used in the characteristic
   equation find eigen values

I_lambda := lambda*IdentityMatrix(5): # create an identity
   matrix of order 5
Char_Eqtn := JE0-I_lambda
det_Char_Eqtn := Determinant(Char_Eqtn) # Eigen values
   using the determint
eigen_JE0 := Eigenvalues(JE0) # Eigenvalues using the Maple
```

```
    function
33
34 # Numerical calculations
35
36 JE1 := subs({T = 1,N = 1},JE)
37
38 JE1C := CharacteristicPolynomial(JE1,lambda):
39 JEE := Eigenvalues(JE1):
```

Appendix B: Matlab codes

Listing 5: **Matlab code for Figure 3.1**

```
%{
THIS SCRIPT SOLVES THE DIFFERENTIAL EQUATIONS ANALYTICALLY
AND PLOTS THE RESULTS. NOTE THAT NUMERICAL METHODS COULD
   ALSO HAVE BE USED
%}

% define the symbolic expressions (variables & parameters)
% r = lambda
syms K r N(t)
% define parameter values
N0 = 0.1;
rg = 1;
Kg = 1;
% Solving the models with initial tumour size of 0.1
% Exponential
fE = dsolve(diff(N) == r*N,N(0) == N0);
fEs = subs(fE,r,rg); % substitute for r
% Logistic
fL = dsolve(diff(N) == r*N*(1-N/K),N(0) == N0);
fL = simplify(fL);
fL1 = subs(fL,[r,K],[rg,Kg]); % substitute for r and k
fLp = simplify(fL1);
% Gompertz
fG = dsolve(diff(N) == r*N*log(K/N),N(0) == N0);
fG = simplify(fG);
fG1 = subs(fL,[r,K],[rg-0.1,Kg]); % substitute for r and k.
% Note that r was reduced by 0.1 to avoid overlap of
% logistic and Gompertz graphs
fGp = simplify(fG1);

% Plotting the results
close all
limits = [0 10];
ezplot(fEs,limits) % exponential model
hold on
ezplot(fLp,limits) % logistic model
```

```
hold on
ezplot(fGp,limits) % Gompertz model

% graph options

E = '$$ \frac{dN}{dt} = r\,N $$';
L = '$$ \frac{dN}{dt} = r\,N\left(1-\frac{N}{K}\right) $$';
G = '$$ \frac{dN}{dt} = r\,N\,ln\left(\frac{N}{K}\right) $$
   ';

title('Exponential, Logistic and Gompertz models')
xlabel('time (t)')
ylabel('Size of tumour, N(t)')
grid minor
legend({E,L,G},'Interpreter','latex','Location','Best')

hold off
```

Listing 6: **Function file for Equation 3.3 with parameter values**

```
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
% ODE system in Equation 3.3 %
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
function dy = modelequations(t,y)

dy = zeros(6,1);

% Tumour parameters
beta_t = 4.31e0;              alpha_t = 1.020e-9;
delta_t = 2.908e-13;          delta_d = 2.908e-13;
nu_t = 9e-1;                  lambda_t = 1.833e0;

% NK cells parameters
beta_n = 8.889e0;             delta_n = 1.250e-2;
p = 6.680e-2;                 q = 2.504e5;
nu_n = 6.750e-2;              lambda_n = 1.833e0;

% CD8+ cells parameters
j = 1.245e-2;                 k = 2.019e7;
omega_l = 2.908e-11;          sigma_l = 5.847e-13;
delta_l = 5e-3;               nu_l = 4.860e0;
lambda_l = 1.833e0;

% Lymphocytes paramters
beta_c = 1.890e7;             delta_c = 6.3e-3;
nu_c = 3.4e-2;                lambda_c = 1.833e0;

% Erythrocytes parametrs
beta_r = 0.75*1.890e7;         delta_r = 0.75*6.3e-3;
nu_r = 0.75*3.4e-2;            lambda_r = 0.75*1.833e0;

% Chemotherapy parameter
varphi_m = 5.199e-2;
gammat = 0;

T = y(1); % Tumour cell populations
N = y(2); % Natural kill cells
L = y(3); % CD8+ T cells
```

```
C = y(4); % Other circulating lymphocytes
R = y(5); % Red blood cells
M = y(6); % Chemotherapy drug

% System of equations

% Tumour: dT/dt
dy(1) = beta_t*T*(-T*alpha_t+1)-delta_t*N*T-delta_d*L*T-
   nu_t*(1-exp(-lambda_t*M))*T;

% Natural killer: dN/dt
dy(2) = beta_n*C+p*T*N/(q+T)-delta_n*N-nu_n*(1-exp(-
   lambda_n*M))*N;

% CD8+ T: dL/dt
dy(3) = j*T*L/(k+T)+(C*sigma_l+N*omega_l)*T-delta_l*L-nu_l
   *(1-exp(-lambda_l*M))*L;

% Other Lymphocytes: dC/dt
dy(4) = beta_c-delta_c*C-nu_c*(1-exp(-lambda_c*M))*C;

% Erythrocytes: dR/dt
dy(5) = beta_r-delta_r*R-nu_r*(1-exp(-lambda_r*M))*R;

% Chemotherapy drugs: dM/dt
dy(6) = gammat-varphi_m*M;

% END
```

Listing 7: **M-Script to run the function in Listing 6**

```
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
% Script runs the function in Listing 6 %
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
clear; clc
close all
start_time = 0;
interval = 7*3;
end_time = interval*17*2;
time = start_time:interval:end_time;
length(time);
Ti = 4.65928e9;      Ni = 3.33333e8;      Li = 5.268e5;
Ci = 3e9;            Ri = 4.25e9;         Mi = 2.5;
initialconditions = [Ti;Ni;Li;Ci;Ri;Mi];
[t,y] = ode45(@modelequations,time,initialconditions);
% Organize results in a matrix and display on the screen
odeTable = [t,y]';
fprintf('%6s','
   ------------------------------------------
   ------------------------------------------------')
fprintf('\n%6s %14s %14s %14s %14s %14s %12s\n','Time','
   Tumour','NK','CD8+ T','Lymphocytes','Erythrocites','Drug
   ')
fprintf('%6s\n','
   ------------------------------------------
   ------------------------------------------------')
fprintf('%6g %14g %14g %14g %14g %14g %12g\n',odeTable)
fprintf('%6s\n','
   ------------------------------------------
   ------------------------------------------------')
% Create list with the cell populations
varslabel = {'1. Tumour cells','2. Natural killer cells','
   3. CD8+ T-cells','4. Other Lymphocytes','5. Erythrocytes
   ','6. Drug concentration'};
vars = size(y,2);
% Create figures for T(t), N(t), L(t), C(t), R(t) and M(t)
close all
for i = 1:(vars)
    figure(i)
```

```
    plot(t,y(:,i))
    title([varslabel(i)])
    xlabel('Time (days)')
    if (i < 6)
        ylabel('Concentration (cells per litre)')
    else
        ylabel('Concentration (mg/l)')
    end
end
% combine into one figure
figure(i+1)
for i = 1:(vars)
    subplot(3,2,i)
    plot(t,y(:,i))
    title([varslabel(i)])
    xlabel('Time (days)')
    if (i < 6)
        ylabel('Conc. (cells per litre)')
    else
        ylabel('Conc. (mg/l)')
    end
end
```