DYNAMICS AND OPTIMAL CONTROL OF CANCER CELLS

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ABSTRACT

The study carried out in this thesis deals with deterministic cancer models. They explore the relationship/interaction between immune system, immune checkpoints, and BCG in superficial bladder cancer treatment. The study is divided into three categories.

Firstly, we present a model that reveals the dynamics of checkpoints in BCG immunotherapy of bladder cancer. Three scenarios are considered; model without treatment, model without checkpoints, and model with checkpoints and treatment. The purpose is to establish the negative effects of checkpoints on the immune system. Numerical simulations disclose that in the absence of checkpoints, the immune system kills the tumor, while the tumor grows exponentially in the presence of checkpoints. Thus, the checkpoints have negative influence on the immune system.

Secondly, a control function is introduced into our model. We aim for a BCG optimal dose required to, activate the immune system regardless of checkpoints activities and reduce toxicity to normal cells. Pontryagin's principle is used to characterize the control demanding to minimize the objective function. Thus, the optimal dose that kills the tumor, minimizes checkpoints activity and reduces toxicity to normal cells is 3.14×10^5 colony forming unit.

Lastly, we introduce two control functions; one block the activities of checkpoints (immune checkpoint inhibitors) and the other activate immune system (BCG). The maximum principle is utilized to find the characterization of the optimal control pair. The controls show the cancer cells eliminated, the checkpoints activities minimized, and the normal cells maximized.

Hence, the medical practitioners should adopt single therapy with BCG only, or combination therapy of BCG and immune checkpoint inhibitors.

Keywords: Bladder cancer; immune system; immune checkpoints; Bacillus Calmette Guerin (BCG); mathematical model; optimal control

ÖZET

Bu tezin araştırması belirleyici kanser modelerini inceler. Modeller, yüzeyel mesane kanseri tedavisinde bağışıklık sistemi, bağışıklık kontrol noktalarını ve BCG aşısı arasındaki ilişkiyi ve etkileşimi araştırmaktadır. Çalışma üç kategoriye ayrılmıştır. Öncelikle, mesane kanserinin BCG aşısı immünoterapisinde immün kontrol noktalarının dinamiklerini ortaya koyan bir model sunuyoruz. Üç senaryo çıkarılır ve dikkate alınır. Bunlar viz., tedavi olmadan model, kontrol noktaları olmayan model ve kontrol noktaları ve tedavi ile model. Amaç, kontrol noktalarının bağışıklık hücreleri ve tüm tedavi üzerindeki olumsuz etkilerini tespit etmektir. Sayısal simülasyonlar şunu açıklar ki; kontrol noktalarının yokluğunda, aktifleştirilmiş bağışıklık sistemi kanser hücrelerini öldürür. Ancak, kontrol noktaları mevcut olduğunda, kontrol noktalarının bağışıklık sistemi üzerindeki baskılama nedeniyle tümör olarak büyür. Böylece kontrol noktalarının bağışıklık sistemi ve tüm terapi üzerinde olumsuz etkisi vardır.

İkinci olarak, optimal kontrol teorisi kavramını modelimize tanıtıyoruz. Amaç, kontrol noktaları aktivitelerinden bağımsız olarak bağışıklık sistemini aktive etmek için gerekli BCG tüberküloz aşısı optimal dozunu taklit eden ve reaktif maddenin normal hücrelere toksisitesini azaltan bir kontrol fonksiyonu bulmaktır. Pontryagin'in maksimum prensibi, kanser hücrelerinin sayısına, normal hücrelere, kontrol noktalarına ve kontrol maliyetine bağlı olan objektif işlevi en aza indirgemek için kontrolü talep etmek için kullanılır. Nümerik sonuçlar, BCG aşısı 'nın 3.14×10^5 koloni oluşturan bir biriminin gerekli olduğunu göstermektedir.

Son olarak, başka bir tedavi seçeneğine sahip olmak için kombinasyon terapisi fikrini sunuyoruz. Optimal kontrol çiftinin karakterizasyonunu bulmak için maksimum prensip kullanılır. Kontroller kanser hücrelerinin elimine edildiğini, kontrol noktaları aktivitelerinin en aza indirildiğini ve normal hücrelerin maksimize edildiğini gösterdi. Böylece, optimal çift etkili olur. Bu nedenle, pratisyen hekimler sadece BCG aşısı ile tek terapiyi veya BCG ve immün kontrol noktası inhibitörlerinin kombinasyon tedavisini benimsemelidir.

Anahtar Kelimeler: Mesane kanseri; bağışıklık sistemi; bağışıklık kontrol noktaları; Bacillus Calmette Guerin (BCG) tüberküloz aşısı; matematiksel model; optimal kontrol; asimptotik kararlılık; Pontryagin maksimum prensibi

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BCG: Bacillus-Calmette Guerin

OCP: Optimal Control Problem

CV: Calculus of Variation

CHAPTER 1

INTRODUCTION

The phrase "cancer" originated from the Greek phrases *"carcinos"* and *"carcinoma"* as first described by Hippocrates (a Greek doctor, from 460 to 370 BC) - the father of medicine. He used those words to characterize tumors (malignant in particular) and hence called cancer as *"karkinos"*. A crab; is what actually the Greek terms were referred to, which Hippocrates' idea likened them to tumor because of their shape (Deeley, 1983). Later, the Greek terms were translated into *cancer* by Celsus (a Roman physician 28-50 BC), which is Latin for crab. The word *oncos* which means swelling in Greek was used by Galen (a Greek physician, 130-200 AD) to represent tumors. This description by Galen is termed for cancer specialists these days, viz. oncologists (Deeley, 1983).

Cancer are family of fatal and serious diseases characterized by out-of-control abnormal cell growth which results in the formation of malignant tumors that destroy or damage body tissues as well as the DNA. It is among the top two principal reasons of death around the world (Hassanpour and Dehghani, 2017). Worldwide, it is estimated that approximately 8.2 million people die per year because of the disease (Carter et al., 2016). In particular, about 7.6 million deaths were recorded in 2008, and this figure accounts to 13% of all deceases same year (Hegadoren et al., 2014).

The death and incidence rates are high in Europe. Norway experienced a rapid yearly increase of about 3.5% after the millennium (Robsahm et al., 2018). Similarly, Denmark, Slovakia, Hungary, and Slovenia, are experiencing raises in deaths due to cancer. However, in countries like Japan, Turkey, Switzerland, Mexico, and Finland, the prevalence of cancer is very low(Wiencke, 2004; Anand et al.,2008; OECD, 2013). In USA, over one million and fivehundred thousand individuals are suffering from cancer, and around 600000 died from the disease in 2014 (Siegel et al., 2013).It is reported that over 100 distinct types of cancers exist with majority named from the organ they start with. Age and genetics are among the risk factors of getting the disease, accounting to at most 10% of the cases. The remaining 90% are,

but not limited to obesity, excessive exposure to sunlight, smoking and drinking, environment, sluggishness, poor consumption behaviors, and lack of exercise (Anand et al.,2008; OECD, 2013).

The death rates in males are always higher than in females across the globe. The gap is predominantly eclectic in Turkey, Spain, Korea, Estonia, and Portugal, because the rate in men is at least twice that of women. This can be attributed to the superiority of pervasiveness of some risk factors among men, for example smoking (Wiencke, 2004; Brayand and Moller 2006; Anand et al.,2008). In men, the cancers with the highest incidences are lung and bronchus, prostate, colon and rectum, and urinary bladder. Lung cancer in particular accounts to about 26% of all cancer deaths (Scolyer et al., 2018).

However, breast, lung, colon and rectum, uterine corpus, and thyroid cancers have the highest prevalence in women. We can out rightly state that prostate and breast cancer are the most common cancers that frequently occur in males and females respectively (Scolyer et al., 2018; Robsahm et al., 2018; Anand et al.,2008). The cancers with the highest prevalence in children are leukemia and cancers associated to lymph nodes and brain (Amin et al., 2017; Tryggvadottir et al., 2010).

Prevention, prompt detection, and treatment are the vanguards in the fight against cancer (OECD, 2013). The mode and type of treatment depends on the type, location, stage, sensitivity of the cancer, and patient's body system. Surgery, immunotherapy, chemotherapy, radiotherapy, virotherapy, and hormonal therapy are the most frequently used ways of treating the disease (Bohle and Brandau, 2003). Immunotherapy is the process of stimulating, activating, and triggering the immune cells in order to fight malignant tumors. Whereas, radiotherapy refers to, applying high energy rays to stop or control the growth of malignant tumors (Kirschner and Panetta, 1998).

1.1 Urinary Bladder Cancer

The urinary bladder is a hollow membranous organ or sack in the lower abdomen of animals that is used to amass urine produced by the kidneys. The size and shape of the bladder when empty is that of a pear. The urine reaches the bladder via two tubes named as ureters. The bladder is lined with muscle tissue that is stretchable in order to hold the urine. Normally, it

has a capacity of about 400 to 600 milliliters. In the process of urination, the bladder usually squeezes through its muscles, forcing the valves to open and allow urine to exit out of the body via the urethra. In men, the urethra is usually around 8 inches; which is five times lengthier than in women (1.5 inches), since it passes through the penis (Picture of the bladder, 2014).

The growth of malignant tumors starting from the urinary bladder is referred to as bladder cancer. It is very common among men and women worldwide, with almost 400000 new incidences and approximately 150000 people dying as a result of the disease every year (Saad et al., 2017;Kapoor et al., 2008). In USA, there are 38000 males and 15000 females that are diagnosed annually (Svetlana et al., 2016). It was reported in 1997 that, 54500 new cases were detected and almost 12000 patients died from the disease. Ten years later, the number of newly diagnosed patients and deaths due to bladder cancer increased to 67160 and 13750 respectively (Pasin et al., 2008; Schenkman et al., 2004). The rate at which new cases of bladder cancer are occurring is on the rise. The US alone experienced an increase of 36% in the span of 34 years (viz. from 1956 to 1990). However, bladder cancer-death related cases decelerated to 8% between 1980 and 1995 (Kapoor et al., 2008).

Bladder cancer can be categorized into two different groups; that is invasive and superficial (non-muscle invasive). The latter represents almost 67% (two thirds) of all freshly diagnosed cases. It is also referred to as tumor confined to the mucosa of the bladder (Heney et al., 2008). It consists of CIS (carcinoma in situ), T1 (disease spreading into the sub mucosa), and superficial papillary disease (Ta). They have dissimilar reaction rates to therapy (intravesical), thus, they ought to be considered as distinct entities (Schenkman et al., 2004). Vast majority of these cases in the Western Hemisphere are of transitional cell type (TCC) also known as urothelial carcinoma (UC). UC is a type of bladder tumor that occurs most frequently. It accounts for 90% of the total diagnoses, followed by Squamous cell carcinoma with 5% and adenocarcinoma with 2% (Heney et al., 2008; Schenkman et al., 2004). Tobacco smoking is one of the most communal reasons of bladder cancer.

1.1.1 Bacillus Calmette-Guerin (BCG)

Intravesical Bacillus Calmette-Guerin (BCG) is referred to as living mitigated non-pathogenic strain of Mycobacterium bovis; primarily utilized as a vaccine for TB (tuberculosis).

Nevertheless, BCG is now adopted as a form of immunotherapy in treating superficial bladder cancer for the past 40 years (Friberg, 1993). Essentially, BCG has been labeled as "a new standard for superficial Bladder Cancer"(Lamm and Karger, 1992). It is basically applied after malignant tumor has been removed through local surgery to stop its reoccurrence and end decline of malignancy in recurrences. Nonetheless, its influence on survival is unclear. The instillation of BCG has shown to effectively treat superficial bladder cancer more than chemotherapy (Eric et al., 2012; Friberg, 1993).

A thin, hollow, and flexible tube known as catheter is used to transfer the BCG into the urinary bladder through the urethra. As a result, the BCG will create an inflammatory environment (inside the bladder) which provokes a prompt and effective anti-tumor response from the immune system (Moss and Kadmon, 1991). This is because the antigens of the BCG activate the CD4+ T cells and persuade a primary T helper type 1 immune response (Andius and Holmang, 2004). The major function of BCG is to stimulate and trigger the body defense mechanism (immune system) so that the immune cells can have the strength, resilience, and freedom to spread, discover, attack, and neutralize the cancer cells (Redelman-Sidi et al., 2014).

Ratliff and his co-workers suggested that BCG instillation needs “attachment, retention, and internalization of the bacteria”. This will later be followed by prompt immunological response that eventually leads to demolition of the cancer cells (Ratliff, 1989). This robust immune response is as a result of a monumental transitory secernment of cytokines in voided urine, consisting of interleukin-1 (IL-1) and its likes, interferon γ, TNF-α (tumor necrosis factorα), granulocyte-monocyte colony stimulating factor and interferon inducible protein 10 (Redelman-Sidi et al., 2014).

The results of BCG treatment of bladder cancer are quite encouraging. It can cause regression of residual disease, concisely stop progression from superficial to invasive cancer, and further lengthen the disease-free era. This was observed on a study involving thousands of patients. However, one of the studies shows that BCG instillation increases patients’ survival (Herr et al., 1988 and Friberg, 1993).

Some of the side-effects of BCG immunotherapy of bladder cancer are fever, cystitis, excessive pain while urination, dysuria, flu-like symptoms, fatigue, joint pain, and hematuria.

They are believed to be as a result of BCG toxicity to healthy cells (Lamm et al., 1980). Prolonged BCG instillation is expensive and harmful in some cases (Friberg, 1993).

1.2 Immune Checkpoints

Immune checkpoints are defined as negative controls of immune stimulation. Their roles in preserving autoimmunity, stopping body tissues from immune damage, and maintaining a procedure in the body that preserves the immune system functioning properly known as immune homeostasis is noted and important as well (Sharpe et al., 2007).

However, in cancer, they function as immune suppressors, in which their activation blocks or suppresses the prompt/promising anti-tumor immune reaction. Moreover, the cancer cells typically hijack checkpoints pathways to hide, resist, confine, and runaway from a massive anti-tumor immune attack (Postow et al., 2015). The immune checkpoint pathways hijacked by the tumors serves as a way of bypassing detection and resisting immune attack. As a result, the tumors develop and eventually metastasize to other organs of the body if left untreated (Postow et al., 2015). Therefore, the immune checkpoint blocks/prevent the immune system from launching a powerful anti-tumor response (Postow et al., 2015; Sharpe et al., 2007).

Some examples of immune checkpoints includes Cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), Programmed cell protein-1 (PD-1), Lymphocyte-activation gene 3 (LAG-3), T cell immunoglobulin mucin 3 (TIM-3),and Killer immunoglobulin-like receptors (KIRs) (Robert C et al., 2011).

1.3 Mathematical Model

A mathematical model is the representation or interpretation of systems and their dynamics, processes, or different aspects of real life problems using mathematical techniques, tools and/or set of equations. The phenomenon or process of achieving the aforementioned scenario is called mathematical modeling. Recently, mathematical modeling has played a key role in engineering, environment and industry, health sciences and so on. Its emergence in other fields is also on the rise and is now a distinctive tool for quantitative and qualitative analysis (Quarteroni et al., 2006).

Scientific computation is one of the key reasons that lead to successful transition of mathematical modeling, because it allows appropriate translation of a mathematical model into some algorithms which can be analyzed and solved by influential computers (Quarteroni and Formaggia, 2004). Meanwhile, numerical analysis is the major tool used in solving mathematical models in the field of engineering and applied sciences (Parolini and Quarteroni, 2005). The success rate motivates other new disciplines like biomedical engineering, financial engineering, health sciences, information and communication technology to start using mathematical modeling to solve problems, and explore their ideas and thoughts (Quarteroni et al., 2006).

Additionally, mathematical models propose new options to explain the increasing complex behavior of technology, which is the foundation of current industrial production (Quarteroni et al., 2006). They are important in simulation, investigation, analysis, and decision making; and hence, their role to technological progress is obvious. Moreover, mathematical models can suggest novel answers and solutions in a very short period of time, therefore allowing the increase of swiftness in innovation cycles (Parolini and Quarteroni, 2005).This guarantees a possible benefit to production industries and health sciences because they can save money and time in authentication and development phases (Quarteroni and Formaggia, 2004).

Mathematical modeling is usually used to explain the dynamics and spread of numerous infections. Moreover, it can also be used to elucidate the outcome of a treatment and explore complex biological processes. These models are commonly compartmental models that are represented using systems of ordinary and/or partial differential equations. Studying mathematical models is of great importance because they gave an insight and crucial understanding of the essential features of the spread of transmitted diseases, growth and mechanism of other diseases, and appraise the probable effect of control strategies in reducing persistence, sickness and mortality (Hethcote, 1994).

We can thus out rightly state that, scientific computation and mathematical modeling are progressively and determinedly expanding in life sciences, environment, applied sciences, industry, sports and so on (Detomi, et al., 2008; Parolini and Quarteroni, 2005).

1.3.1 Mathematical Biology (Biomathematics)

Mathematical biology or biomathematics is a branch of mathematical modeling that deals with the mathematical and computational studies of real life problems in biological systems and health sciences (EPSRC, 2015). The history of the application of mathematical models in medicine and biology is long and broad. In 1202, Leonardo of Pisa was one of the first scientists to propose a mathematical model in his math book titled *Liber abbaci*. It was an exercise related to the reproduction of rabbits. A question was raised on the pattern and number of rabbits likely to be reproduced at the end of each reproductive period when a pair of male and female immature rabbits is selected at the start of a breeding period. The answer leads to the famous series known as Fibonacci series - every number is the summation of the preceding two. In the seventeenth century, he was later named from Leonardo of Pisa to Fibonacci (Murray, 2012).

Daniel Bernoulli suggested the first thoughtful mathematical model with a differential equation to measure the consequence of cow-pox vaccination on the spread of smallpox. His paper gave certain fascinating records on the death of children and it is further used to evaluate the useful benefits of a vaccination control program (Bernoulli, 1760; Murray, 2012).

Lotka and Volterra model the interaction of a prey and its predator for two populations popularly now known as Lotka-Volterra model (Lotka, 1925; Volterra, 1926). Kermack and McKendrick formulated the famous susceptible, infected, and recovery (SIR) mathematical model that studies the number of infected individuals with an infectious disease in a completely susceptible and closed population over time (Kermack and McKendrick, 1932). The mathematical model on genetics and natural selection was given by Fisher (Fisher, 1930), while Fisher and Kolmogoroff introduced diffusion into their models for some biological phenomena (Kolmogoroff et al., 1937; Fisher, 1937).

Biomathematics started to develop in the 1950s where the work of Hodgkin and Huxley on nerve transmission and excitation won them a standard Nobel Prize (Murray, 2012; Hodgkin and Huxley, 1952). There were prompt rise of interest in the area between 1960s and 1970s particularly in reaction-diffusion models - which Turing, Nicolis, Gierer and Meinhardt published their papers on (Murray, 2012). The models on enzyme kinetics built on oxygen diffusion into pea nodules and effect of hemoglobin and myoglobin in aiding oxygen in

various physiological conditions were developed in (Murray, 1968; Murray, 1971; Murray, 1974; Murray and Wyman, 1971).

In the 1980s, it was extensively becoming further familiar that any factual contribution to biological sciences from mathematical modeling needs to genuinely be interdisciplinary and therefore interrelated to actual biology (Murray, 2012).This implies that, an outstanding and best research was/is a mathematical model(s) proposed for particular biological phenomena and by which its forecasts were established, or else, by experiment and, essentially, aid our clear understanding of the real biological problems (Murray, 2012). As of now, there are countless of such models and many more are expected to follow in the future as J.D. Murray says "Mathematical biology is a fast-growing, well-recognized, albeit not clearly defined subject and is, to my mind, the most exciting modern application of mathematics" (Murray, 2002).

1.3.2 Deterministic Models

Deterministic models are the type of models that snub random deviation, and thus continuously forecast similar result from specified starting points- which are fixed. They have no parameters that are described by probability distributions i.e. none of the constituents are characteristically uncertain. In other words, the output of a deterministic model is completely determined by parameter values and initial conditions.

1.3.3 Stochastic Models

Stochastic models are just an improvement of deterministic models. They have some essential randomness and uncertainty. Therefore, same parameter values and initial conditions will lead to a group of different and dissimilar outputs. Moreover, the set of parameters are described by probability distributions.

1.4 Properties of a Mathematical Model

For any mathematical model to be meaningful and robust, it has to be well-posed. A mathematical model is said to be well-posed if it has the following properties:

1. Existence of solutions

2. Uniqueness of solutions

3. Stability of solutions

1.4.1 Existence and Uniqueness

Given the following initial value problem (IVP):

$$y' = f(t, y), \qquad y(t_0) = y_0 \tag{1.1}$$

where f is continouous in a closed and bounded domain and t_0, y_0 are fixed constants.

Our aim here is to check whether or not the solution of the IVP exists, if it exists is it unique? To address the above question we state the following theorems.

Theorem 1.1. (Cauchy-Peano local existence theorem). Assume that the function f in (1.1) is continouous and bounded in some region $\mathfrak{B} = \{(t, y): |t - t_0| \leq a, |y - y_0| \leq b\}$ with $a, b > 0$. Then the IVP (1.1) has at least one solution $y = y(t)$ defined on the interval $|t - t_0| \leq \delta$, where $\delta = min\left\{a, \frac{b}{R}\right\}$ and R is an upper bound for f which is positive.

Proof. (Coddington and Levinson, 1955)

Theorem 1.2. (Picard-Lindelof uniqueness theorem). Presume that $f$isa continouous and bounded function in $\mathfrak{B}$ (defined in Theorem 1.1). In addition, let the function$f$be Lipschitz continuous in the second variable, that is to say, $|f(t, y_1) - f(t, y_2)| \leq F|y_1 - y_2| \ \forall (t, y_k) \in \mathfrak{B}$, with a Lipschitz constant F. Then, the IVP (1.1) possess a unique solution $y = y(t)$defined on the interval $|t - t_0| \leq \delta$, where $\delta = min\left\{a, \frac{b}{R}\right\}$ and R is an upper bound for f which is positive.

Proof. (Coddington and Levinson, 1955)

1.4.2 Stability

The characteristic that a minor alteration in the initial point t_0 of a solution has merely a minor influence on the behavior of the solution as $t \to \infty$ is referred to as stability of the solution. Suppose $y = y(t)$ and $\tilde{y} = \tilde{y}(t)$ are solutions to the IVP (1.1) with initial conditions

$y(t_0) = y_0$ and $\tilde{y}(t_0) = \tilde{y}_0$. Then, $\tilde{y} = \tilde{y}(t)$ is said to be stable if, given any $\varepsilon > 0$, $\exists$ a $\delta > 0$ such that if $|y_0 - \tilde{y}_0| < \delta$, then $|y(t) - \tilde{y}(t)| < \varepsilon \forall\ t > t_0$.

Moreover, the solution $\tilde{y} = \tilde{y}(t)$ is said to be asymptotically stable if it is stable and $\exists$ a $\delta_0 > 0$ (fixed) such that if $|y_0 - \tilde{y}_0| < \delta_0$, then $\lim_{\to\infty}\big(y(t) - \tilde{y}(t)\big) = 0$.

We will need stability of every given solution to which we attribute biological meaning, viz.when a slight disruption could brought a huge alteration in the solution, then it is irrationally and unreasonably appropriate to regard the solution significant and meaningful (Brauer and Castillo-Chavez, 2011).

In analyzing a biological model, we need an equilibrium solution, because the system is difficult to analyze while in motion, therefore equilibrium solutions are needed to study the stability of solutions.

Consider the following autonomous differential equation,

$$y' = f(y) \qquad (1.2)$$

An equilibrium point of the autonomous differential equation (1.2) is a point y^* such that $f(y^*) = 0$. In other words, it represents a constant solution $y(t) = y^*$ of (1.2).

The concept of linearization is a process that describes the manner of solutions close to equilibrium. To establish it, we make the following assumptions and change of variables:

Suppose y^* is equilibrium of (1.2), and then let $z(t) = y(t) - y^*$; which describes the solution deviating from the equilibrium point. Now, differentiating, substituting (in (1.2)), and applying Taylor's theorem yields $z'(t) = f(y^*) + f'(y^*)z(t) + \frac{1}{2!}f'(a)\big(z(t)\big)^2$, where $a \in (y^*, y^* + u(t))$. Since y^* is an equilibrium point, then $f(y^*) = 0$.

Therefore, $z'(t) = f'(y^*)z(t) + w(z)$, where $w(z) = \frac{1}{2!}f'(a)z^2$. Hence, the linearization of the autonomous differential equation (1.2) at the equilibrium y^* is obtained by ignoring the higher-order term w, and it is given by the linear homogenous differential equation;

$$x' = f'(y^*)x. \qquad (1.3)$$

The main aim of the linearization is that, the behavior of its solutions is simple and friendly to examine, thus, this manner and behavior also defines the behavior of solutions of the given original autonomous differential equation (1.2) close to the equilibrium. Moreover, the linearization can be used to derive asymptotic stability- which is what is usually needed or preferred in dealing with biological models rather than just stability. This is due to the fact thatan asymptotically stable equilibrium is not bothered significantly by a perturbation of the differential equation. Again stability cannot be obtained from the linearization (Brauer and Castillo-Chavez, 2011).

Theorem 1.3. When all solutions of the linearization (1.3) at an equilibrium y^*approaches zero as t tends to $+\infty$, then all solutions of (1.2) with $y(t_0)$sufficiently neary^*tends tothe equilibrium y^*as $t$approaches ∞.

Proof.(Brauer and Castillo-Chavez, 2011).

From theorem 1.3, it follows that all solutions of the linearization approaches zero if $f'(y^*) < 0$. Therefore, the equilibrium point y^* is asymptotically stable when $f'(y^*) < 0$, and unstable when $f'(y^*) > 0$.

However, majority of the real life circumstances and biological models involve at least two species. Therefore, we are going to briefly give a general framework for a finite multispecies interaction.

Suppose y_i, $i = 1, 2, 3, \dots m$, are distinct sizes (of a population) of m interrelating species. Assume also that, at any given time, every population's growth rate is dependent on the different sizes of the population at that time. Thus, the model is given by a system of m first order autonomous differential equations

$$\begin{aligned} \dot{y}_1 &= f_1(y_1, y_2, y_3, \dots, y_m), \\ \dot{y}_2 &= f_2(y_1, y_2, y_3, \dots, y_m), \\ &\vdots \\ \dot{y}_m &= f_m(y_1, y_2, y_3, \dots, y_m), \end{aligned} \qquad (1.4)$$

where f_i, $i = 1,2,3,\dots m$, are continuously differentiable functions. The equilibrium points of system (1.4) are points $y_1^*, y_2^*, y_3^*, \dots, y_m^*$ such that

$$\begin{aligned} &f_1(y_1^*, y_2^*, y_3^*, \dots, y_m^*) = 0, \\ &f_2(y_1^*, y_2^*, y_3^*, \dots, y_m^*) = 0, \\ &\vdots \\ &f_m(y_1^*, y_2^*, y_3^*, \dots, y_m^*) = 0. \end{aligned} \tag{1.5}$$

The linearization of (1.4) around the equilibrium $y_1^*, y_2^*, y_3^*, \dots, y_m^*$ is given by the linear system of differential equations

$$\dot{z}_1 = \frac{\partial f_1}{\partial y_1}(y_1^*, y_2^*, \dots, y_m^*)z_1 + \cdots + \frac{\partial f_1}{\partial y_m}(y_1^*, y_2^*, \dots, y_m^*)z_m,$$

$$\dot{z}_2 = \frac{\partial f_2}{\partial y_1}(y_1^*, y_2^*, \dots, y_m^*)z_1 + \cdots + \frac{\partial f_2}{\partial y_m}(y_1^*, y_2^*, \dots, y_m^*)z_m,$$

$$\vdots$$

$$\dot{z}_m = \frac{\partial f_m}{\partial y_1}(y_1^*, y_2^*, \dots, y_m^*)z_1 + \cdots + \frac{\partial f_m}{\partial y_m}(y_1^*, y_2^*, \dots, y_m^*)z_m,$$

which can be written in a vector form as $Z' = AZ$,where $A = \left(\frac{\partial f_i}{\partial y_k}(y_1^*, y_2^*, \dots, y_m^*)\right)$ is referred to as the community matrix of (1.4) at the given equilibrium $Y = (y_1^*, y_2^*, \dots, y_m^*)$ (Brauer and Castillo-Chavez, 2011).

Theorem 1.4. Suppose that all eigenvalues of the community matrix of system (1.4) at equilibrium Y possess negative real part. Then, the equilibrium Y is asymptotically stable.

Proof. (Brauer and Castillo-Chavez, 2011).

From theorem 1.4, we can deduce that, if all the eigenvalues of the community matrix of (1.4) at the equilibrium Y possess negative real part, then all solutions of the linearization at this equilibrium approaches zero as t tends to ∞. Thus, the equilibrium Y is asymptotically stable.

For two species, the eigenvalues of the community matrix Ahave negative real part if we know the sign of trace and determinant of$A$. That is to say if$tr(A) > 0 \ \ and \ \det(A) < 0$.

A general criterion used in implicitly determining the sign (negative real parts or otherwise) of the eigenvalues from a given characteristic equation is known as the Routh–Hurwitz criterion. Suppose the characteristic equation for m dimension is given by

$$\lambda^m + b_1\lambda^{m-1} + b_2\lambda^{m-2} + b_3\lambda^{m-3} + \cdots + b_{m-2}\lambda^2 + b_{m-1}\lambda + b_m = 0.$$

Now, applying the Routh–Hurwitz criterion when $m = 2$, the roots of the characteristic equation have negative real part if $b_1 > 0$ and $b_2 > 0$, and this is equivalent to the trace of A to be positive and determinant of A to be negative.When $m = 3$, the Routh–Hurwitz condition is, $b_3 > 0, \ b_1 > 0, \ and \ b_1 b_2 > b_3$.

However, if $m = 4$, then the condition is, $b_4 > 0, \ b_2 > 0, \ \ b_1 > 0, \ and \ \ b_3(b_1 b_2 - b_3) > {b_1}^2 b_4$.

Note that the number of conditions depends on the degree of the polynomial equation.

Hence, to establish the asymptotic stability of equilibrium, it suffices to obtain the community matrix by the concept of linearization about the given equilibrium, and then apply the Routh–Hurwitz criterion or otherwise to check whether the sign of the real part of all the eigenvalues of the community matrix. If all the eigenvalues have negative real part then the equilibrium is asymptotically stable, else unstable.

1.5 Mathematical Oncology

The application of mathematical modeling in studying the growth, evolution, dynamics and treatment of cancer is called mathematical oncology. The problem is first understood by the applied mathematicians, and later formulates the mathematical models in partnership with clinicians (in particular oncologist) and/or biologist. Thus, this makes the field of study actually interdisciplinary. The aim here is to use the joint knowledge to increase and develop the recent treatment options that will benefit the cancer patients (Stadtländer, 2016).

Chauviere et al. (2010) and Stadtländer (2016) published review articles on mathematical modeling of cancer approaches. The review was based on forecasting tumor evolution and

mass, drug supply focusing on measuring the diffusion blockade so that unfortunate reactions to chemotherapy should be understood, and multi scale cancer modeling- which is believed to be important clinically for surgery, imaging, radiotherapy, and chemotherapy. Several mathematical models that study the dynamics and growth of cancer have been established (Basanta and Anderson, 2017; Maley et al., 2017; Egeblad et al., 2010).

1.5.1 Mathematical Models of Cancer Growth

A mathematical model of tumor growth is a mathematical expression of how the tumor size depends on time. The models are based on some principle that states that the rate of change of tumor size with respect to time is given by the difference between growth rate and the rate of degeneration. That is to say, if y is the tumor size, then the general form is given by $\dot{y} = yG(y)$, where $G(\cdot)$ models the net proliferation of the tumor viz. the difference between its growth rate and its rate of degeneration. It is tough to deduce the growth and degeneration rates in general using experimental data; hence, we use net-proliferation rate instead (Schattler and Ledzewicz, 2015). Some of the mathematical models of cancer growth are:

i) Exponential Growth

Provided environmental factors and conditions are unchanged over a small period of time, it is usually sensible and rational to make the assumption that both the growth and degradation rates are constant (Schattler and Ledzewicz, 2015). Thus, the tumor growth then becomes exponential which can simply be written as follows

$$\dot{y} = ry, \tag{1.6}$$

where r is a growth factor (Wheldon, 1988). Assuming $y(t_0) = y_0$, that is the initial size of the tumor is given at $t = t_0$, then the tumor evolution is $y(t) = y_0 e^{rt}$, with r associated to tumor replication time T^* defined by; $r = \frac{\ln 2}{T^*}$.

It is usually amongst the most common models used in describing tumor evolution (Wheldon, 1988; Schattler and Ledzewicz, 2015). However, it is mostly applicable at the early stages of the cancer where the growth is rampant (somewhat exponential). The exponential growth does not adequately describe evolution of the tumor for a long time period, because the proliferation rate $G(y)$ decreases (decreasing function) over time with the growth of the tumor (Wheldon,

1988). This is due to the fact that, the nutrients and oxygen accessible are limited, the struggle for resources and spaces also increases. Thus, the growth rate decreases and the degeneration rate increases (Schattler and Ledzewicz, 2015).

As the tumor increase in size, the exponential growth needs to be replaced or adjusted with other growth models like the logistic or Gompertz model (Schattler and Ledzewicz, 2015).

ii) Gompertz Growth Model

This model is one of the most frequently used models to describe cancer growth at its advanced phases (Wheldon, 1988). It has a record of supporting experimental data for breast cancer (Schattler and Ledzewicz, 2015; Norton and Simon, 1977; Norton, 1988). The model was developed by Benjamin Gompertz in 1825. The net proliferation rate $G(y)$ is given by

$$G(y) = a - b\ln y, \text{ where } a > b > 0. \tag{1.7}$$

The parameters a and b represents growth and death rates respectively (Norton, 1988). Therefore, the Gompertz model with a normalized initial condition is given by

$$\dot{y} = y(a - b\ln y), \quad y(0) = 1.$$

To solve the above differential equation, we make the following change of variable $x = \ln y$, then, $\dot{x} = a - bx, \quad x(0) = 0$. Then, $x(t) = \frac{a}{b}(1 - e^{-bt})$. Hence, the evolution of the tumor is given by, $y(t) = exp\left(\frac{a}{b}(1 - e^{-bt})\right)$.

iii) Logistic and Generalized Logistic Growth Model

The generalized logistic growth model's net proliferation $G(y)$ is as follows:

$$G(y) = r\left(1 - \left(\frac{y}{k}\right)^{\beta}\right), \quad r > 0, \ \beta > 0.$$

The model is established on struggle amongst systems related with growth and degeneration. The resulting differential equation for the tumor size becomes,

$$\dot{y} = ry\left(1 - \left(\frac{y}{k}\right)^{\beta}\right), \quad y(t_0) = y_0, \tag{1.8}$$

where k here is the carrying capacity of the tumor. The tumor carrying capacity refers to maximum tumor volume the surroundings can withstand indeterminately. However, in 1838, Verhulst developed the classical so-called logistic growth model ($\beta = 1$). His work was based on the description of a self-limiting biotic population. He assumed that the reproduction rate is directly proportional to the quantity of accessible resources and current population (Schattler and Ledzewicz, 2015). The logistic model is given by

$$\dot{y} = ry\left(1 - \frac{y}{k}\right), \quad y(t_0) = y_0, \tag{1.9}$$

Later in the 1930s Richards gave the generalized version in (1.8). The advantage of the generalized version is, it is applicable to both sluggishly and fast developing tumors, and can distinguish between them. The speed of the growth of the tumor is dependent on β value. The greater the βvalue, the more rigorous and faster the tumor develops and approaches the exponential growth as β tends to ∞ (Schattler and Ledzewicz, 2015). The evolution of the tumor is obtained by solving the Bernoulli differential equation in (1.8), and the solution is given by

$$y(t) = y_0\left(\left(\frac{y_0}{k}\right)^{\beta} + exp(-\beta rt)\left(1 - \left(\frac{y_0}{k}\right)^{\beta}\right)\right)^{-\frac{1}{\beta}}.$$

1.6 Optimal Control Theory

Optimal control theory objectively deals with finding control signals that will maximize (or minimize) a given performance index or criterion and at the same time causing the process to fulfill some physical constraints (Kirk, 2004).In other words, it is a way of deriving control function(s) and state trajectories over time-period for a dynamical system, in order to maximize (or minimize) a performance criterion (Bryson, 1996; Kirk, 2004). It is originated and an extension of the calculus of variation (CV) (Bryson, 1996).

The earliest and most important scientist that leads to the discovery and development of optimal control and theory of calculus of variation comprises of Pierre dc Fermat (1601-1665), Isaac Newton (1642-1727), Johann Bernoulli (1667-1748), Leonhard Euler (1707-1793), Ludovico Lagrange (1736-1813), Andrien Legendre (1752-1833), Carl Jacobi (1804-1851),

William Hamilton (1805-1865), Karl Weierstrass (1815-1897), Adolph Mayer (1839-1907), and Oskar Bolza (1857-1942)(Bryson, 1996).

In particular, Fermat initiated calculus of variation in 1662 through a principle – for a minimum amount of time, light travels via a sequence of optical media. Galileo's "brachistochrone" and "heavy chain" problems postured in 1638 were later solved in the mid-1600 by calculus of variation. CV was also used by Isaac Newton to determine the minimum drag nose shape of a projectile (Bryson, 1996). In 1967, Benoulli adopted Fermat's concepts to establish the solution of a discrete-step type of the brachistochrone problem. The continuous version was later solved in 1699 by Leibniz, L'Hospital, and Newton after they were challenged by Bernoulli (Goldstine, 1980; Bryson, 1996). The CV was further developed in the 17^{th} century by Newton, Bernoulli, Fermat, and Leibniz. Euler/Lagrange and Legndre/Jacobi/Hamilton/Weistrass further enhanced the evolution of CV in the 18^{th} and 19^{th} century, respectively.

The generality of the CV to optimal control theory was established enormously in the 1950s and 1960s. Some of the significant landmarks were accomplished by Lev Pontryagin (1908-1988) and his associates (coworkers) - V. G. Boltyanskii, R. V. Gamkrelidz and E. F. Misshchenko in establishing the maximum principle (Pontryagin's maximum principle), Richard Bellman (1920-1984) for invention of dynamic programming, and Rudolf Kalman (1930-2016) credited for the development of Kalman filter and construction of the linear quadratic regulator (Pontryagin, 1962; Bryson, 1996).

The emergence of the Pontryagin's maximum principle defines a new era in optimal control theory because; it provides mathematicians with appropriate conditions in optimization problems consisting of differential equations as their constraints and paves way for extensive research in the area (Pontryagin, 1962). Solving optimization problems comprising of constraints on the derivatives of functions by CV is problematic, thus, optimal control is applied to obtain the solutions (Leitmann, 1997).

Optimal control theory is extensively applied in various fields of study, which includes economics and management, finance, biology and health sciences, aerospace and aeronautics,

biomedical engineering, control theory, robotics and so on. The emergence of fast and high resolution computers helps in applying optimal control methods to solve difficult and complicated problems (Bryson, 1996). Various approaches exist in the formulation of optimal control problems where the principal process can be expressed by PDE (partial differential equations), SDE (stochastic differential equations), ODE (ordinary differential equations), and difference equations and so on. However, this thesis is devoted to studying optimal control theory with ODE.

1.6.1 Optimal Control Problem (OCP)

The setting of an OCP involves:

1. Explaining the process to control (Mathematical model).

2. Declaring physical constraints.

3. Describing some performance index or criterion.

Given the following ordinary differential equation,

$$\begin{cases} \dot{\boldsymbol{y}}(t) = \boldsymbol{f}(t, \boldsymbol{y}(t)) \\ \quad \boldsymbol{y}(t_0) = \boldsymbol{y_0} \end{cases}, \quad t > 0, \tag{1.10}$$

where $\boldsymbol{f} : \mathbb{R}^n \to \mathbb{R}^n$, $\boldsymbol{y} : \mathbb{R}_+ \to \mathbb{R}^n$ to be continuous and piecewise differentiable, and the initial condition $\boldsymbol{y_0} \in \mathbb{R}^n$. System (1.10) gives the mathematical model, which can also be taken as dynamical development of state for some process - "state system". Now, we introduce a new function to make some generalization by assuming that $\boldsymbol{f}$ further depends on some "control" parameters from a set, say, $B \subset \mathbb{R}^m$. Thus, we define $\boldsymbol{f} : \mathbb{R}^n \times B \to \mathbb{R}^n$. Let $\boldsymbol{u} \in B$ such that $\boldsymbol{u} : \mathbb{R}_+ \to B$ is defined as

$$\boldsymbol{u}(t) = \begin{cases} u_1, & t_0 \le t \le t_1 \\ u_2, & t_1 < t \le t_2 \\ u_2, & t_2 < t \le t_3 \\ & \cdot \\ & \cdot \\ & \cdot \\ u_m, & t_{n-1} < t \le t_n \end{cases}$$

where $t_0 < t_1 < t_2 < \cdots < t_n$, and $u_1, u_2, \ldots, u_m \in B$. In general, the function $\boldsymbol{u}$ is called a control and analogous to every control we consider (1.11) - usually referred to as the

"controlled system", and the solution $\boldsymbol{y}(t)$ (trajectory; which is dependent on the control and initial condition) as the resultant response to the system.

$$\begin{cases} \dot{\boldsymbol{y}} = \boldsymbol{f}(t, \boldsymbol{y}(t), \boldsymbol{u}(t)) \\ \quad \boldsymbol{y}(t_0) = \boldsymbol{y_0} \end{cases}, \qquad t > 0 \tag{1.11}$$

It is important to note that $\boldsymbol{y}$, $\boldsymbol{f}$,and$\boldsymbol{u}$can be written as follows:

$$\boldsymbol{y}(t) = \begin{bmatrix} y_1(t) \\ y_2(t) \\ . \\ . \\ . \\ y_n(t) \end{bmatrix}, \boldsymbol{u}(t) = \begin{bmatrix} u_1(t) \\ u_2(t) \\ . \\ . \\ . \\ u_m(t) \end{bmatrix}, \text{ and}$$

$$\boldsymbol{f}(t, \boldsymbol{y}(t), \boldsymbol{u}(t)) = \begin{bmatrix} f_1\big(y_1(t), \dots, y_n(t), u_1(t), \dots u_m(t)\big) \\ f_2\big(y_1(t), \dots, y_n(t), u_1(t), \dots u_m(t)\big) \\ . \\ . \\ . \\ f_n\big(y_1(t), \dots, y_n(t), u_1(t), \dots u_m(t)\big) \end{bmatrix}.$$

Define a set $U = \{\boldsymbol{u} : \mathbb{R}_+ \to B, such\ that\ u\ is\ piecewise\ continuous\}$ representing the pool or collection of all admissible controls, with $\boldsymbol{u}(t) = \begin{bmatrix} u_1(t) \\ u_2(t) \\ . \\ . \\ . \\ u_m(t) \end{bmatrix}$.

The class of admissible controls cannot be considered to consist of continuous functions because of the jumps expected from the control. Thus, they are considered to be piecewise continuous functions.

A piecewise continuous function $\boldsymbol{u}$, defined on some time interval, say $t_0 \leq t \leq t_f$, with range in the control region U, $\boldsymbol{u} \in U$, for all $t \in [t_0, t_f]$, is said to be an admissible control. Since, they are piecewise continuous, thus, controls $\boldsymbol{u} = \boldsymbol{u}(t)$are continuous for all t under consideration, with the exception of only a finite number of t, at which $\boldsymbol{u}(t)$may have discontinuities of the first kind. We can observe that every admissible control is bounded.

A usual control problem needs a performance criterion/index or objective function to be maximized (or minimized) as mentioned earlier. The objective function J is generally defined as

$$J[\boldsymbol{y}(t), \boldsymbol{u}(t)] = \vartheta\left(\boldsymbol{y}(t_f)\right) + \int_{t_0}^{t_f} g\big(\boldsymbol{y}(t), \boldsymbol{u}(t)\big)dt, \qquad (1.12)$$

where $\boldsymbol{y}$ solves (1.11) for the control $\boldsymbol{u}$**.** The functions $g: \mathbb{R}^n \times B \to \mathbb{R}$ and $\vartheta: \mathbb{R}^n \to \mathbb{R}$ are continuously differentiable, denoting running and terminal payoffs, respectively. The functions g and ϑ will be given as well as the final time, t_f, and g is generally referred to as the *Lagrangian, L*.

Our overall goal is to determine a control u^* that maximize (or minimize) the performance criterion (objective function) subject to (1.11). That is to say, we determine u^* such that

$$J(u^*) \geq J(u), \qquad (1.13)$$

for all controls $u \in U$. Such a control $u^*(t)$ if found is referred to as *optimal.* In a nutshell, we aim to find an optimal control that will maximize or (minimize) a given performance index subject to the state system describing the process.

There are three main formulations of an optimal control problem, that is, Bolza, Lagrange, and Mayer formulations. The Bolza formulation of an optimal control is given by

$$\begin{aligned} \max_{\boldsymbol{u}\in\boldsymbol{U}} \quad & J[\boldsymbol{y}(t), \boldsymbol{u}(t)] = \vartheta\left(t_f, \boldsymbol{y}(t_f)\right) + \int_{t_0}^{t_f} g\big(t, \boldsymbol{y}(t), \boldsymbol{u}(t)\big)dt \\ \textbf{subject to} \quad & \dot{\boldsymbol{y}}(t) = \boldsymbol{f}\big(t, \boldsymbol{y}(t), \boldsymbol{u}(t)\big) \qquad (1.14) \\ & \boldsymbol{y}(t_0) = \boldsymbol{y}_0, \end{aligned}$$

where the value of $\boldsymbol{y}$at the final time, $\boldsymbol{y}(t_f)$,can be fixed or free.

However, the Lagrange formulation can be obtained from Bolza (1.14) as follows:

$$\begin{aligned} \max_{\boldsymbol{u}\in\boldsymbol{U}} \quad & J[\boldsymbol{y}(t), \boldsymbol{u}(t)] = \int_{t_0}^{t_f} g\big(t, \boldsymbol{y}(t), \boldsymbol{u}(t)\big)dt \\ \textbf{subject to} \quad & \dot{\boldsymbol{y}}(t) = \boldsymbol{f}\big(t, \boldsymbol{y}(t), \boldsymbol{u}(t)\big) \qquad (1.15) \end{aligned}$$

$$\boldsymbol{y}(t_0) = \boldsymbol{y}_0.$$

Moreover, we can get the Mayer formulation from Bolza as well. It is given by:

$$\begin{aligned} \max_{\boldsymbol{u}\in\boldsymbol{U}} \quad & J[y(t), u(t)] = \vartheta\left(t_f, \boldsymbol{y}(t_f)\right) \\ \textbf{subject to} \quad & \dot{\boldsymbol{y}}(t) = \boldsymbol{f}\left(t, \boldsymbol{y}(t), \boldsymbol{u}(t)\right) \\ & \boldsymbol{y}(t_0) = \boldsymbol{y}_0. \end{aligned} \tag{1.16}$$

Theorem 1.5. Bolza, Lagrange, and Mayer formulations are equivalent.

Proof. (Fleming and Rishel, 1975)

Some natural and obvious questions to ask are as follows:

i. Do the optimal controls exist?

ii. In what way could we characterize the controls mathematically?

iii. How can we construct an optimal control?

1.6.2 Existence of Optimal Control

Before attempting to solve and find an optimal control, we need to ensure that the solution exists, that is to say, in particular the optimal control exist.

Theorem 1.6. Given the objective functional in (1.13), where the set of controls are Lebesgue integrable functions on $t_0 \le t \le t_f$ in the set of real numbers. Assume there exists some constants C_1, C_2, > 0 such that;

1. The class of all initial conditions with a control u, $(\boldsymbol{y}_0, \boldsymbol{u})$, in the admissible control set along with each state equation being satisfied is nonempty.

2. $|\boldsymbol{f}(t, \boldsymbol{y}, \boldsymbol{u})| \le C_1(1 + |\boldsymbol{y}| + |\boldsymbol{u}|)$.

3. $|\boldsymbol{f}(t, \boldsymbol{y^1}, \boldsymbol{u}) - \boldsymbol{f}(t, \boldsymbol{y}, \boldsymbol{u})| \le C_2\left|\boldsymbol{y^1} - \boldsymbol{y}\right|(1 + |\boldsymbol{u}|)$.

4. U is closed and convex, $\boldsymbol{f}(t, \boldsymbol{y}, \boldsymbol{u}) = \alpha(t, \boldsymbol{y}) + \beta(t, \boldsymbol{y})\boldsymbol{u}$, and $g\left(t, \boldsymbol{y}(t), \boldsymbol{u}(t)\right)$ is convex on U.

5. $g\left(t, \boldsymbol{y}(t), \boldsymbol{u}(t)\right) \ge C_3|\boldsymbol{u}|^{\beta} - C_4$, $C_3 > 0$ and $\beta > 1$.

Then, there exist $(\boldsymbol{y}_0{}^*, \boldsymbol{u}^*)$ that minimize $J(\boldsymbol{y}_0, \boldsymbol{u})$.

Proof. (Fleming and Rishel, 1975).

Theorem 1.6 guarantees the existence of an optimal that will minimize (or maximize) the objective function of a control problem subject to its physical constraints.

1.6.3 Hamiltonian Function

The function $H: \mathbb{R} \times \mathbb{R}^n \times \mathbb{R}^n \times U \to \mathbb{R}^n$ defined by

$$H(t, \boldsymbol{y}(t), \boldsymbol{\lambda}(t), \boldsymbol{u}(t)) = g(t, \boldsymbol{y}(t), \boldsymbol{u}(t)) + \boldsymbol{\lambda} \boldsymbol{f}\big(t, \boldsymbol{y}(t), \boldsymbol{u}(t)\big), \qquad (1.17)$$

is referred to as Hamiltonian function, where $\boldsymbol{\lambda}$(to be explained later) is the adjoint variable.

1.6.4 Pontryagin's Principle

The essence of the Pontryagin's principle also known as Maximum principle is to establish the optimality conditions and characterization of OCP. That is to say, to give the fundamental necessary conditions for a controlled trajectory to be optimal (Schattler and Ledzewicz, 2012). L.S Pontryagin and his colleagues developed this principle around 1955 in the Soviet Union.

The necessary conditions are obtained using the principle by reducing the problem to a two-point BVP (boundary value problem) for a set of differential equations together with a maximization (or minimization) side condition. The solutions or computations of the BVP give the characterization of the optimal control (Fleming and Rishel, 1975).

Nevertheless, the solution of the two point boundary value problem might be complicated in difficult examples. Thus, numerical methods like shooting, multiple shooting, and forward-backward sweep methods are employed to compute the numerical solution of the optimization problem (Fleming and Rishel, 1975).

Theorem 1.7. (Pontryagin's maximum principle). Given the objective function J and suppose $\boldsymbol{u}^*$ is optimal for (1.13), and $\boldsymbol{y}^*$ is the resultant state solution. Then, there exists a function $\boldsymbol{\lambda}: \big[t_0, t_f\big] \to \mathbb{R}^n$ such that

$$H(t, \boldsymbol{y}(t)^*, \boldsymbol{\lambda}(t), \boldsymbol{u}(t)) \leq H(t, \boldsymbol{y}(t)^*, \boldsymbol{\lambda}(t), \boldsymbol{u}(t)^*), \qquad (1.18)$$

for all control $\boldsymbol{u} \in U$ and $t \in \big[t_0, t_f\big]$,

$$\dot{\boldsymbol{y}}^*(t) = \frac{\partial H(t, \boldsymbol{y}(t)^*, \boldsymbol{\lambda}(t), \boldsymbol{u}(t)^*)}{\partial \boldsymbol{\lambda}}, \qquad (1.19)$$

$$\dot{\boldsymbol{\lambda}}(t) = -\frac{\partial H(t,\boldsymbol{y}(t)^*,\boldsymbol{\lambda}(t),\boldsymbol{u}(t)^*)}{\partial \boldsymbol{y}}, \tag{1.20}$$

and lastly, $$\boldsymbol{\lambda}(t_f) = 0. \tag{1.21}$$

Proof. (Fleming and Rishel, 1975).

From Theorem 1.7, (1.20) is referred to as the adjoint equations, and the transversality condition is given by (1.21); which can be used only when y_f is free. The maximization principle is specified in (1.18). Furthermore, the theorem reduces the optimal control problem to maximizing the Hamiltonian function. As a result, we find the critical point of the Hamiltonian using what is known as the optimality condition, that is to say,

$$\frac{\partial H(t,\boldsymbol{y}(t)^*,\boldsymbol{\lambda}(t),\boldsymbol{u}(t)^*)}{\partial \boldsymbol{u}} = 0. \tag{1.22}$$

Therefore, we do not have to evaluate the integral in the objective function to determine the necessary conditions for optimality; instead we use Hamiltonian only to achieve that.

The version of the Pontryagin's principle for Bolza formulation is given by the following corollary.

Corollary 1.1. Suppose $\boldsymbol{y}^*$and $\boldsymbol{u}^*$are optimal for (1.14), Then, there exists a function $\boldsymbol{\lambda}: [t_0, t_f] \to \mathbb{R}^n$ such that

$$H(t, \boldsymbol{y}(t)^*, \boldsymbol{\lambda}(t), \boldsymbol{u}(t)) \leq H(t, \boldsymbol{y}(t)^*, \boldsymbol{\lambda}(t), \boldsymbol{u}(t)^*), \tag{1.23}$$

for all control $\boldsymbol{u} \in U$ and $t \in [t_0, t_f]$,

$$\dot{\boldsymbol{y}}^*(t) = \frac{\partial H(t,\boldsymbol{y}(t)^*,\boldsymbol{\lambda}(t),\boldsymbol{u}(t)^*)}{\partial \boldsymbol{\lambda}}, \tag{1.24}$$

$$\dot{\boldsymbol{\lambda}}(t) = -\frac{\partial H(t,\boldsymbol{y}(t)^*,\boldsymbol{\lambda}(t),\boldsymbol{u}(t)^*)}{\partial \boldsymbol{y}}, \tag{1.25}$$

and lastly, $$\boldsymbol{\lambda}(t_f) = \dot{\vartheta}(y(t_f)). \tag{1.26}$$

Proof. (Kamien and Schwartz, 1991).

In real life applications, most of the controls are bounded, thus, we should establish the necessary conditions for bounded controls.

Corollary 1.2. Given the following optimal control problem

$$\max_{u \in U} \quad J[y(t), u(t)] = \int_{t_0}^{t_f} g\big(t, y(t), u(t)\big)dt$$

$$\textbf{subject to} \quad \dot{y}(t) = f\big(t, y(t), u(t)\big) \tag{1.27}$$

$$y(t_0) = y_0.$$

$$a \leq u(t) \leq b,$$

for any given constants a and b such that $a < b$. Suppose that $u^*$and $y^*$are optimal for (1.27), then therexists a piecewise differentiable function $\lambda$with

$$H(t, y(t)^*, \lambda(t), u(t)) \leq H(t, y(t)^*, \lambda(t), u(t)^*), \tag{1.28}$$

for all control $u \in U$ and $t \in [t_0, t_f]$,

$$\dot{y}^*(t) = \frac{\partial H(t, y(t)^*, \lambda(t), u(t)^*)}{\partial \lambda}, \tag{1.29}$$

$$\dot{\lambda}(t) = -\frac{\partial H(t, y(t)^*, \lambda(t), u(t)^*)}{\partial y}, \tag{1.30}$$

$$\lambda\big(t_f\big) = \dot{\vartheta}\big(y(t_f)\big). \tag{1.31}$$

Moreover, the optimality condition is given by

$$u^* = \begin{cases} a, & if \quad \frac{\partial H}{\partial u} < 0 \\ a < \breve{u}(t) < b, & if \quad \frac{\partial H}{\partial u} = 0 \\ b, & if \quad \frac{\partial H}{\partial u} > 0 \end{cases} \tag{1.32}$$

or in compact form

$$u^*(t) = min(max(\breve{u}, b), a). \tag{1.33}$$

Proof. (Fleming and Rishel, 1975).

1.6.5 Applications of Pontryagin's Maximum Principle

Now, we are going to give some examples to illustrate how the Pontryagin's maximum principle works.

Example 1. Use the Pontryagin's principle and solve the OCP.

$$\min_{y,u} \; J[y(t),u(t)] = \int_0^1 (y+u^2)dt$$

$$subject\ to \quad \dot{y}(t) = -2y + u$$

$$y(0) = 1$$

$$y(1) = 0.$$

The first step is to outline the Hamiltonian for the optimal control problem as follows:

$$H(t,y,\lambda,u) = y + u^2 + \lambda(-2y+u).$$

The adjoint variable is obtained from the Hamiltonian and given by $\dot{\lambda}(t) = -\frac{\partial H}{\partial y} = 2\lambda - 1.$

This implies that, $\dot{\lambda}(t) = 2\lambda - 1$. The optimality condition is as follows:

$$\frac{\partial H}{\partial u} = 0 \leftrightarrow \; u^* = {-\lambda}/{2}.$$

The transversality condition, $\lambda(1) = 0$, is used to solve the adjoint equation, that is to say, we solve the first order linear ordinary differential equation with transversality condition in (1.34),

$$\begin{cases} \dot{\lambda}(t) = 2\lambda - 1, \\ \lambda(1) = 0. \end{cases} \tag{1.34}$$

The solution is given by $\lambda(t) = \frac{1}{2}(1 - e^{2t-2})$.

Thus, $u^* = -\frac{1}{4}(1 - e^{2t-2})$ (from the optimality condition). To find the corresponding trajectory, y^*, we solve the following initial value problem:

$$\begin{cases} \dot{y} = -2y - \frac{1}{4}(1 - e^{2t-2}) \\ y(0) = 1. \end{cases}$$

The trajectory is $y(t)^* = -\frac{1}{8} + 16(e^{2t-2} - e^{-2t-2})$.

Therefore, $y(t)^* = -\frac{1}{8} + 16(e^{2t-2} - e^{-2t-2})$ is the solution of the problem corresponding to the optimal control $u^* = -\frac{1}{4}(1 - e^{2t-2})$.

The next example will be for an optimal control problem with terminal payoffs and bounded controls.

Example 2. Consider the optimal control below

$$\min_{y,u} \; J[y(t), u(t)] = y(t_f) + \int_0^2 \left(y + \frac{1}{2}u^2\right) dt,$$

$$\text{subject to} \quad \dot{y}(t) = 3y + u,$$

$$y(0) = 1,$$

$$a_1 \le u(t) \le b_1.$$

Form the Hamiltonian as follows: $H(t, y, \lambda, u) = y + \frac{1}{2}u^2 + \lambda(3y + u)$. The adjoint equation is given by,

$$\dot{\lambda}(t) = -\frac{\partial H}{\partial y} = -3\lambda - 1,$$

and the transversality condition is $\lambda(2) = 1$, since $\dot{\vartheta}\big(y(t_f)\big) = 1$. Thus,

$$\lambda(t) = \tfrac{1}{3}\big(4e^{(6-3t)} - 1\big).$$

The optimality condition is given by

$$\frac{\partial H}{\partial u} = 0 \leftrightarrow \; u^* = -\lambda.$$

Then, $\tilde{u} = -\frac{1}{3}\left(4e^{(6-3t)} - 1\right)$. Thus, by the Pontryagin's maximum principle,

$$u^* = \begin{cases} a_1, & if \quad \dfrac{\partial H}{\partial u} < 0 \\ -\dfrac{1}{3}\left(4e^{(6-3t)} - 1\right), & if \quad \dfrac{\partial H}{\partial u} = 0 \\ b_1, & if \quad \dfrac{\partial H}{\partial u} > 0. \end{cases}$$

However, if the state equations and controls are system of ordinary differential equations, analytic solutions are difficult to get. Hence, we employ some numerical methods to solve the optimality system - it is obtained when state equations with their initial conditions are *coupled* together with the adjoint equations and their transversality conditions. In this thesis, we are going to explain the forward-backward sweep method – a method used in finding the numerical solutions of optimality systems.

1.6.6 Forward-Backward Sweep Method

It is a type of an indirect method used to numerically find the optimality conditions of an OCP. The application of maximum principle reduces the problem to a multiple point boundary value problem (optimality system). The optimality system is solved to determine the optimal values for the original control problem. In indirect methods, it is basically essential to have adjoint equations, transversality conditions, and the control equations. The procedure for the forward-backward sweep method is as follows:

1. We start by making an initial estimate (guess) for the control function.

2. Then, state equations in the optimality system are solved forward in time using the initial conditions and the control value (guessed in 1). This process is conducted using the fourth order Runge-Kutta scheme or the solver ode45 for Matlab (Lenhart and Workman, 2007; Wang, 2009).

3. Next, we use the updated values of the state, control value, and the transversality conditions to solve the adjoint equations backward in time with fourth order Runge-Kutta scheme or the solver ode45 for Matlab (Wang, 2009).

4. The control is then updated when the latest updated values of the states and adjoints are substituted in the representation of the optimal control obtained from the maximum principle.

5. The process is repeated until we have convergence viz. - the difference between newest and previous values of the variables is within an acceptable error range. Thus, the current values will be the solution of the optimality system when convergence is achieved.

1.7 Mathematical Modeling and Optimal Control of Superficial Bladder Cancer

Several mathematical studies have been conducted on superficial bladder cancer treatment. Bunimovich-Mendrazitsky et al (2007) presented the first model of bladder cancer immunotherapy using BCG. Stability analysis of the model with exponential and logistic growth of the cancer was also conducted. Their research aims to illustrate relation between the immune system and bladder cancer cells in consequence to BCG immunotherapy. In 2008, they modified the model by changing the mode of infusion of the BCG from continuous to pulsing. Thus, they used impulsive differential equations to study the dynamics and stability analysis of the model (Bunimovich-Mendrazitsky et al., 2008).

Mathematical modeling of combination therapy for bladder cancer with BCG and interleukin-2 (IL-2) was studied in (Bunimovich-Mendrazitsky et al., 2011; Bunimovich-Mendrazitsky et al., 2016). A nine-dimensional model of bladder cancer immunotherapy (BCG therapy) that provide cancer clearance conditions was developed in 2015 (Starkov and Bunimovich-Mendrazitsky, 2015).

Optimal control theory is applied to various cancer treatment models in order to find the best optimal dose or best control strategy required to minimize or eradicate cancer cells. An isoperimetric optimal control problem on a BCG immunotherapy model was utilized to determine optimal BCG dose needed in activating the immune system in (Elmouki and Saadi, 2014). Meryem et al. developed a free-final time optimal control approach that determines the optimal dosage and time of applying the BCG in bladder cancer treatment (Alkama et al., 2018).

Many researchers used the Pontryagin’s principle in finding optimal BCG dose required to stimulate the immune system, in order to launch a rigorous and robust anti-tumor attack (Elmouki and Saadi, 2016; Aboulaich et al., 2017; Saadi et al., 2015; Alkama et al., 2017).

More literature will be revealed in the subsequent chapters of the thesis.

1.8 Framework of the Thesis

The central aim of this thesis is to develop and formulate mathematical models of bladder cancer immunotherapy using Bacillus Calmette Guerin (BCG), with a special focus on the negative influence/effect of immune checkpoints on the immune cells and the entire treatment. Additionally, it is in our target to structure the treatment into a OCP demanding the maximization (or minimization) of certain specified objective functions; which are dependent on the number/concentration of cancer cells, concentration of immune checkpoints, number of immune cells, and costs of controls, for some known and specified initial conditions.

Thus, this will enable us to explain, suggest, propose, and give the best treatment strategy or outcome - optimal dose in particular, required to eradicate or minimize the severity of the disease.

The thesis comprises of three manuscripts. The manuscripts can be read independently because of their self-sufficient nature. Chapter 1 presents the mathematical and biological backgrounds that support the original results of the thesis.

The first result (first paper) is presented in chapter 2, that is,

Dynamics of immune checkpoints, immune system, and BCG in the treatment of superficial bladder cancer, Saad F.T., Hincal E., Kaymakamzade B., Computational and Mathematical Methods in Medicine, Volume 2017, Article ID 3573082, 9 pages.

The model formulated in this chapter explores the interaction of bladder tumor, immune system, BCG, and immune checkpoints in bladder cancer treatment. Moreover, we establish mathematically the negative influence of the immune checkpoints on the immune system and the therapy at large.

Chapter 3 deals with the second result of this thesis. A control function, $u(t)$, is introduced into the model of chapter 2 to mimic the optimal BCG dose required to activate and stimulate a powerful anti-tumor attack, regardless of the interference and blockade from the immune checkpoints, as well as reducing the toxicity on normal cells. The title of the article for this chapter is:

An optimal control approach for the interaction of immune checkpoints, immune system, and BCG in the treatment of superficial bladder cancer, Saad F.T., Hincal E., European Physical Journal Plus (2018) 133:241.

In chapter 4, the third result is established. Two control functions $u_1(t)$ and $u_2(t)$are incorporated into the model. The first control, $u_1(t)$, represent the optimal dose of an immune checkpoint inhibitor (drug therapy) needed to take the breaks off the immune system by blocking the activity of the checkpoints, while the second control, $u_2(t)$, denote the optimal dose of BCG administered in order to stimulate and activate the immune system. This result yields the following manuscript:

Optimal Control Applied to Immune Checkpoint Inhibitors and BCG for Superficial Bladder Cancer Model, F.T. Saad, E. Hincal, under review in Applied Mathematics and Computation.

Summary and conclusion of the thesis is given in chapter 5.

CHAPTER 2

DYNAMICS OF IMMUNE CHECKPOINTS, IMMUNE SYSTEM AND BCG IN THE TREATMENT OF SUPERFICIAL BLADDER CANCER

2.1 Introduction

Cancer as defined earlier, is a class of illnesses characterized by out-of-control cell growth which affects and damages the DNA. Cancer prevalence is increasing in many countries (Bohle and Brandau, 2003). Many treatment options of cancer exist which include surgery, immunotherapy, chemotherapy, radiotherapy, vaccine therapy, and hormonal therapy (Bohle and Brandau, 2003; Kirschner and Panetta, 1998). The mode and type of treatment depends on the type, location, grade of the cancer, and the patient's body system. The bladder is a hollow organ in the lower abdomen which collects urine produced by the kidneys. Bladder cancer is a growth of malignant cells initiating in the urinary bladder. It is common, with around 38,000 men and 15,000 women diagnosed every year in the United States. Approximately 400,000 new cases are diagnosed and about 150,000 die directly from the disease every year across the globe (Kapoor et al., 2008; Bunimovich-Mendrazitsky et al., 2016).

The bladder wall is lined with transitional and squamous cells. The most communal kind of bladder cancer is the UC or TCC. It mostly originates from the transitional cells and further progressed and develops quickly on the inner surface of the bladder. Thus, it occupies the bladder vessels and wall, dispersing to nearby organs in addition to establishing distant metastases (Fuge et al., 2015; Bunimovich-Mendrazitsky et al., 2007; Kawai et al., 2013).

Immunotherapy is among the most effective ways of treating bladder cancer. BCG is a form of immunotherapy used in treating cancer. The attenuation (of the BCG) is reached via manipulation of the bacillus by serial growths on a culture medium. As a result, the genes causing virulence will be lost and inoculated into humans (Redelman-Sidi et al., 2014; Askeland et al., 2012). It is also used for various types of cancers. For example, skin cancer, bladder cancer and acute lymphoblastic leukemia (Askeland et al., 2012).

The first successful report on BCG therapy of bladder cancer was in 1976 by Morales and his coworkers (Lamm et al., 1980; Starkov et al., 2016). They obtained the efficacy of the therapy and established it as a pillar for treating nonmuscle-invasive bladder cancer after transurethral resection (Fuge et al., 2015; Andius and Holmang, 2004).BCG therapy is undoubtedly the most efficient and successful immunotherapy of superficial bladder cancer.

It is usually applied after local surgery to prevent tumor reoccurrence. The intravesical instillation of 1.5×10^8 bacteria over a 6 weeks period is administered. This has proved to be superior to chemotherapy in decreasing tumor relapse rates (Lamm et al., 1980; Starkov et al., 2016; Bunimovich-Mendrazitsky et al., 2011)".

When the BCG is infused and processed within the bladder, it creates an inflammatory environment which in turns stimulates an immune response resulting in attacking the cancer cells. Therefore, many researchers believed that BCG reduces tumor progression and henceforth stated that, the principal aim of BCG treatment is stimulating the immune effector cells to attack the tumor. Even though BCG instillation is regarded as the 'gold standard' treatment, it has many side effects that include hematuria, fever, dysuria, pain and so on (Kawai et al., 2013; Bunimovich-Mendrazitsky et al., 2008; Redelman-Sidi et al., 2014; Askeland et al., 2012; Andius and Holmang, 2004; Lamm et al., 1980; Starkov et al., 2016; Bunimovich-Mendrazitsky et al., 2011)".

Immune checkpoints are damaging regulators of the immune system which play important roles in preserving self-tolerance, keeping tissues from immune collateral harm, and inhibiting autoimmunity. These checkpoints are often hijacked by tumors to restrain the ability of the immune system to launch a real anti-tumor reaction. The tumors neutralize some immune checkpoint pathways in order to maintain immune resistance, principally against T cells - specific tumor antigens. Examples of checkpoints include PD-1 protein and CTLA4 (Bunimovich-Mendrazitsky et al., 2011; Thibult et al., 2013).

Programmed cell death protein 1 (PD-1), is a protein that is encoded by the PDCD1 gene in humans. It is a cell surface receptor which is a member to the immunoglobulin superfamily and is expressed on T cells and pro-B cells. PD-1 binds two ligands, PD-L1 and PD-L2. The PD-1 acts as an immune checkpoint, which plays an important role in down regulating the

immune system by preventing the activation of the T-cells. Hence, decreases autoimmunity and encourages self-tolerance (Pallard, 2000; Kim et al., 2015).

The immune system is directly affected by the activities of PD-1 protein in the sense that it suppresses, blocks, and deactivates the immune system from disseminating, and fighting the tumor. Therefore, PD-1 protein aids in growth, development, and progression of the cancer. In conclusion, it disrupts and affects immunotherapy (Keir et al., 2008; Hofmeyer et al., 2011; Latchman et al., 2001; Wang et al., 2014; Iwai et al., 2002).

Transforming growth factor-beta 1 (TGF-β1), is a regulatory cytokine which suppresses immune function in cancers and in chronic viral infections. It inhibits the activation of the T-cells and subdues their proliferation. Hence, cancer cells take advantage of this immune checkpoint pathway as a way to escape and evade detection. This leads to the inhibition of anti-tumor immune response, resulting in cancer growth and development (Yoshimura and Muto, 2011; Banerjee et al., 2015).

Mathematical modeling and simulation helps in predicting treatments outcome, as well as describing the behavior and complex dynamics involved. Mathematical models that study the use of BCG in non-invasive bladder cancer were developed in (Bunimovich-Mendrazitsky et al., 2011, Bunimovich-Mendrazitsky et al., 2008; Bunimovich-Mendrazitsky et al., 2007). These articles identified fixed points and presented the conditions for stability of the dynamical systems. Bunimovich-Mendrazitsky et al (2015) constructed a new mathematical model for combined BCG and IL-2 bladder cancer treatment which introduces the effect of TAA T-cells. Furthermore, Starkov et al (2016) utilized a mathematical approach for bladder cancer treatment model in the derivation of ultimate upper and lower bounds. He also presented tumor clearance conditions for BCG treatment of bladder cancer.

In this chapter, we formulate a deterministic model which studies the dynamics of immune suppressors/checkpoints, immune system in BCG immunotherapy of bladder cancer. Moreover, we highlight the negative effects of checkpoints on the immune system and the therapy numerically.

The chapter is organized as follows; section 2.1 is the introduction, section 2.2 gives the formulation and presentation of the model. We give the stability analysis and numerical

simulations in section 2.3 and 2.4 respectively. In the final section, we state our conclusion and discussions.

2.2 Formulation of the Model

The model consists of system of four non-linear ordinary differential equations; which characterize the dynamics of the interaction between cancer cells (C), different categories/arms of the immune system regarded as effector cells (E), BCG (B), and all categories of immune suppressors/checkpoints as (P). The model equations are generated as follows:

i) Dynamics of Cancer Cells

The dynamics of cancer cells is given by;

$$\frac{dC}{dt} = rC - \frac{\alpha_1 EC}{P + k}.$$

In the absence of immune system, we assume the cancer cells grow exponentially with growth rate r. The next term shows the elimination of cancer cells by the effector cells at rate α_1, while $\frac{1}{P+k}$ is the immunosuppressive factor by the immune checkpoints/checkpoints which interrupts the activities of the effector cells and$k$ being an inhibitory parameter.

ii) Dynamics of the Effector Cells

The dynamics of the effector cells is given by;

$$\frac{dE}{dt} = \frac{a_1 CE}{P + k} + \frac{a_2 BE}{P + k} - \alpha_2 EC - \mu_1 E.$$

The first term here gives the recruitment of effector cells at the rate a_1 which is directly proportional to the population of cancer cells (i.e. occurring due to the direct presence of cancer cells), $a_2 BE$ shows the activation of effector cells by BCG at the rate a_2. a_1 is the antigenicity of cancer cells which triggers an immune response in the host. It is believed that the immune checkpoints will distort both the recruitment and activation of effector cells, hence, $\frac{1}{P+k}$ is the immunosuppressive response which put limitation to the recruitment level and interrupts the activation of effector cells, with k here being an inhibitory parameter. The

next term gives the destruction of effector cells by the tumor at rate α_2, and the last term refer to the degradation of effector cells at rate μ_1.

iii) Dynamics of BCG

The dynamics of BCG is given by;

$$\frac{dB}{dt} = b - \alpha_3 EB - \mu_2 B.$$

The first term b is the constant and continuous rate of introduction of BCG into the bladder, the second term describes the eradication of BCG by immune effector cells at rate α_3, and the third term presents the decay of BCG at rate μ_2.

iv) Dynamics of Checkpoints

The dynamics of immune checkpoints is given by;

$$\frac{dP}{dt} = \delta - \mu_3 P.$$

The evolution of the checkpoints starts with their source at a continuous rate δ, followed by their degradation rate, μ_3. Finally, the interactions of tumor, BCG, immune checkpoints, and effector cells lead to the following non-linear ordinary differential equations:

$$\frac{dC}{dt} = rC - \frac{\alpha_1 EC}{P+k}$$

$$\frac{dE}{dt} = \frac{a_1 CE}{P+k} + \frac{a_2 BE}{P+k} - \alpha_2 EC - \mu_1 E \qquad (2.1)$$

$$\frac{dB}{dt} = b - \alpha_3 EB - \mu_2 B$$

$$\frac{dP}{dt} = \delta - \mu_3 P,$$

with initial conditions $C(0) = C_0 > 0$, $E(0) = E_0 > 0$, $B(0) = B_0 > 0$, $P(0) = P_0 > 0$.

2.3 Invariance of Positive Orthant

We show the system is positively invariant.

From system (2.1), assume $C(0) > 0$, $E(0) > 0$, $B(0) > 0$, $P(0) > 0$.

From $\frac{dC}{dt} = rC - \frac{\alpha_1 EC}{P+k}$, the solution is given by$C(t) = C_0 \exp\left(\int_0^t \left(r - \frac{\alpha_1 E}{P+k}\right) dt\right)$. This implies $C(t) > 0$since$C_0 > 0$.

Now, consider $\frac{dE}{dt} = \frac{(a_1 C + a_2 B)E}{P+k} - \alpha_2 EC - \mu_1 E,$ then,

$$E(t) = E_0 \exp\left(\int_0^t \left(\frac{a_1 C + a_2 B}{P+k} - \alpha_2 C - \mu_1\right) \mathrm{dt}\right) > 0.$$

This implies that $E(t) > 0 \; \forall t \;\; if \; E_0 > 0$.

More so, equation 3 and 4 from system (2.1) gives linear first order ordinary differential equations, which can be solved using integrating factor method. Solving the equations reveals that $B(t) > 0 \;\; and \;\; P(t) > 0 \;\; \forall t$, since $B(0) > 0 \;\; and \;\; P(0) > 0$.

Hence, the positive orthant R_+^4 is invariant, moreover, $C(t) > 0$, $E(t) > 0$, $B(t) > 0$, $P(t) > 0 \;\; \forall t$.

2.4 Model without Treatment

The model without treatment is obtained from (2.1)by setting $\boldsymbol{b} = \mathbf{0}$.Thus, It is given as follows

$$\frac{dC}{dt} = rC - \frac{\alpha_1 EC}{P+k}$$

$$\frac{dE}{dt} = \frac{a_1 CE}{P+k} + \frac{a_2 BE}{P+k} - \alpha_2 EC - \mu_1 E \qquad (2.2)$$

$$\frac{dB}{dt} = -\alpha_3 EB - \mu_2 B$$

$$\frac{dP}{dt} = \delta - \mu_3 P.$$

We now analyze model (2.2) viz. in the absence of treatment.

2.4.1 Equilibrium and Stability Analysis of Model (2.2)

The steady states are obtained by equating the right-hand sides of equations in (2.2) to zero and solving concurrently for the variables C, E, B, and P. They steady states are as follows:

$$U_0 = \left\{0,0,0,\frac{\delta}{\mu_3}\right\},\ U_1 = \left\{0,-\frac{\mu_2}{\alpha_3},\frac{\mu_1(\delta+k\mu_3)}{a_2\mu_3},\frac{\delta}{\mu_3}\right\},\ \text{and}$$

$$U_2 = \left\{\frac{\mu_1(\delta+k\mu_3)}{a_1\mu_3-\alpha_2(\delta+k\mu_3)},\frac{r(\delta+k\mu_3)}{\alpha_1\alpha_3},0,\frac{\delta}{\mu_3}\right\}.$$

From the positivity of invariance, we concentrate solely on nonnegative steady states presumptuous that all initial conditions are positive. As a result, the steady state U_1 will not be considered. Moreover, U_2 exists only if the following condition is satisfied

$$a_1\mu_3 > \alpha_2(\delta+k\mu_3).$$

The Jacobian matrix obtained from (2.2) is given by

$$\hat{J}(C^*,E^*,B^*,P^*) = \begin{bmatrix} r-\frac{\alpha_1E^*}{P^*+k} & \frac{-\alpha_1C^*}{P^*+k} & 0 & \frac{\alpha_1E^*C^*}{\left(P^*+k\right)^2} \\ \frac{a_1E^*}{P^*+k}-\alpha_2E^* & \frac{a_1C^*+a_2B^*}{P^*+k}-\alpha_2C^*-\mu_1 & \frac{a_2E^*}{P^*+k} & \frac{-\left(a_1C^*E^*+a_2B^*E^*\right)}{\left(P^*+k\right)^2} \\ 0 & -\alpha_3B^* & -\alpha_3E^*-\mu_2 & 0 \\ 0 & 0 & 0 & -\mu_3 \end{bmatrix}$$

The stability of the equilibria is as follows:

i) Immune Checkpoints Equilibrium: $U_0 = \left\{0,0,0,\frac{\delta}{\mu_3}\right\}$.

The Jacobian matrix $\hat{J}$evaluated at U_0 yields:

$$\hat{J}(U_0) = \begin{bmatrix} r & 0 & 0 & 0 \\ 0 & -\mu_1 & 0 & 0 \\ 0 & 0 & -\mu_2 & 0 \\ 0 & 0 & 0 & -\mu_3 \end{bmatrix}$$

The eigenvalues of $J(U_0)$ are:

$$\lambda_1 = r,\quad \lambda_2 = -\mu_1,\ \lambda_3 = -\mu_2\ ,\ \text{and}\ \lambda_4 = -\mu_3.$$

Since one of the eigenvalues is always positive, then U_0 is an unstable saddle point. Clinically, U_0 is referred to as the death equilibrium.

ii) BCG-free equilibrium: $U_2 = \left\{\frac{\mu_1 r(\delta+k\mu_3)^2}{\alpha_1 a_1 {\mu_3}^2 - r\alpha_2(\delta+k\mu_3)^2},\frac{r(\delta+k\mu_3)}{\alpha_1\alpha_3},0,\frac{\delta}{\mu_3}\right\}$

Assume U_2 exists, that is $a_1\mu_3 > \alpha_2(\delta+k\mu_3)$, then substituting U_2 in $\hat{J}$ yields the following eigenvalues:

$\lambda_1 = -\mu_3, \lambda_2 = -\frac{r\alpha_3\delta + \alpha_3 rk\mu_3 + \mu_2\alpha_1\mu_3}{\alpha_{1\mu_3}}$, $\lambda_3 = \frac{\sqrt{-(\delta r\mu_3\mu_1 + rk\mu_1{\mu_3}^2)}}{(\delta + k\mu_3)}$, and

$\lambda_4 = \frac{\sqrt{-(\delta r\mu_3\mu_1 + rk\mu_1{\mu_3}^2)}}{(\delta + k\mu_3)}$.

Two of the eigenvalues have real part equal to zero, which signifies neutral stability. Therefore, the equilibrium point U_2 is neutrally stable.

Conclusively, in the absence of treatment, none of the equilibrium points was found to be stable.

2.5 Model without Immune Checkpoints

Now, we analyze the model without any suppression of checkpoints against the immune system. The mathematical model is as follows:

$$\frac{dC}{dt} = rC - \alpha_1 EC$$

$$\frac{dE}{dt} = a_1 CE + a_2 BE - \alpha_2 EC - \mu_1 E \qquad (2.3)$$

$$\frac{dB}{dt} = b - \alpha_3 EB - \mu_2 B$$

2.5.1 Equilibrium and Stability Analysis of Model (2.3)

The equilibrium points are as follows:

$U_0 = \left\{0, 0, \frac{b}{\mu_2}\right\}, U_1 = \left\{0, \frac{ba_2 - \mu_1\mu_2}{\mu_1\alpha_3}, \frac{\mu_1}{a_2}\right\}$, and

$U_2 = \left\{\frac{\mu_1\mu_2\alpha_1 + \alpha_3 r\mu_1 - a_2 b\alpha_1}{(\alpha_3 ra_1 - \alpha_3 r\alpha_2 + \alpha_1\mu_2 a_1 - \alpha_1\alpha_2\mu_2}, \frac{r}{\alpha_1}, \frac{b\alpha_1}{(\alpha_3 r + \alpha_1\mu_2)}\right\}$.

The equilibrium point U_1 exists only if $ba_2 \geq \mu_1\mu_2$. This means that, the cancer cells will disappear if the constant rate of introduction of BCG and activation rate of BCG is bigger than the degradation rates of both the effector cells and the BCG.

The equilibrium point U_2 also exist if,

$$\mu_2\alpha_1\mu_1 + \alpha_3 r\mu_1 \geq a_2 b\alpha_1 \quad and \quad \alpha_3 a_1 r + a_1\alpha_1\mu_2 \geq \alpha_3 ra_2 + \mu_2\alpha_1\alpha_2,$$

OR

$$\mu_2\alpha_1\mu_1 + \alpha_3 r\mu_1 \leq a_2 b\alpha_1 \quad and \quad \alpha_3 a_1 r + a_1\alpha_1\mu_2 \leq \alpha_3 ra_2 + \mu_2\alpha_1\alpha_2.$$

From model (2.3), we have the following Jacobian matrix;

$$\bar{J}(C^*, E^*, B^*) = \begin{bmatrix} r - \alpha_1 E^* & -\alpha_1 C^* & 0 \\ a_1 E^* - \alpha_2 E^* & a_2 B^* + a_1 C^* - \alpha_2 C^* - \mu_1 & a_2 E^* \\ 0 & -\alpha_3 B^* & -\alpha_3 E^* - \mu_2 \end{bmatrix}.$$

The stability of the equilibria of model (2.3) is as follows:

i) BCG equilibrium: $U_0 = \left\{0, 0, \frac{b}{\mu_2}\right\}$.

The eigenvalues of $\bar{J}$ evaluated at U_0 are;

$$\lambda_1 = r, \lambda_2 = \frac{ba_2 - \mu_1\mu_2}{\mu_2}, \text{ and } \lambda_3 = -\mu_2.$$

The eigenvalue λ_1 is always positive and the rest are negative. Therefore, the equilibrium point U_0 is an unstable saddle point.

ii) Cancer-free equilibrium: $U_1 = \left\{0, \frac{ba_2 - \mu_1\mu_2}{\mu_1\alpha_3}, \frac{\mu_1}{a_2}\right\}$.

Assume the equilibrium point U_1 exist, then substituting U_1 in $\bar{J}$ will give the following matrix:

$$\bar{J}(U_1) = \begin{bmatrix} \frac{r\alpha_3\mu_1 - a_1 ba_2 + \mu_2\mu_1}{\alpha_3\mu_1} & 0 & 0 \\ \frac{a_1 ba_2 - a_1\mu_2\mu_1 - \alpha_2 ba_2 + \alpha_2\mu_2\mu_1}{\alpha_3\mu_1} & 0 & \frac{{a_2}^2 b - a_2\mu_2\mu_1}{\alpha_3\mu_1} \\ 0 & -\frac{\alpha_3\mu_1}{a_2} & -\frac{ba_2}{\mu_1} \end{bmatrix}$$

The eigenvalues of $\bar{J}(U_2)$ are:

$$\lambda_1 = \frac{r\alpha_3\mu_1 + \mu_2\mu_1 - a_1 ba_2}{\alpha_3\mu_1}, \lambda_2 = \frac{-ba_2 + \sqrt{(ba_2)^2 - 4ba_2{\mu_1}^2 + 4\mu_2{\mu_1}^3}}{2\mu_1}, \text{ and}$$

$$\lambda_2 = \frac{-ba_2 - \sqrt{(ba_2)^2 - 4ba_2{\mu_1}^2 + 4\mu_2{\mu_1}^3}}{2\mu_1}.$$

Now, if λ_2 and λ_3 are complex roots, then U_1 is a stable fixed point if

$$a_1 ba_2 > \mu_1(r\alpha_3 + \mu_2), \ \boldsymbol{OR,}$$

if λ_2 and λ_3 are real roots, then U_1 is a stable fixed point when

$$ba_2 > \mu_1\mu_2 \text{and } a_1 ba_2 > \mu_1(r\alpha_3 + \mu_2).$$

But, since we already assume that the equilibrium point U_1 exists then $ba_2 > \mu_1\mu_2$, thus, we can conclude that U_1 is a stable fixed point if $a_1 ba_2 > \mu_1(r\alpha_3 + \mu_2)$.

This means that, the effector cells activated by BCG will eradicate/destroy the cancer cells, if the constant rate of introduction of BCG, effector cells recruitment rate, and rate of activation of effector cells by BCG is *bigger than or can overcome* the cancer growth rate, rate of elimination of BCG by effector cells, and degradation rates of effector cells and BCG

altogether. Therefore, to eliminate the cancer, we *increase* the rate of introduction of BCG, recruitment rate of effector cells, along with rate of effector cells activation by BCG, and concurrently *decrease* the elimination rate of BCG (by effector cells), degradation rates of both effector cells and BCG, as well as the cancer growth rate.

2.6 Model with Treatment and Immune Checkpoints

We now consider the dynamics of tumor, immune effector cells, BCG, and checkpoints. It is given by

$$\frac{dC}{dt} = rC - \frac{\alpha_1 EC}{P+k}$$

$$\frac{dE}{dt} = \frac{a_1 CE}{P+k} + \frac{a_2 BE}{P+k} - \alpha_2 EC - \mu_1 E \qquad (2.1)$$

$$\frac{dB}{dt} = b - \alpha_3 EB - \mu_2 B$$

$$\frac{dP}{dt} = \delta - \mu_3 P.$$

2.6.1 Equilibrium and Stability Analysis of Model (2.1)

The equilibrium points of model (2.1) are as follows:

$$U_0 = \left\{0,0,\frac{b}{\mu_2},\frac{\delta}{\mu_3}\right\}, U_1 = \left\{0,\frac{b\mu_3 a_2 - \mu_2\mu_1\delta - \mu_2\mu_1 k\mu_3}{\mu_1\alpha_3(\delta+k\mu_3)},\frac{\mu_1(\delta+k\mu_3)}{\mu_3 a_2},\frac{\delta}{\mu_3}\right\}, \text{ and}$$

$$U_2 = \left\{\begin{matrix} \alpha_3 r\delta^2\mu_1 + 2\alpha_3 r\delta\mu_1\mu_3 k \\ +\alpha_3 rk^2{\mu_3}^2\mu_1 + \mu_2\alpha_1{\mu_3}^2\mu_1 k \\ +\mu_2\alpha_1\mu_3\mu_1\delta - {\mu_3}^2 a_2 b\alpha_1 \\ \hline \alpha_3\mu_3 r\delta a_1 - r\delta^2\alpha_3\alpha_2 \\ -2\alpha_3 r\delta\alpha_2 k\mu_3 + \alpha_3 rk{\mu_3}^2 a_1 \\ -\alpha_3 rk^2{\mu_3}^2\alpha_2 + \mu_2{\mu_3}^2\alpha_1 a_1 \\ -\mu_2\alpha_1\mu_3\alpha_2\delta - \mu_2\alpha_1{\mu_3}^2\alpha_2 k \end{matrix}, \frac{r(\delta+k\mu_3)}{\mu_3\alpha_1}, \frac{b\alpha_1\mu_3}{\alpha_3 r(\delta+k\mu_3) + \alpha_1\mu_3\mu_2}, \frac{\delta}{\mu_3}\right\}.$$

The equilibrium point U_1 exists if,

$$\frac{b\mu_3 a_2}{\mu_2\mu_1(\delta+k\mu_3)} \geq 1. \qquad (2.4)$$

Also, U_2 exists

If $\alpha_3 r\delta^2\mu_1 + 2\alpha_3 r\delta\mu_1\mu_3 k + \alpha_3 rk^2{\mu_3}^2\mu_1 + \mu_2\alpha_1{\mu_3}^2\mu_1 k + \mu_2\alpha_1\mu_3\mu_1\delta \geq {\mu_3}^2 a_2 b\alpha_1$ **and**

$\alpha_3\mu_3 r\delta a_1 + \alpha_3 rk{\mu_3}^2 a_1 + \mu_2{\mu_3}^2\alpha_1 a_1 \geq r\delta^2\alpha_3\alpha_2 + 2\alpha_3 r\delta\alpha_2 k\mu_3 + \alpha_3 rk^2{\mu_3}^2\alpha_2 + \mu_2\alpha_1\mu_3\alpha_2\delta + \mu_2\alpha_1{\mu_3}^2\alpha_2 k.$

OR

If, $\alpha_3 r\delta^2\mu_1 + 2\alpha_3 r\delta\mu_1\mu_3 k + \alpha_3 rk^2{\mu_3}^2\mu_1 + \mu_2\alpha_1{\mu_3}^2\mu_1 k + \mu_2\alpha_1\mu_3\mu_1\delta \leq {\mu_3}^2 a_2 b\alpha_1$

and $\alpha_3\mu_3 r\delta a_1 + \alpha_3 rk{\mu_3}^2 a_1 + \mu_2{\mu_3}^2\alpha_1 a_1 \leq r\delta^2\alpha_3\alpha_2 + 2\alpha_3 r\delta\alpha_2 k\mu_3 + \alpha_3 rk^2{\mu_3}^2\alpha_2 + \mu_2\alpha_1\mu_3\alpha_2\delta + \mu_2\alpha_1{\mu_3}^2\alpha_2 k.$

From model (2.4), we obtain the following Jacobian matrix:

$$\tilde{J}(C^*, E^*, B^*, P^*) = \begin{bmatrix} r - \frac{\alpha_1 E^*}{P^* + k} & \frac{\alpha_1 C^*}{P^* + k} & 0 & \frac{\alpha_1 E^* C^*}{\left(P^* + k\right)^2} \\ \frac{a_1 E^*}{P^* + k} - \alpha_2 E^* & \frac{a_1 C^* + a_2 B^*}{P^* + k} - \alpha_2 C^* - \mu_1 & \frac{a_2 E^*}{P^* + k} & -\frac{\left(a_1 E^* C^* + a_1 B^* C^*\right)}{\left(P^* + k\right)^2} \\ 0 & -\alpha_3 B^* & -\alpha_3 E^* - \mu_2 & 0 \\ 0 & 0 & 0 & -\mu_3 \end{bmatrix}$$

The stability analysis of the equilibria of model (2.1) is as follows:

i) BCG and Immune checkpoints equilibrium: $\mathrm{U}_0 = \left\{0, 0, \frac{\mathrm{b}}{\mu_2}, \frac{\delta}{\mu_3}\right\}$.

The eigenvalues of the $\tilde{J}$ evaluated at U_0 are:

$$\lambda_1 = r\ ,\ \lambda_2 = \frac{b\mu_3 a_2 - \mu_2\mu_1\delta - \mu_2\mu_1\mu_3 k}{\mu_2(\delta + k\mu_3)},\ \ \lambda_3 = -\mu_2,\ and\ \ \lambda_4 = -\mu_3.$$

Since one of the eigenvalues is always positive, then U_0 is an unstable saddle point.

ii) Tumor-free equilibrium: $\mathrm{U}_1 = \left\{0, \frac{\mathrm{b}\mu_3 a_2 - \mu_2\mu_1\delta - \mu_2\mu_1 k\mu_3}{\mu_1\alpha_3(\delta + k\mu_3)}, \frac{\mu_1(\delta + k\mu_3)}{\mu_3 a_2}, \frac{\delta}{\mu_3}\right\}$.

Assume this equilibrium point exists, then the eigenvalues of $\tilde{J}$ evaluated at U_1 are as follows:

$$\lambda_1 = -\mu_3,$$

$$\lambda_2 = \frac{\alpha_3 r\delta^2\mu_1 + 2\alpha_3 r\delta\mu_3\mu_1 k + \alpha_3 rk^2{\mu_3}^2\mu_1 + \mu_2\alpha_1{\mu_3}^2\mu_1 k + \mu_2\alpha_1\mu_3\mu_1\delta - {\mu_3}^2 a_2 b\alpha_1}{\alpha_3\mu_1(\delta + k\mu_3)^2},$$

$$\lambda_3 = \frac{-b\mu_3 a_2 + \sqrt{\begin{matrix}(b\mu_3 a_2)^2 + 4{\mu_1}^3\delta^2\mu_2 + 8{\mu_1}^3\delta\mu_2 k\mu_3 + 4{\mu_3}^2{\mu_1}^3 k^2\mu_2 \\ -4{\mu_1}^2\delta b\mu_3 a_2 - 4{\mu_3}^2{\mu_1}^2 kba_2\end{matrix}}}{2\mu_1(\delta + \mu_3 k)}, \text{ and}$$

$$\lambda_4 = \frac{-b\mu_3 a_2 - \sqrt{\begin{matrix}(b\mu_3 a_2)^2 + 4{\mu_1}^3\delta^2\mu_2 + 8{\mu_1}^3\delta\mu_2 k\mu_3 + 4{\mu_3}^2{\mu_1}^3 k^2\mu_2 \\ -4{\mu_1}^2\delta b\mu_3 a_2 - 4{\mu_3}^2{\mu_1}^2 kba_2\end{matrix}}}{2\mu_1(\delta + \mu_3 k)}.$$

The equilibrium point U_1 is a stable fixed point if,

$$\frac{a_2 b\mu_3}{\mu_1\mu_2(\delta + k\mu_3)} > \max\left\{1, \frac{(r\mu_3 k\alpha_3 + \mu_3\mu_2\alpha_1 + \alpha_3 r\delta)\mu_2}{\alpha_1\mu_3}\right\}.$$

However, condition (2.5) is already true, then U_1 is a stable fixed point if,

$$\frac{a_2 b\mu_3}{\mu_1\mu_2(\delta + k\mu_3)} > \frac{(r\mu_3 k\alpha_3 + \mu_3\mu_2\alpha_1 + \alpha_3 r\delta)\mu_2}{\alpha_1\mu_3}.$$

iii) Interior equilibrium: $U_2 = \left\{C^*, \frac{r(\delta+k\mu_3)}{\mu_3\alpha_1}, \frac{b\alpha_1\mu_3}{\alpha_3 r(\delta+k\mu_3)+\alpha_1\mu_3\mu_2}, \frac{\delta}{\mu_3}\right\}$

The eigenvalues of the Jacobian matrix $\tilde{J}(U_2)$ are very long, complicated and difficult to analyze. Therefore, we use numerical simulations to show the stability of the equilibrium point U_2.

2.7 Numerical Illustrations

In this section, the numerical simulations of the three models will be shown. The aim here is to show the effect of immune checkpoints on the effector cells. We use MATLAB version 2016b to plot the graphs with initial populations of the compartments involved taken to be equal. Other parameters used in the numerical simulations are given in Table 2.1.

We first plot the graph of model (2.2) to illustrate what happens in the absence of treatment. As expected, the cancer cells develop because the effector cells are being suppressed and blocked by immune checkpoints activities, as such; they dominate the immune system and results in growth and maturation of the cancer. Therefore, the numerical simulations of model (2.2) support this notion as shown in Figure 2.1.

Next, we show the behavior of model (2.3) i.e. without the immune checkpoints. Here, we will see how the effector cells attacks and kill the cancer cells as a result of the stimulation/activation by the BCG. Unlike in Figure 2.1, Figure 2.2 shows the way tumor evolution/growth is restricted and thus, eventually results in its extinction by the effector cells.

Table 2.1: List of all parameters used in numerical simulations

Parameter	Interpretation (units)	Estimated value
r	Growth rate of the tumor $t^{-1} = day^{-1}$	0.0033
α_1	Elimination rate of cancer cells by effector cells $cell\ day^{-1}$	1.1×10^{-7}
k	Inhibitory parameter	2×10^{3}
a_1	Recruitment rate of effector cells $t^{-1} = day^{-1}$	0.25
a_2	Activation rate of effector cells by the BCG $cells^{-1}day^{-1}$	0.052
δ	Internal production of immune checkpoints	1.51932×10^{5}
α_3	Destruction of BCG by effector cells $cells^{-1}day^{-1}$	1.25×10^{-7}
μ_3	Degradation rate of immune checkpoints $\mathrm{t}^{-1} = day^{-1}$	166.32
α_2	Elimination rate of effector cells by cancer cells $cells^{-1}day^{-1}$	3.45×10^{-10}
μ_1	Degradation rate of effector cells $t^{-1} = day^{-1}$	0.041
μ_2	Rate of BCG decay $t^{-1} = day^{-1}$	0.1
b	Bio-effective concentration of BCG $c.f.u/day$	6.5×10^{5}

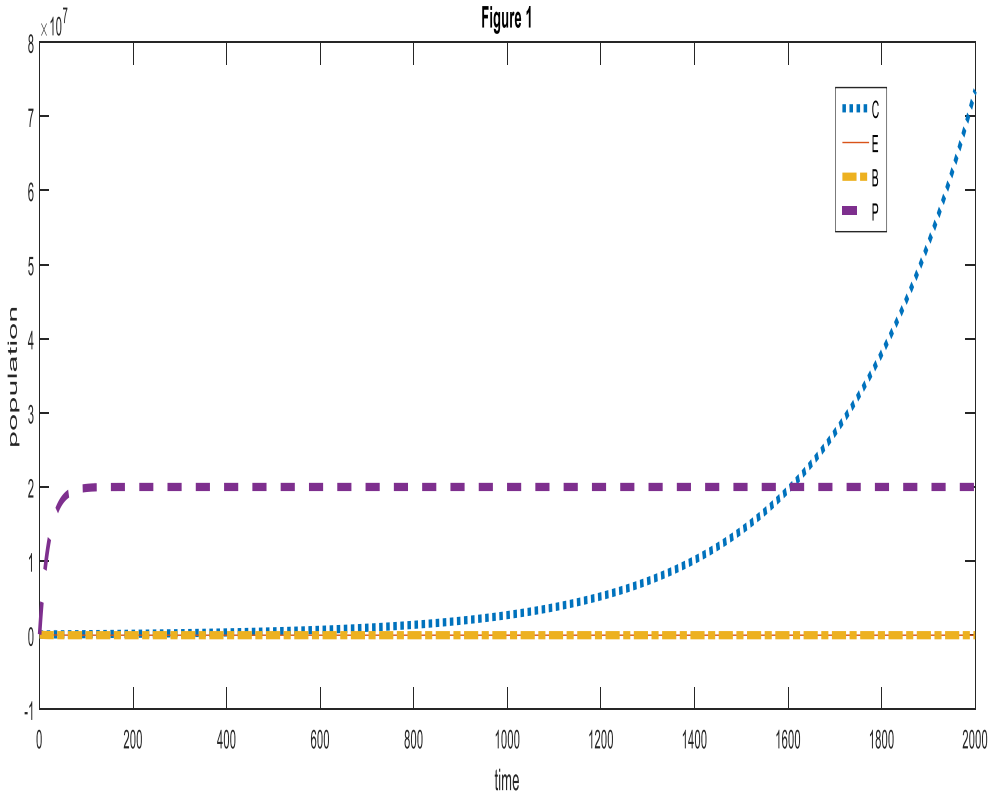

Figure 2.1: The model without treatment (Model 2.2)

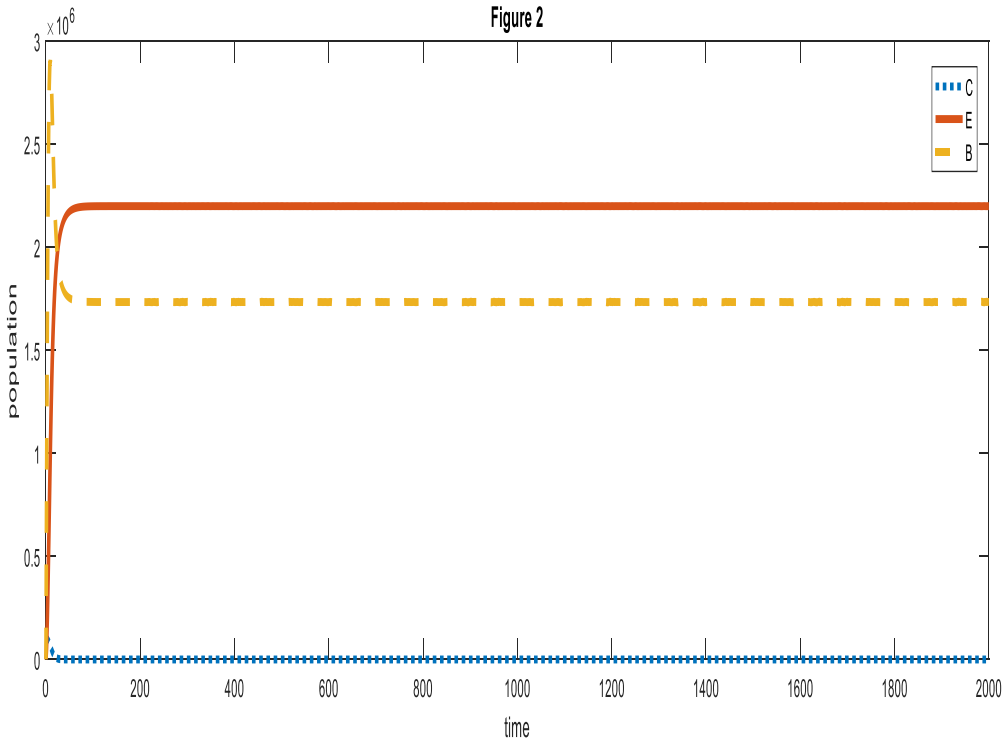

Figure 2.2: The model without immune suppressors (Model 2.3)

The general model will now be considered. Despite stimulation and activation of the effector cells by the BCG, the immune suppressors block and deactivate their function; hence, this leads to the reduction of autoimmunity of the effector cells. Therefore, the cancer develops and grows exponentially as shown in Figure 2.3.

Therefore, comparing Figure 2.2 and Figure 2.3, we will notice the effect of immune checkpoints on the effector cells. In Figure 2.2, the effector cells in the absence of immune suppressors, fights the cancer cells resulting in stopping their development and progression. While Figure 2.3 shows the progression and development of cancer cells, as a result of the presence of immune suppressors.

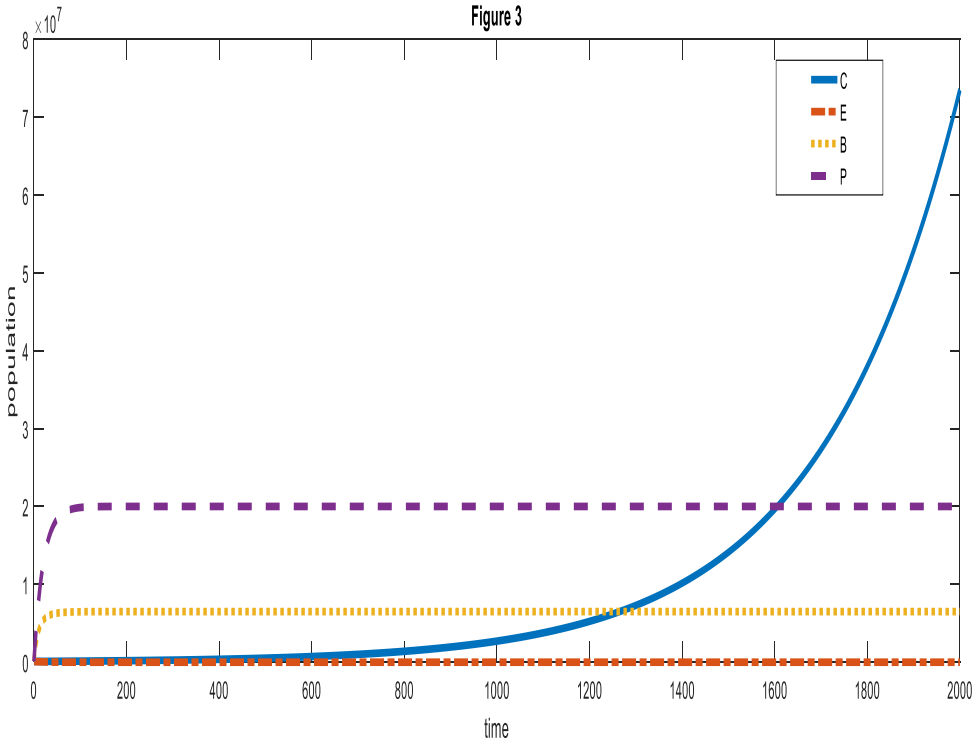

Figure 2.3: The model with treatment and immune checkpoints (Model 2.4)

2.8 Conclusion and Discussion

In this chapter, we used a system of nonlinear ODE to model the dynamics of cancer, effector cells, BCG, and checkpoints in bladder cancer immunotherapy. We derived three possible dynamics from our model. Firstly, the model was analyzed in the absence of treatment and we

study the stability analysis of the equilibria involved. Figure 2.1 showed how the cancer progressed in the absence of treatment and presence of immune checkpoints/suppressors.

Secondly, we study the model without the immune checkpoints/suppressors. Stability conditions for the equilibria involved were also given. We saw that when the immune checkpoints/suppressors are not present, the effector cells activated by the BCG have limitless independence to ramble around and detect the cancer cells; as a result, they kill them and stop the cancer from progressing. This was shown in Figure 2.2.

Thirdly, we considered the dynamics of the model with treatment and the immune checkpoints/suppressors. Conditions for stability of the equilibrium points were given, and Figure 2.3 showed how the cancer cells grow and develop despite the application of the treatment (BCG). This is believed to be as a result of the blockage and suppression the effector cells suffered by the immune checkpoints.

Therefore, the figures used in this chapter assist in showing the effect of immune suppressors/checkpoints against effector cells and the overall therapy. To avoid cancer progression and advancement, there is need for action to block or limit the production of the immune checkpoints. This will take the brakes off the immune system and thereby allowing it to mount a stronger and more effective attack against cancer cells. (Postow et al., 2015; Padoll, 2012).

CHAPTER 3

AN OPTIMAL CONTROL APPROACH FOR THE INTERACTION OF IMMUNE CHECKPOINTS, IMMUNE SYSTEM, AND BCG IN THE TREATMENT OF SUPERFICIAL BLADDER CANCER

3.1 Introduction

The bladder is a distensible membranous sac at the lower abdomen that gather urine produced by the kidneys, whose wall is seamed with cells usually called transitional and squamous cells. Superficial bladder cancer or non-muscle invasive bladder cancer is a type of bladder cancer that is seen on the surface of the inside lining of the bladder. It is arguably the most common type of bladder cancer accounting for 75% of new incidences associated with the disease (Moss and Kadmon, 1991).

Intravesical Bacillus Calmette-Guerin (BCG) is a live attenuated nonpathogenic strain of Mycobacterium bovis that was previously used as a vaccine against tuberculosis. Superficial bladder cancer is the fifth most usual cancers in the USA accounting to at least 14,000 deaths yearly.

Additionally, about 73,000 incidences were recorded in 2012. A thin flexible tube known as catheter is introduced through the urethra in order to convey the BCG into the bladder where it is internalized and processed. Typically, BCG is administered once every week for a period of six weeks. It may be reapplied for the same period if there is a suspicion of tumor recurrence and/or persistence (Eric et al., 2012). Morales et al. in 1976, was the first to highlight the mechanism of action of BCG inside the bladder. The positive response to BCG treatment was estimated to be 55-65% for papillary tumors and 70-75% for carcinoma in situ (CIS). However, this automatically results to 30-45% failures (Morales et al., 1981; Morales et al., 1976).

It is evident BCG has many side effects that include dysuria, excessive pain, fever, hematuria, cystitis, and symptoms of life-threatening BCG sepsis. Most patients are reported to be BCG

intolerant because of these aforementioned side effects. The side effects are partly believed to be as a result of the damage suffered by the normal cells (Vander Meijden et al., 2003).The BCG is internalized by both the normal and cancer cells resulting in creating an inflammation inside the bladder. As a result, it triggers an immediate immune response, where CD4+ cells and other immune effector cells are activated. As a result, the immune cells spread, locate, and attack the cancer cells in order to neutralize their threat (Luo et al., 2003).

One of the major drawbacks of immunotherapy of the bladder cancer is the presence and action of the immune checkpoints. They are negative regulators of the immune system that block the immune effector cells from spreading, attacking, and killing the cancer cells. More so, tumors hijack these immune checkpoints to escape an efficient anti-tumor activity from the immune cells (Padoll, 2012; Thibultet al., 2013). PD-1 protein, Transforming growth factor-beta 1 (TGF-β1), and CTLA4 are some of the examples of immune checkpoints/suppressors (Leach et al., 1996; Postow et al., 1982).

Transforming growth factor-beta 1 (TGF-β1) subdues the activation and spread of the immune T-cells, as a result, the cancer cells use this checkpoint pathway as a means of evading detection. Thus, the cancer cells gain unlimited freedom to roam about, develop and that lead to fatal consequences (Yoshimura and Muto, 2010).

Bunimovich-Mendrazitsky et al, proposed the first mathematical model of bladder cancer immunotherapy using BCG (Bunimovich-Mendrazitsky et al., 2007). They later presented another model of bladder cancer with pulsed immunotherapy (Bunimovich-Mendrazitsky et al., 2008). In 2015, Svetlana Bunimovich-Mendrazitsky developed a new mathematical model for combined BCG and IL-2 bladder cancer treatment which introduces the effect of TAA T-cells (Bunimovich-Mendrazitsky et al., 2016).

Saad et al developed a mathematical model that studied the dynamics of immune checkpoints, immune system, and BCG in the treatment of superficial bladder cancer. They established the effects of immune checkpoints on the immune system and the treatment at large (Saad et al., 2017). Thalya et al investigated a mathematical model for the dynamics between tumor cells, immune cells, and the cytokine interleukin-2 (IL-2). They applied optimal control theory and determined the circumstances on how the tumor was eliminated (Thalya et al., 2004).

Pontryagin's maximum principle was used in (Elmouki and Saadi, 2016) to outline different resolutions of an optimal control problem in BCG immunotherapy of bladder cancer. Forward-backward sweep method and secant-method were used to numerically solve the two-point boundary value problem with an isoperimetric constraint on the control process function representing the optimal concentration suggested to use in each instillation of BCG. Meryem et al proposed a free final time optimal control approach applied to a model of tumor-immune interactions in the bladder after the injection of BCG of a hypothetical patient (Alkama et al., 2018). They found the optimal amount needed in each instillation of BCG for activating the immune cells to kill cancer cells. In addition, they determined the optimal duration of treatment required stop the therapy with minimum side effects.

The aim of this section is to adopt the model from chapter 1 and apply optimal control theory to find an optimal dosage (BCG dosage) required to minimize the actions of immune checkpoints on the immune system and cancer cells, while maximizing the number of effector and normal cells. We incorporate a compartment for normal cells (inside the bladder) into the model in order to relate the direct effect of continuous BCG instillation (side effects) on normal cells.

The chapter is organized as follows; section 3.1 is the introduction. In section 3.2, we reconstruct and explain the model. The analysis of the model without control is given in section 3.3. We present the necessary conditions for optimality of the control in section 3.4. In the last section we give the numerical simulations of the controlled system followed by conclusion and discussion.

3.2 Construction of the model

We construct a deterministic model using ordinary differential equations to describe the interaction between cancer cells, normal cells, immune checkpoints and BCG immunotherapy. In our model, C represents the concentration or population of cancer cells in the bladder, Ndenotes the collective population of normal cells, Brepresent the concentration of BCG injected into the bladder, Edenotes different arms of the immune system called effector cells, and P is the concentration or population of immune checkpoints. Our approach is similar to the work in (Kuznetsov et al., 1994; Kirschner and Panetta, 1998; De Pillis et al., 2005), despite the fact that their models were not on bladder cancer.

Thus, the model equations are given as follows:

$$\frac{dC}{dt} = r_1 C(1 - k_1 C) - \frac{\alpha_1 EC}{P + h} - \mu_1 NC$$

$$\frac{dN}{dt} = r_2 N(1 - k_2 N) - \mu_2 NC - \mu_8 NB - \mu_4 N$$

$$\frac{dB}{dt} = b - \alpha_4 EB - \mu_6 B \qquad (3.1)$$

$$\frac{dE}{dt} = \frac{a_1 CE}{P+h} + \frac{a_2 BE}{P+h} - \alpha_2 EC - \alpha_3 EB - \mu_5 E$$

$$\frac{dP}{dt} = \delta - \mu_7 P$$

$$C(0) = C_0 > 0, N(0) = N_0 > 0, E(0) = E_0 > 0, B(0) = B_0 > 0, \;\; P(0) = P_0 > 0.$$

The first equation in (3.1) describes the dynamics of cancer cells inside the bladder. The first term gives the growth of cancer cells which is considered to be logistic with intrinsic rate r_1 and carrying capacity $\frac{1}{k_1}$. The second term is the elimination of cancer cells by the effector cells at the rate α_1. This is believed to be disturbed by the immune checkpoints with $\frac{1}{P+h}$ to be the immunosuppressive term and$h$ being an inhibitory parameter. The third term gives the competition of space and nutrients between cancer and normal cells with normal cells wining at the rate μ_1.

The second equation gives the dynamics of normal cells with logistic growth where r_2 is the growth rate and carrying capacity $1/k_2$, $\mu_2 NC$ describe how the cancer cells win the competition with normal cells (by either killing, displacement for space and/or nutrients) at the rate μ_2. The BCG also affect the normal cells because of its toxicity and is given by $\mu_8 NB$. Lastly, the normal cells naturally die through apoptosis or other means at the rate μ_4.

The dynamics of BCG is given in the third equation; where b gives the constant and continuous infusion of the BCG inside the bladder, $\alpha_4 EB$, gives the elimination of BCG by effector cells at the rate α_4, and $\mu_6 B$ gives the degradation of the BCG at the rate μ_6.

The fourth equation describes the dynamics of the effector cells. The first term gives the recruitment of effector cells at the rate a_1 which is related to the population of cancer cells present, the immunosuppressive term $\frac{1}{P+h}$ is believed to be limiting the recruitment process, the second term describe the activation of the effector cells by the BCG which again is distorted and disturbed by the immune checkpoints with immunosuppressive term $\frac{1}{P+h}$. The term $\alpha_2 EC$, explains the elimination of effector cells by the cancer cells at the rate α_2, $\mu_9 EB$, gives the elimination of effector cells by the BCG at the rate μ_9, and lastly effector cells die naturally (through apoptosis) at the rate μ_5.

The fifth equation describes the dynamics and action of the immune checkpoints with δ being their source at constant rate and $\mu_7 P$ their natural degradation at the rate μ_7.
Similar analysis in chapter 1 reveals that the solutions of model (3.1) are all positive for any value of t.

3.3 Model without treatment ($b = 0$)

We use equations in (3.1) with $b = 0$ to obtain the model without treatment.

3.3.1 Equilibrium Analysis

Equating the right-hand side of the model without treatment to zero and solving simultaneously for C, N, B, E, and P gives the following steady states:

i)Immune checkpoints steady state: $U_1 = \left\{0,0,0,0,\frac{\delta}{\mu_7}\right\}$.

ii)Death steady state: $U_2 = \left\{\frac{1}{k_1},0,0,0,\frac{\delta}{\mu_7}\right\}$.

iii) Cancer free steady state: $U_3 = \left\{0,\frac{r_2-\mu_4}{r_2 k_2},0,0,\frac{\delta}{\mu_7}\right\}$.

iv) Dangerous steady state: $U_4 = \left\{\frac{-\mu_2 r_2+\mu_1\mu_4+r_1 r_2 k_2}{-\mu_1\mu_2+r_2 k_2 r_1 k_1},\frac{-r_1\mu_2+r_1 k_1 r_2-r_1 k_1\mu_4}{-\mu_1\mu_2+r_2 k_2 r_1 k_1},0,0,\frac{\delta}{\mu_7}\right\}$.

v) Normal cells and BCG free steady state:

$$U_5 = \left\{\frac{\mu_5(\delta+h\mu_7)}{a_1\mu_7-\alpha_2\delta-\alpha_2 h\mu_7},0,0,\frac{(\delta+h\mu_7)[(\delta+h\mu_7)(\alpha_2+k_1\mu_5)-a_1\mu_7]}{(-a_1\mu_7+\alpha_2\delta+\alpha_2 h\mu_7)},\frac{\delta}{\mu_7}\right\}.$$

vi) BCG free steady state:

$$U_6 = \left\{ \frac{\mu_5(\delta + h\mu_7)}{a_1\mu_7 - \alpha_2\delta - \alpha_2 h\mu_7}, \frac{\begin{matrix}(\delta + h\mu_7)[\mu_2\mu_5 + \alpha_2(r_2 - \mu_4)] \\ +a_1\mu_7(\mu_4 - r_2)\end{matrix}}{r_2k_2(-a_1\mu_7 + \alpha_2\delta + \alpha_2 h\mu_7)}, 0, E^*, \frac{\delta}{\mu_7} \right\}.$$

Due to the positivity of solutions of the model, we have the following remarks:

a. The steady statesU_1 and U_3 always exists.

b. The steady stateU_2 exists only if

$$R_1 = \frac{r_2}{\mu_4} > 1.$$

c. The steady stateU_4 exists if

$$R_2 = \frac{a_1\mu_7}{\alpha_2(\delta + h\mu_7)} > 1 \; and \; R_3 = R_2\frac{\alpha_2}{(\alpha_2 + k_1\mu_5)} > 1.$$

d. The steady stateU_5 exists if

$$R_4 = \frac{k_1 r_2}{\mu_2 + k_1\mu_4} > 1, \qquad R_5 = \frac{r_2k_2r_1k_1}{\mu_1\mu_2} > 1, \;\; and \;\; R_6 = \frac{\mu_1\mu_4 + r_2k_2r_1}{\mu_1 r_2} > 1\,.$$

e. The steady statesU_6 exists if

$$R_2 > 1 \;\; and \;\; R_7 = \frac{\alpha_2\mu_4}{\mu_5\mu_2 + \alpha_2 r_2} > 1.$$

The steady state U_2 is considered "death equilibrium because the normal cells go to extinction. The patient is considered dead if such a situation happens.

3.3.2 Local stability Analysis of steady states

Theorem 3.1. The steady state U_1 is always unstable.

Proof: From system (3.1), the Jacobian matrix evaluated at the points C^*, N^*, B^*E^*, and P^* is given by:

$$J\left(C^*, N^*, B^*, E^*, P^*\right)`$$

$$= \begin{bmatrix} r_1 - 2r_1k_1C^* - \frac{\alpha_1E^*}{P^*+h} - \mu_1N^* & -\mu_1C^* & 0 & -\frac{\alpha_1C^*}{P^*+h} & -\frac{\alpha_1E^*C^*}{(P^*+h)^2} \\ -\mu_2N^* & r_2 - 2r_2k_2N^* - \mu_2C^* - \mu_4 - \mu_8B^* & -\mu_8B^* & 0 & 0 \\ 0 & 0 & E^* - \mu_6 & -\alpha_4B^* & 0 \\ \frac{a_1E^*}{P^*+h} - \alpha_2E^* & 0 & \frac{a_2E^*}{P^*+h} - \mu_9E^* & \frac{a_1C^*}{P^*+h} + \frac{a_2B^*}{P^*+h} - \alpha_2C^* - \mu_5 - \mu_9B^* & -\frac{a_1E^*C^*}{(P^*+h)^2} - \frac{a_2E^*B^*}{(P^*+h)^2} \\ 0 & 0 & 0 & 0 & -\mu_7 \end{bmatrix}$$

Therefore, evaluating J at U_1 yields;

$$J(U_1)=\begin{bmatrix} r_1 & 0 & 0 & 0 & 0 \\ 0 & r_2-\mu_4 & 0 & 0 & 0 \\ 0 & 0 & -\mu_6 & 0 & 0 \\ 0 & 0 & 0 & -\mu_5 & 0 \\ 0 & 0 & 0 & 0 & -\mu_7 \end{bmatrix}$$

The eigenvalues of $J(U_1)$ are as follows:

$\lambda_1 = r_1,\ \ \lambda_2 = r_2-\mu_4,\ \ \lambda_3 = -\mu_6,\ \ \lambda_4 = -\mu_5,$ and $\lambda_5 = -\mu_7$. Observe that one of the eigenvalues $(\lambda_1)$is always positive. Hence, the steady stateU_1 is always unstable. Medically, this is an unwanted steady state because it implies that the patient is dead.

Theorem 3.2. The steady stateU_2 is asymptotically stable if $R_1 > 1$ and $R_6 < 1$.

Proof: Evaluating the Jacobian matrix at U_2 gives

$$J(U_1)=\begin{bmatrix} r_1-\dfrac{\mu_1(r_2-\mu_4)}{r_2k_2} & 0 & 0 & 0 & 0 \\ -\dfrac{\mu_2(r_2-\mu_4)}{r_2k_2} & -r_2+\mu_4 & -\dfrac{\mu_8(r_2-\mu_4)}{r_2k_2} & 0 & 0 \\ 0 & 0 & -\mu_6 & 0 & 0 \\ 0 & 0 & 0 & -\mu_5 & 0 \\ 0 & 0 & 0 & 0 & -\mu_7 \end{bmatrix}$$

The following are the eigenvalues of matrix$J(U_1)$:

$$\lambda_1 = \frac{\mu_1\mu_4 + r_2k_2r_1 - \mu_1r_2}{r_2k_2},\ \lambda_2 = -r_2+\mu_4,\ \lambda_3 = -\mu_6,\ \lambda_4 = -\mu_5,\ \text{and}\ \lambda_5 = -\mu_7.$$

We can see that $\lambda_1 = \dfrac{\mu_1\mu_4 + r_2k_2r_1 - \mu_1r_2}{r_2k_2} < 0$ if and only if $\mu_1\mu_4 + r_2k_2r_1 < \mu_1r_2$. This implies that,

$$\frac{\mu_1\mu_4 + r_2k_2r_1}{\mu_1r_2} < 1.$$

Therefore, $\lambda_1 < 0$ if and only if $R_6 = \frac{\mu_1\mu_4+r_2k_2r_1}{\mu_1r_2} < 1$. Similarly, $\lambda_2 < 0$ if and only $R_1 = \frac{r_2}{\mu_4} > 1$. The proof is complete.

Theorem 3.3: The steady stateU_3 is a asymptotically stable if $R_3 < 1$ and $R_4 < 1$.

Theorem 3.4: The steady state is U_4asymptotically stable if $R_2 > 1$ and $R_6 < 1$.

Theorem 3.5: The steady state U_5 is a stable fixed point if $R_2 < 1,\ R_7 < 1$.

The proofs of the following theorems are similar to the proof of theorem 3.2.

Hence, the conditions for the stability of the steady states are established. Now, we state our optimal control problem.

3.4 Optimal Control

Recall that, a real optimal control problem needs a cost functional or performance index $(J[x(t), u(t)])$, set of state variables $(x(t) \in X)$, and a set of control variables $(u(t) \in U)$ with $t_0 \leq t \leq t_f$. The aim is to find a piecewise continuous function $u(t)$ (control) and the related state variable $x(t)$ that will maximize a given objective function. Moreover, the basic optimal control problem in Lagrange formulation is of the form

$$\max_{u} \qquad J[x(t), u(t)] = \int_{t_0}^{t_f} g\big(t, x(t), u(t)\big)dt$$

$$\textbf{\textit{subject to}} \quad \dot{x}(t) = f\big(t, x(t), u(t)\big)$$

$$x(0) = x_0,$$

where $x(t_f)$ could be free or fixed viz. $x\big(t_f\big) = x_f$, and f and g are always continuously differentiable. The control set U is assumed to be a piecewise continuous function. We can interchange between maximization and minimization by simply negating the objective functional, that is:

$$\min\{ J \} = -\max\{ -J \}.$$

The generalization of the calculus of variations to optimal control theory was developed massively since 1950. The major breakthrough was accomplished by Lev S. Pontryagin (1908-1988)and his co-workers (V. G. Boltyanskii, R. V. Gamkrelidz and E. F. Misshchenko) with the expression and presentation of the Pontryagin Maximum Principle (Pontryagin et al., 1962). This principle has catered for many researches with desirable conditions and strategies for optimization problems with differential equations as constraints.

In this section, we incorporate a control function $u(t)$ in the form of injection, representing an external source of BCG. For model (3.1), we now seek for a control that will minimize the

number of cancer cells, maximize the number of effector and normal cells, minimize the action of immune checkpoints, and minimize the total BCG injection/cost of control.

The controlled system is given by

$$\frac{dC}{dt} = r_1 C(1 - k_1 C) - \frac{\alpha_1 EC}{P + h} - \mu_1 NC$$

$$\frac{dN}{dt} = r_2 N(1 - k_2 N) - \mu_2 NC - \mu_4 N - \mu_8 BN$$

$$\frac{dB}{dt} = su(t) - \alpha_4 EB - \mu_6 B \qquad (3.2)$$

$$\frac{dE}{dt} = \frac{a_1 CE}{P+h} + \frac{a_2 EB}{P+h} - \alpha_2 EC - \mu_5 E - \mu_9 EB$$

$$\frac{dP}{dt} = \delta - \mu_7 P$$

with initial conditions: $C(0) = C_0$, $N(0) = N_0$, $E(0) = E_0$, $B(0) = B_0$, $P(0) = P_0$, u is the control function and s is the strength of the treatment. In general, the problem may be stated as follows:

$$\dot{X}_i(t) = f_i\left(\vec{X}(t), u(t)\right)$$

$$\vec{X}(0) = \vec{X}_0$$

where $\vec{X} = \begin{pmatrix} C \\ N \\ E \\ B \\ P \end{pmatrix}$ and $u(t)$ is the control function bounded as follows; $a < u(t) < b$. The objective functional J in Bolza form is usually given by

$$J = \emptyset\left(\vec{X}(t_f)\right) + \int_{t_0}^{t_f} g\left(\vec{X}(t), u(t)\right) dt$$

where $t_f = T$ is the given final time, g is the objective value of each stage (Lagrangian) and $\emptyset$ is the performance index at the end of the procedure.

As a result, the objective functional to be minimized for our problem is given by;

$$J = \omega_1 C(T) - \omega_2 N(T) + \int_0^T \left(P(t) + C(t) + \frac{1}{2} Du(t)^2 - E(t) - N(t)\right) dt,$$

where D is a weight factor that represents the patient's level of acceptance of BCG treatment. A quadratic control $\frac{1}{2}Du(t)^2$ is used for convenience in finding an analytic representation of the control $u \in U$ and

$$U = \{u(t): \lambda_1 \leq u(t) \leq \lambda_2,\ \ u\ is\ a\ piecewise\ continuous\ function,\ \ t \in [0,T]\},$$

where $\lambda_1 = 3.14 \times 10^5\ c.f.u\ (colony\ forming\ unit)$ and $\lambda_2 = 9.14 \times 10^5\ c.f.u$ are the values found to bound the BCG optimal dose (Elmouki and Saadi, 2016; Alkama et al., 2018; Elmouki and Saadi, 2016).

Now, we show that an optimal control u^* for system (3.2) actually exists. To establish that, we need to show that system (3.2) is bounded for finite time (Fleming and Rishel, 1975). We proceed by finding solutions that are upper bounds (supersolutions) of $C, N, B, E, and\ P$ in model (3.2).

Consider first the last equation of (3.2). Let P_{max} serve as upper bound solution associated with P and given that $P(t) \geq 0$ for all $t \in [0,T]$. Then,

$$\frac{dP_{max}}{dt} = \delta, implying\ that\ P_{max} = \delta T + P_0.$$

Assume C_{max} as an upper bound solution associated with C in (2). Given $C(t) \geq 0$, $N(t) \geq 0$, and $E(t) \geq 0$, then

$$\frac{dC_{max}}{dt} = r_1 C \ \rightarrow\ C_{max} = C_0 e^{r_1 T}.$$

Similar analysis implies that $N_{max} = N_0 e^{r_2 T}$, $B_{max} = B_0 + sT$, and $E_{max} = C_0 e^{HT}$, where H depends on C_{max}, B_{max}, and P_{max}.

By using the bounds, we can form a set of upper bound solutions for system (3.2). Denoting these upper solutions by $\bar{C}, \bar{N}, \bar{B}, \bar{E}$, and $\bar{P}$, we have the following system:

$$\frac{d\bar{C}}{dt} = r_1 \bar{C}$$

$$\frac{d\bar{N}}{dt} = r_2 \bar{N}$$

$$\frac{d\bar{B}}{dt} = s\lambda_2 \qquad (3.3)$$

$$\frac{d\bar{E}}{dt} = \frac{a_1 \bar{E} C_{max}}{P_{max}+h} + \frac{a_2 \bar{E} B_{max}}{P_{max}+h}$$

$$\frac{d\bar{P}}{dt} = \delta$$

that is bounded on a finite time interval. Then we can write system (3.3) as

$$\begin{pmatrix} \bar{C} \\ \bar{N} \\ \bar{B} \\ \bar{E} \\ \bar{P} \end{pmatrix}' = \begin{pmatrix} r_1 & 0 & 0 & 0 & 0 \\ 0 & r_2 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{a_1 C_{\max}}{P_{\max}+h} + \frac{a_1 C_{\max}}{P_{\max}+h} & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} \overline{C} \\ \overline{N} \\ \overline{B} \\ \overline{E} \\ \overline{P} \end{pmatrix} + \begin{pmatrix} 0 \\ 0 \\ s\lambda_2 \\ 0 \\ \delta \end{pmatrix}.$$

Observe that this is a linear system in finite time with bounded coefficients, therefore, the supersolutions $\bar{C}, \bar{N}, \bar{B}, \bar{E}$, and $\bar{P}$ are uniformly bounded. Hence, our original system is ultimately bounded. We can now prove that an optimal control exists.

3.4.1 Necessary Conditions for Optimality

Theorem 3.6. Given the objective functional

$$J = \omega_1 C(T) - \omega_2 N(T) + \int_0^T \left(P(t) + C(t) + \frac{1}{2} B u(t)^2 - E(t) - N(t) \right) dt,$$

where $U = \{u(t): \lambda_1 \leq u(t) \leq \lambda_2,\ u\ is\ lebesgue\ measurable,\ t \in [0,T]\}$, subject to system (3) with $C(0) = C_0$, $N(0) = N_0$, $B(0) = B_0$, $E(0) = E_0$, and $P(0) = P_0$; then there exists an optimal control u^* such that,

$$\min_{\lambda_1 \leq u \leq \lambda_2} J(u) = J(u^*)$$

if the following conditions are satisfied

i) The class of all initial conditions with a control u in the admissible control set along with each state equation being satisfied is not empty.

ii) The admissible control set U is closed and convex.

iii) Each right hand side of the equations in system (3.2) is continouous, bounded above by the sum of the bounded control and the state, and can be written as a linear function of u with coefficients depending on time and state.

iv) The integrand of $J(u)$ is convex on U and is bounded below by $-c_2 + c_1 u^2$ with $c_1 > 0$.

Proof. Because system (3.2) possesses bounded coefficients and the solutions are bounded on the finite time interval, we can apply a result from (Lukes, 1982) to obtain the existence of solution of system (3.2).

Note that by definition U is closed and convex which prove (ii). For the third condition, the right hand side of system (3.2) is continouous since the denominators of each of the equations of the system is nonzero.

Let $\vec{\varphi}(t,\vec{X})$ be the right hand side of system (2) except for the terms of u and define

$$f(t,\vec{X},u) = \vec{\varphi}(t,\vec{X}) + su,$$

where $\vec{X} = \begin{pmatrix} C \\ N \\ E \\ B \\ P \end{pmatrix}$ and $\vec{\varphi}$ is a vector valued function of $\vec{X}$.

Using the boundedness of the solutions, we see that

$$|f(t,\vec{X},u)| \leq \left| \begin{pmatrix} r_1 & 0 & 0 & 0 & 0 \\ 0 & r_2 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{a_1 C_{\max}}{P_{\max}+h} + \frac{a_2 B_{\max}}{P_{\max}+h} & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} C \\ N \\ B \\ E \\ P \end{pmatrix} \right| + \left| \begin{matrix} 0 \\ 0 \\ su \\ 0 \\ \delta \end{matrix} \right| \leq C_1(|\vec{X}| + s|u|),$$

$$|f(t,\vec{X},u)| \leq C_1|\vec{X}| + s|u|$$

where C_1 is dependent on the coefficients on the system. This implies condition (iii).

We now prove (iv). The integrand of $J(u)$ is given by

$$P(t) + C(t) + \frac{1}{2}Du(t)^2 - E(t) - N(t) = g(t,C,N,E,P,u).$$

We need to show g is convex on U. Let u_1, $u_2 \in U$, and $\rho \in (0,1)$. Then, we have to establish

$$g(t,C,N,E,P,(1-\rho)u_1 + \rho u_2)$$
$$\leq (1-\rho)g(t,C,N,E,P,u_1) + \rho g(t,C,N,E,P,u_2).$$

Evaluating the difference we get,

$$g(t,C,N,E,P,(1-\rho)u_1 + \rho u_2) - \big((1-\rho)g(t,C,N,E,P,u_1)\big)$$
$$+\rho g(t,C,N,E,P,u_2) = \tfrac{D}{2}(\rho^2 - \rho)(u_1 - u_2)^2 \leq 0. \qquad (3.4)$$

Equation (3.4) is true because $\rho^2 - \rho < 0$ since $\rho \in (0,1)$ and $(u_1 - u_2)^2 > 0$ implying that,

$$(\rho^2 - \rho)(u_1 - u_2)^2 < 0.$$

Therefore,

$$g(t, C, N, E, P, (1-\rho)u_1 + \rho u_2)$$
$$\leq (1-\rho)g(t, C, N, E, P, u_1) + \rho g(t, C, N, E, P, u_2),$$

from (3.4).

Thence g is convex.Finally, from the integrand of $J(u)$, we've;

$$P(t) + C(t) + \frac{1}{2}Du(t)^2 - E(t) - N(t) \geq -E(t) - N(t) + \frac{1}{2}Du(t)^2$$
$$\geq -C_2 + C_1|u(t)|^2,$$

where $C_1 = \frac{D}{2}$ and C_2 are dependent on the lower bound on E and N. The proof is now complete. This implies that an optimal control u^* exists.

Since an optimal control exist that will minimize the objective functional $J(u)$ subject to system (3.2), we then use a version of Pontryagin's maximum principle to characterize the optimal control.

3.4.2 Characterization of Optimal control

Theorem 3.7. Given an optimal control u^* and solutions of the corresponding state system, there exist adjoint variables σ_i, $i = 1, 2, 3, 4, 5$, that satisfy the following

$$\frac{d\sigma_1}{dt} = \left(-1 - \sigma_1\left(r_1 - 2r_1k_1C - \frac{\alpha_1 E}{P+h} - \mu_1 N\right) + \sigma_2\mu_2 N - \sigma_4\left(\frac{a_1 E}{P+h} - \alpha_1 E\right)\right),$$
$$\frac{d\sigma_2}{dt} = \left(1 + \sigma_1\mu_1 C - \sigma_2(r_2 - 2r_2k_2N - \mu_2 C - \mu_4 - \mu_8 B)\right),$$
$$\frac{d\sigma_3}{dt} = \left(\sigma_2\mu_8 N - \sigma_3(-\alpha_4 E - \mu_6) - \sigma_4\left(\frac{a_1 E}{P+h} - \mu_9 E\right)\right),$$
$$\frac{d\sigma_4}{dt} = \left(1 + \frac{\sigma_1\alpha_1 C}{P+h} + \sigma_3\alpha_4 B - \sigma_4\left(\frac{a_1 C}{P+h} + \frac{a_2 B}{P+h} - \alpha_2 C - \mu_5 - \mu_9 B\right)\right),$$
$$\frac{d\sigma_5}{dt} = \left(-1 - \frac{\sigma_1\alpha_1 EC}{(P+h)^2} + \frac{\sigma_4 a_1 EC}{(P+h)^2} + \sigma_5\mu_5\right),$$

where $\sigma_1(T) = \omega_1, \sigma_2(T) = -\omega_2, \sigma_3(T) = 0, \sigma_4(T) = 0$, and $\sigma_5(T) = 0$. In addition, u^* is represented by

$$u^*(t) = min\left(max\left(-\frac{s\sigma_3(t)}{D}, \lambda_1\right), \lambda_2\right).$$

Proof. Given the existence of the control, we can now use a version of Pontryagin's maximum principle to derive necessary conditions for the optimal control (Kamien and Schwartz, 1991). Define the Lagrangian as

$$L(C, N, B, E, P, \sigma_1, \sigma_2, \sigma_3, \sigma_4, \sigma_5) = H + \theta_2(u - \lambda_1) + \theta_1(\lambda_2 - u)$$

where $\theta_1, \theta_2 \geq 0$ are penalty multipliers satisfying:$\theta_1(\lambda_2 - u^*) = 0$ and $\theta_2(u^* - \lambda_1) = 0$, and H is the Hamiltonian given by

$$H = P(t) + C(t) + \frac{1}{2}Du(t)^2 - E(t) - N(t) + \sigma_1(\dot{C}) + \sigma_2(\dot{N}) + \sigma_3(\dot{B}) + \sigma_4(\dot{E})$$
$$+\sigma_5(\dot{P})$$
$$= P(t) + C(t) + \frac{1}{2}Du(t)^2 - E(t) - N(t) + \sigma_1\left(r_1C(1 - k_1C) - \frac{\alpha_1EC}{P + h} - \mu_1NC\right)$$
$$+\sigma_2(r_2N(1 - k_2N) - \mu_2NC - \mu_4N - \mu_8BN) + \sigma_3(su - \alpha_4EB - \mu_6B)$$
$$+\sigma_4\left(\frac{a_1CE}{P + h} + \frac{a_2EB}{P + h} - \alpha_2EC - \mu_5E - \mu_9EB\right) + \sigma_5(\delta - \mu_7P).$$

Therefore,

$$L = P(t) + C(t) + \frac{1}{2}Bu(t)^2 - E(t) - N(t) + \sigma_1\left(r_1C(1 - k_1C) - \frac{\alpha_1EC}{P + h} - \mu_1NC\right)$$
$$+\sigma_2(r_2N(1 - k_2N) - \mu_2NC - \mu_4N - \mu_8BN) + \sigma_3(su - \alpha_4EB - \mu_6B)$$
$$+\sigma_4\left(\frac{a_1CE}{P + h} + \frac{a_2EB}{P + h} - \alpha_2EC - \mu_5E - \mu_9EB\right) + \sigma_5(\delta - \mu_7P) + \theta_1(\lambda_2 - u)$$
$$+\theta_2(u - \lambda_1).$$

Calculation of the adjoint system variables from the Lagrangian is as follows:

$$\frac{d\sigma_1}{dt} = -\frac{\partial L}{\partial C} = -\left(1 + \sigma_1\left(r_1 - 2r_1k_1C - \frac{\alpha_1E}{P + h} - \mu_1N\right) - \sigma_2\mu_2N\right)$$
$$-\sigma_4\left(\frac{a_1E}{P + h} - \alpha_1E\right)$$
$$\frac{d\sigma_2}{dt} = -\frac{\partial L}{\partial N} = \left(1 + \sigma_1\mu_1C - \sigma_2(r_2 - 2r_2k_2N - \mu_2C - \mu_4 - \mu_8B)\right)$$
$$\frac{d\sigma_3}{dt} = -\frac{\partial L}{\partial B} = \left(\sigma_2\mu_8N - \sigma_3(-\alpha_4E - \mu_6) - \sigma_4\left(\frac{a_1E}{P + h} - \mu_9E\right)\right)$$
$$\frac{d\sigma_4}{dt} = -\frac{\partial L}{\partial E} = \left(1 + \frac{\sigma_1\alpha_1C}{P + h} + \sigma_3\alpha_4B - \sigma_4\left(\frac{a_1C}{P + h} + \frac{a_2B}{P + h} - \alpha_2C - \mu_5 - \mu_9B\right)\right)$$

$$\frac{d\sigma_5}{dt} = -\frac{\partial L}{\partial P} = \left(-1 - \frac{\sigma_1 \alpha_1 EC}{(P+h)^2} + \frac{\sigma_4 a_1 EC}{(P+h)^2} + \sigma_5 \mu_5\right)$$

where the adjoint vector $\sigma = \begin{pmatrix} \sigma_1(t) \\ \sigma_2(t) \\ \sigma_3(t) \\ \sigma_4(t) \\ \sigma_5(t) \end{pmatrix} \in \Re^5$, defines the vector solution of the system above with transversality conditions in the time T; $\sigma_1(T) = \omega_1, \sigma_2(T) = \omega_2, \sigma_3(T) = 0, \sigma_4(T) = 0,$ and $\sigma_5(T) = 0$.

The minimization problem J is equivalent to the following minimization condition

$$L\left(t, \vec{X}^*, \sigma(t), u^*(t), \theta_1(t), \theta_2(t)\right) = min_{u \in U} L(t, \vec{X}, \sigma(t), u(t), \theta_1(t), \theta_2(t)).$$

To complete the representation ofu^*, we get the optimality equation by differentiating the Lagrangian L with respect to$u$ on the set U.

Thus,

$$\frac{\partial L}{\partial u} = Du + s\sigma_3 - \theta_1 + \theta_2. \qquad (3.5)$$

Equating (3.5) to zero to obtain u^* we have,

$$Du^* + s\sigma_3 - \theta_1 + \theta_2 = 0.$$

This implies that

$$u^*(t) = -\frac{s\sigma_3(t) - \theta_1 + \theta_2}{D} \qquad (3.6)$$

We now analyze (3.6).

If $\lambda_1 < u^* < \lambda_2$, then $\theta_1 = \theta_2 = 0$; so,

$$u^*(t) = -\frac{s\sigma_3(t)}{D}.$$

If $\lambda_1 = u^*$, then $\theta_1(t) = 0$; therefore,

$$\lambda_1 = -\frac{(s\sigma_3(t) + \theta_2)}{D} \leftrightarrow \theta_2(t) = -(\lambda_1 D + s\sigma_3).$$

Since $\theta_2(t) \geq 0$ and $D > 0$, we obtain

$$u^*(t) \leq -\frac{s\sigma_3(t)}{D}.$$

If $\lambda_2 = u^*(t)$, then $\theta_2(t) = 0$; thus,

$$\lambda_2 = \frac{-s\sigma_3(t) - \theta_1}{D} \leftrightarrow \theta_1(t) = \lambda_2 D + s\sigma_3.$$

Since $\theta_1(t) \geq 0$ and $D > 0$, we get

$$u^*(t) \geq -\frac{s\sigma_3(t)}{D}.$$

Using these standard optimality arguments, we characterize the control $u^*(t)$ by

$$u^*(t) = \begin{cases} -\frac{s\sigma_3(t)}{D}, & if \ \lambda_1 < -\frac{s\sigma_3(t)}{D} < \lambda_2 \\ \lambda_1, & if \ -\frac{s\sigma_3(t)}{D} \leq \lambda_1 \\ \lambda_2, & if \ -\frac{s\sigma_3(t)}{D} \geq \lambda_2 \end{cases}$$

or in compact form,

$$u^*(t) = min\left(max\left(-\frac{s\sigma_3(t)}{D}, \lambda_1\right), \lambda_2\right).$$

We can also observe that the second derivative of the Lagrangian with respect to u is D and it is positive, thus, a minimum occurs at u^*.

3.5 Numerical Simulations

In this section, we present the numerical simulations of system (3.2) (controlled system) to reconnoiter the possible action of the optimal control of the system. We use MATLAB version 2017b to portray the Figures (3.1 to 3.7) of the numerical solutions of the controlled system with parameter values from Table 1 used. They are obtained from (Saad et al., 2017; Thalya et al., 2004; Bunimovich-Mendrazitsky et al., 2007).

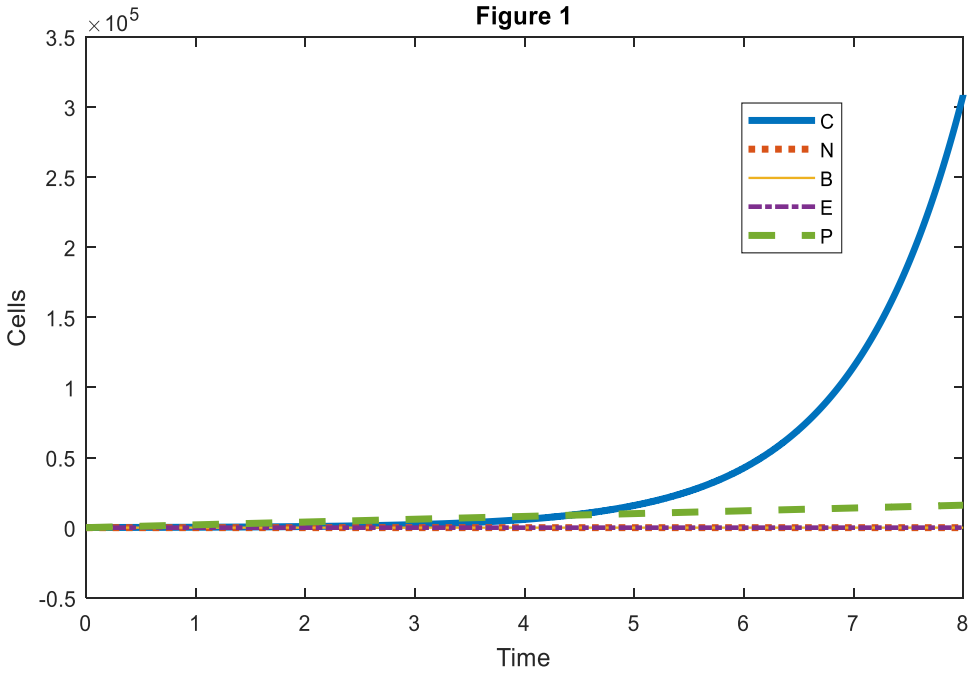

Figure 3.1: Description of model (3.2) (without control).

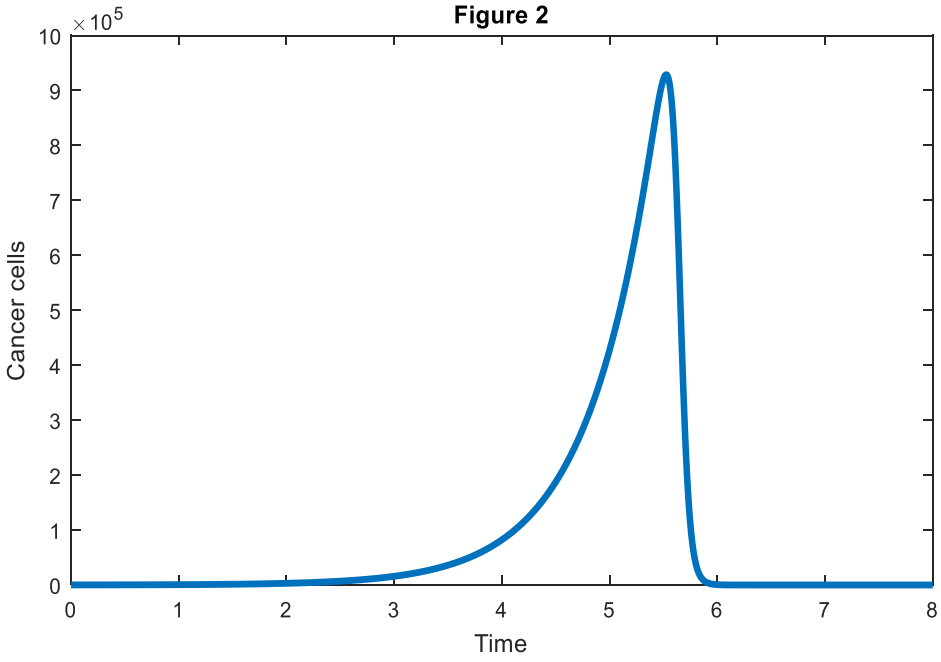

Figure 3.2: Cancer cells with control

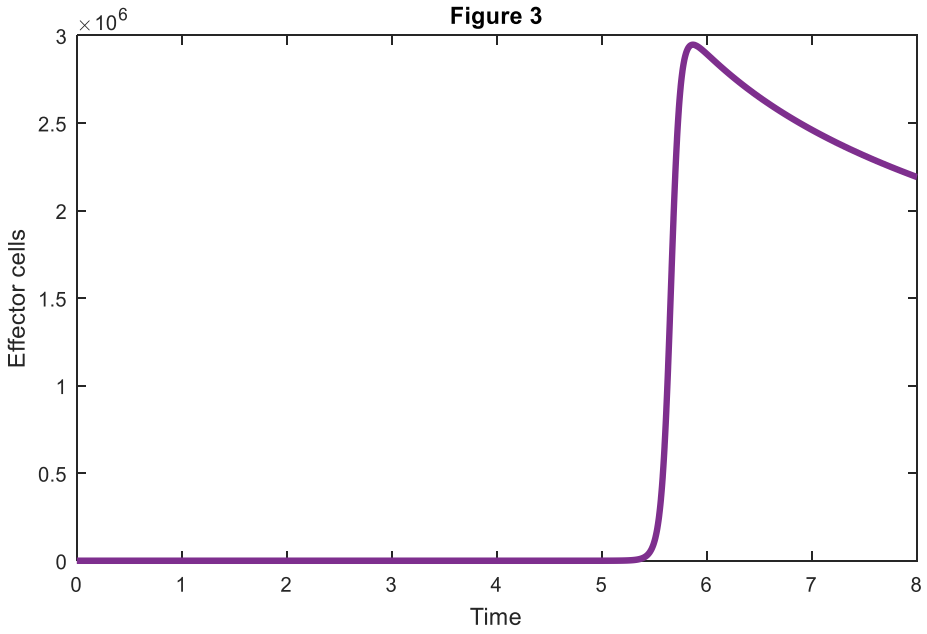

Figure 3.3: Effector cells with control

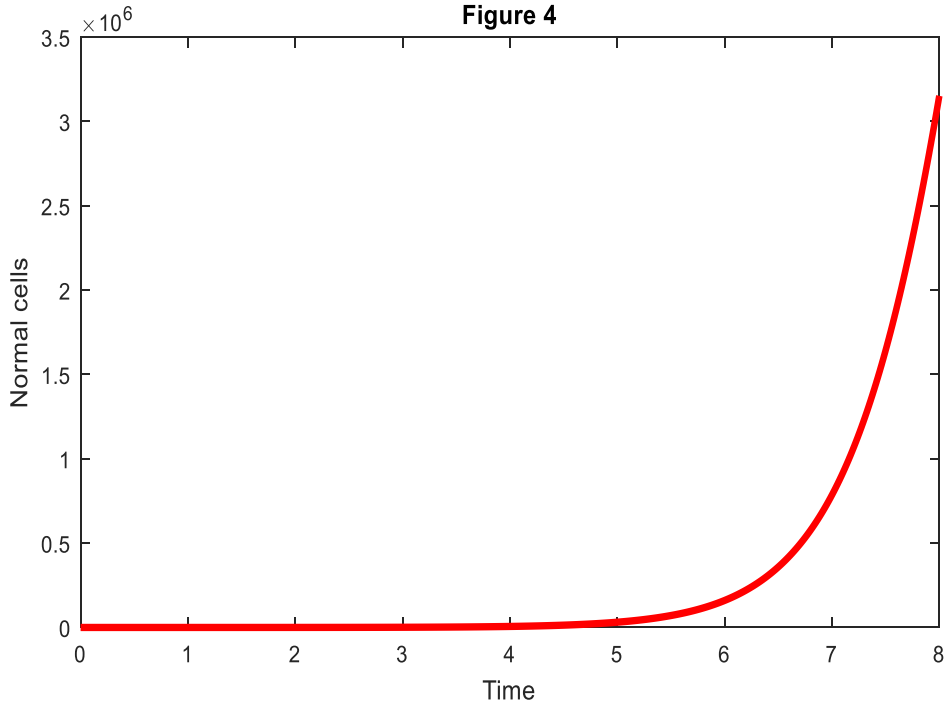

Figure 3.4: Normal cells with control

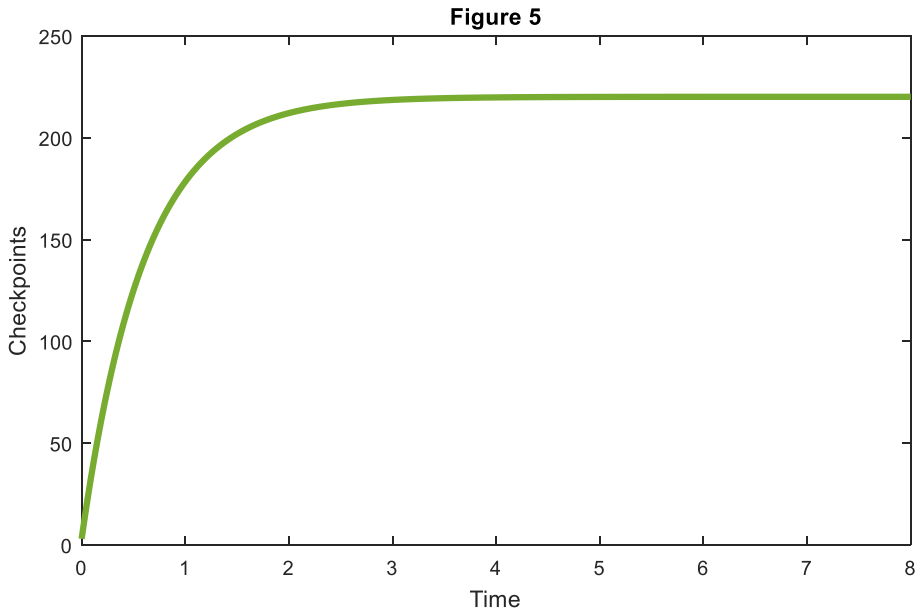

Figure 3.5: Checkpoints with control

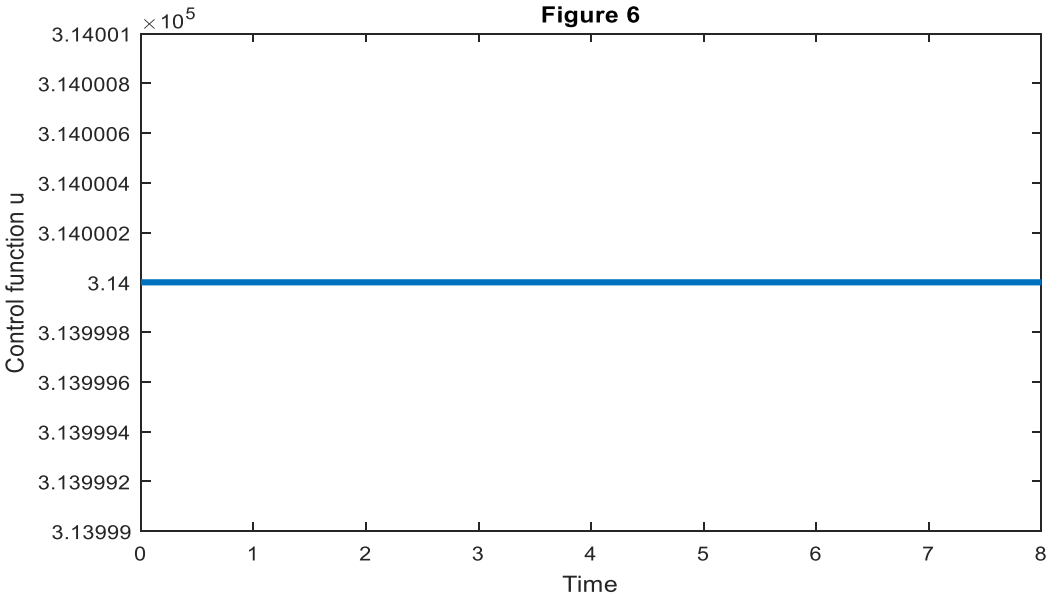

Figure 3.6: Control function

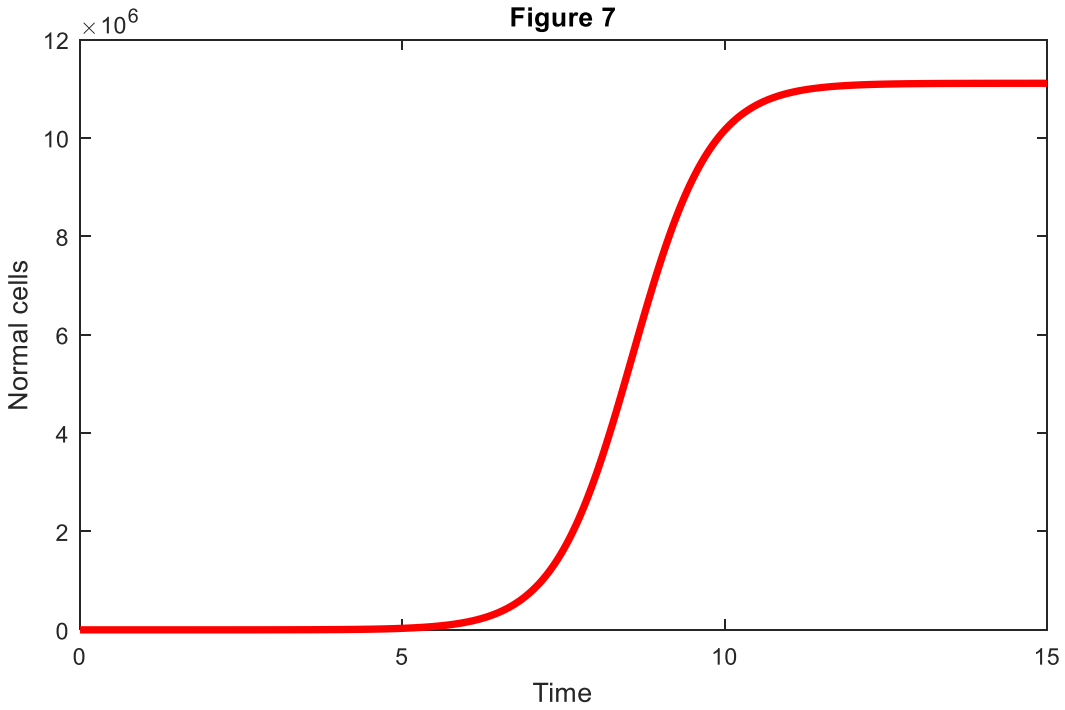

Figure 3.7: Normal cells maintaining a threshold.

From Figure 3.1, we can observe that the cancer cells keep growing in the absence of the control. The effector cells vanish as well. This is believed to be as a result of the action of immune checkpoints on the immune system. Additionally, the normal cells are also eliminated in the absence of control. Thus, the cancer cells and the immune checkpoints obviously win the battle in the absence of control and this is supported by Figure 3.1.

Figure 3.2, 3.3, 3.4, and 3.5 give the graphs of cancer cells, effector cells, normal cells and immune checkpoints respectively when the control u is applied. We can discover that, the cancer cells are reduced and eventually eliminated, the effector cells stays at a higher level, the normal cells keep rising and maintain a threshold level, and the immune checkpoints are decreased to a relatively significant number. Therefore, this shows the effectiveness and use of the control.

The optimal control proposed an amount of the BCG $(u = 3.14 \times 10^5\ c.f.u)$that should be continuously administered throughout the period of treatment.

We can conclude that the optimal dose of $u = 3.14 \times 10^5\ c.f.u$ is enough to minimize the objective functional $J(u)$. In other words, the introduction of the control helps the effector cells to win the fight against cancer and eventually the checkpoints. More so, the immune

checkpoints are minimized in number as can be seen by observing their population in Figure 3.1 and 3.5. In Figure 3.7, the collective concentrations of normal cells maintain a threshold level and lastly, Figure3.6 describe the nature of the control function.

Table 3.1: Parameter values

Parameter	**Values and units**
r_1	0.0033 to 0.99 $\mathrm{t}^{-1} = \mathrm{day}^{-1}$
k_1	1.0×10^{-9} to $0.11 \times 10^{-7}\mathrm{cells}^{-1}$
μ_1	0.8 cell day^{-1}
α_1	1.1×10^{-7} to 0.1 cell day^{-1}
r_2	$0.055\mathrm{t}^{-1} = \mathrm{day}^{-1}$
k_2	$5.0 \times 10^{-12}\mathrm{cells}^{-1}$
μ_2	0.02 to 0.9 cell day^{-1}
μ_4	$0.5\ \mathrm{t}^{-1} = \mathrm{day}^{-1}$
μ_8	0.04 cell day^{-1}
α_4	$1.25 \times 10^{-7}\mathrm{cells}^{-1}\mathrm{day}^{-1}$
μ_6	$0.1\ \mathrm{t}^{-1} = \mathrm{day}^{-1}$
a_1	$0.25\ \mathrm{cells}^{-1}\mathrm{day}^{-1}$
a_2	$0.052\mathrm{cells}^{-1}\mathrm{day}^{-1}$
α_2	$3.45 \times 10^{-10}\mathrm{cells}^{-1}\mathrm{day}^{-1}$
μ_5	$0.041\mathrm{t}^{-1} = \mathrm{day}^{-1}$
μ_7	$166.32\mathrm{t}^{-1} = \mathrm{day}^{-1}$

Table 3.1 Continued

δ	1.51932×10^5
h	2×10^3

3.6 Discussion and Conclusion

We consider a mathematical model that studies the dynamics of immune checkpoints, immune system, normal cells, and BCG in the treatment of superficial bladder cancer. The model produced various equilibrium points. Existence and stability of the equilibria of the model without control was studied. We also presented the conditions for the stability of the equilibria. We verified from Figure 3.1 that, the cancer cells grow in the absence of control, whereas the effector cells, normal cells and the BCG all go to extinction. This is due to the action of the immune checkpoints; blocking/suppressing the immune system. Hence, the cancer cells will have unlimited freedom to proliferate, grow and metastasize.

After the introduction of the control, Figure 3.2 showed how the growth of the cancer cell was restricted, and thus, driven to zero. We also discovered in Figure 3.3 that, the effector cells overcame the suppression and blockage by the immune checkpoints when control was applied, thence, detect, spread, locate, and kill the cancer cells.

Figure 3.4 gave the dynamics of normal cells when the control is also applied. Unlike without the control, the normal cells rose up and stabilize to a threshold level. In Figure 3.5, the immune checkpoints were minimized compared to their population in Figure 3.1. This will eventually remove the majority of the brakes off the immune system in order to detect and kill cancer cells. So the control also helps in minimizing the action of the immune checkpoints on cancer cells.

In conclusion, we can say that, despite the pressure and threat posed by the immune checkpoints on the immune cells and the deadly nature of cancer cells, we were able obtain an optimal dose of BCG that is able to achieve our desired aim, that is, to minimize and eventually eliminate the cancer cells, minimize the action of immune checkpoints, maximize

the action of the immune system, and minimize the toxicity/side effects caused by the BCG and cancer cells on normal cells.

CHAPTER 4

OPTIMAL CONTROL APPLIED TO IMMUNE CHECKPOINT INHIBITORS AND BCG FOR SUPERFICIAL BLADDER CANCER MODEL

4.1 Introduction

In 1997 it was forecasted that 54,500 new incidences of bladder cancer will be diagnosed with 11,700 projected deaths occurring from the disease. Similarly, around 67,160 new cases would be discovered in 2007, and approximately 13,750 bladder cancer deaths will occur. The occurrence of bladder cancer in men is about 4 times higher than in women. It is also ranked among the top five cancers in men and the eight most usual in women. Incidence rate of bladder cancer has elevated to 36% in the USA from 1956 to 1990 and death rates have decreased to 8% from 1980 to 1995. Most of the bladder cancer diagnoses are urothelial carcinoma (90%), followed by squamous cell carcinoma (5%), and lastly adenocarcinoma (2%) (Pasin et al., 2008; Schenkman et al., 2004).

Intravesical Bacillus Calmette-Guerin (BCG) is defined as a live attenuated non-pathogenic strain of Mycobacterium bovis previously utilized as a vaccine against tuberculosis. However, it is recently a form of immunotherapy that is adopted to treat superficial bladder cancer. BCG instillation has been proved to be an effective and superior to any chemotherapeutic drug used in treating superficial bladder cancer. It is usually applied after surgery to avoid/halt tumor reoccurrences (Eric et al., 2012; Friberg, 1993).

A catheter is used to transfuse the BCG into the bladder via the urethra. The normal and cancer cells internalized the mycobacterium which results in inflammatory reactions and consequent urothelial activations inside the bladder (Moss and Kadmon, 1991). The BCG antigens then stimulate the CD4+ T cells (a type of immune cell) and induce a primary T helper type (Th) 1 immune response. In other words, the inflammation caused by the BCG will trigger an immediate immune response (Andius and Holmang, 2004). It is evident that the major function of BCG is to provoke/activate the immune system. Therefore, the immune cells outspread, uncover, fight, and kill the tumor (Redelman-Sidi et al., 2014).

Due to the fact that, the BCG is a live attenuated vaccine, it has but not limited to the following side effects; irritation in the bladder, fatigue, fever, flu-like symptoms, joint pain, difficulty during urination, dysuria, excessive pain, cystitis, and hematuria. These aforementioned side effects are partially because of the toxicity of BCG on the normal cells (Lamm et al., 1980).

Immune checkpoints are negative controllers of immune stimulation. They play a major role in preventing autoimmunity, preserving immune homeostasis, maintaining immune tolerance, and preventing body tissues from immune corroborative damage (Sharpe et al., 2007). In cancer, immune checkpoints are mainly activated to block an effective anti-cancer immune response.

Additionally, the tumors usually commandeer/hijack the immune checkpoints in order to restrain, resist, and escape a powerful attack from the immune system. In a nutshell, the immune checkpoints suppress, block, and stop the immune system to launch a powerful anti-tumor attack. Moreover, they also take over some of the immune checkpoint pathways as a means of bypassing detection and resisting immune attack. Therefore, the tumors continue to grow, develop and metastasize to other parts of the body from its primary source (Postow et al., 2015).

This development has given rise to the evolution of new categories of drugs called immune checkpoint inhibitors. They are responsible for blocking the activities of the immune checkpoints. The blockage is possible using antibodies because most of the immune checkpoints are originated by ligand-receptor association. Blocking the immune checkpoints will then enhance effective antitumor response because the brakes (checkpoints) are taken off the immune system. Some of these drugs are recognized and accepted by the U.S. Food and Drug Administration (FDA) while some are presently under clinical trials (Pardoll, 2012).

The first immune-checkpoint receptor to be aimed clinically is CTLA4; it is expressed entirely on T cells where it mainly controls the magnitude of initial phase of T cell activation. In general, CTLA4 comprehensively regulates activation of T cell. Ipilimumab and tremelimumab are the antibodies (checkpoint inhibitors) that were approved by the FDA in order to block the activities of CTLA4in patients with melanoma (Rudd et al., 2009).

PD-1 is another immune-checkpoint receptor that is emanating as an encouraging target. When an infection (in the body) is detected, the PD-1 will limit the actions of the T cells from launching an inflammatory response. Moreover, it also restricts autoimmunity. Thus, PD-1 generally regulates the actions of the effector T cell in tissues and tumors. Nivolumab is an antibody (checkpoint inhibitor) currently approved by the FDA. It is used in targeting the activities of PD-1 in cancer treatment. This will allow the activation of T cells and cell mediated responses against the tumors (Phan et al., 2003).

The standard treatment for metastatic urothelial carcinoma has been chemotherapy for the past two decades. However, recent researches revealing better understanding of tumor-immune interaction led to the discovery of immune-checkpoint inhibitors. They also serve as alternative for bladder cancer patients that are unsound for standard chemotherapy due to their safety profile (Massari et al., 2018). Thus, immunotherapy of cancer using immune checkpoint inhibitors has become promising and exciting, there by developing quickly in the field of cancer management. In particular, it has a high response rate and survival benefits in urothelial carcinoma of the bladder (Bidnur et al., 2016; Massard et al., 2016).

Atezolizumab is a humanized Ig (immunoglobulin) G1 monoclonal antibody that suppresses the action of PD-1. It was the first immune checkpoint inhibitor that demonstrated clinical activity in urothelial carcinoma of the bladder. The results lead to the approval of Atezolizumab (by the FDA) for treating metastatic urothelial carcinoma patients whose situation has deteriorated within a year of adjuvant platinum-based chemotherapy (Powles et al., 2014; Plimack et al., 2017).

It is well known that cancer cells are generally clever, strong and good at escaping immune attack (immune resistance). At times, treatment using checkpoint inhibitors only is not sufficient in combatting the disease. Therefore, combination therapies with immune checkpoint inhibitors and other agents, radiotherapy, chemotherapy, other immune agents and different checkpoint inhibitors are suggested or tested in order to overcome the resistance by the cancer cells. This led to an interesting strategy of combination therapy that is aimed to strengthen the potency of checkpoint inhibitors. The combination of Bacillus Calmette Guerin (BCG), Pembrolizumab, and Atezolizumab is presently being examined in early phase of high risk urothelial carcinoma of the bladder (Larkin et al., 2015; Postow et al., 2015).

The earliest mathematical models of BCG immunotherapy of superficial bladder cancer were developed and studied (Bunimovich-Mendrazitsky et al., 2007; Bunimovich-Mendrazitsky et al., 2008; Starkov et al., 2016). Saad et al. investigated the interaction between immune system and immune checkpoints in superficial bladder cancer treatment using BCG (Saad et al., 2017). They also established the effects of the immune checkpoints on the effector cells and the overall therapy. Optimal control theory was applied in (Ghafari and Naserifar, 2010; Thalya et al., 2004) to find an optimal dose required to trigger the immune system in order to launch a robust antitumor assault. In (Elmouki and Saadi, 2016), the authors followed a different approach of optimal control (isoperimetric optimal control problem) on a BCG immunotherapy model.

A free final time optimal control approach was developed by (Alkama et al., 2018). Their work finds the optimal dose and time of application of BCG in the treatment of bladder cancer. In (Elmouki and Saadi, 2016), a quadratic control was used instead of linear control in a given objective functional that need to be minimized in a bladder cancer model. They used the maximum principle and the generalized Legendre-Clebsh condition for obtaining the characterization of desired controls. The RK-4 iterative program is applied to numerically find solutions of the optimality system.

Saad et al. established a model which investigates the synergy of effector cells, checkpoints, and normal cells in BCG immunotherapy of bladder cancer. Furthermore, they applied Pontryagin's maximum principle to characterize an optimal dose of BCG needed to trigger an effective anti-tumor response regardless of the activities of the immune checkpoints (Saad and Hincal, 2018).

The purpose of this section is to utilize the mathematical cancer model in chapter 3 and introduce two control functions, one blocks the activities of immune checkpoints (u_1) (because of the emergence of immune checkpoint inhibitors as a new way of treating bladder cancer) and the other activates the immune system (u_2).The control function u_1 mimic dosage of an immune checkpoint inhibitor, while u_2 denotes the BCG dose. We aim to get an optimal control pair (u_1, u_2) which will minimize our objective function.

This chapter is classified as follows; the first section gives the introduction. The model is presented and explained in section 4.2. In section 4.3, the theorem of existence of optimal

control pair is stated and proved; we derive characterization of the controls, and outline the proof of uniqueness of the optimality system. The numerical simulations are presented in section 4.4. In the last section, we state our discussions and conclusions.

4.2 The Mathematical Model

We present a deterministic ODE model developed in (Saad and Hincal, 2018) that studies the interaction between cancer cells (C), normal cells (N), BCG (B), effector cells (E), and immune checkpoints (P). Our aim is to adopt model (3.1) and incorporate two control functions u_1; which represent dosage of an immune checkpoint inhibitor while u_2 denotes the BCG dose. It is important to note that the model (3.1) was with only one control function mimicking the BCG dose. However, because of the advancement and recent development of drugs that blocks the action of the immune checkpoints (checkpoints inhibitors) on the immune system, we wish to incorporate this into the model and analyze it with two control functions.

The model is as follows:

$$\frac{dC}{dt} = r_1 C(1 - k_1 C) - \alpha_1 EC\frac{\boldsymbol{u_1(t)}}{\boldsymbol{P + h}} - \mu_1 NC$$

$$\frac{dN}{dt} = r_2 N(1 - k_2 N) - \mu_2 NC - \mu_8 NB - \mu_4 N$$

$$\frac{dB}{dt} = g u_2(t) - \alpha_4 EB - \mu_6 B \qquad (4.1)$$

$$\frac{dE}{dt} = a_1 CE\frac{\boldsymbol{u_1(t)}}{\boldsymbol{P+h}} + a_2 BE\frac{\boldsymbol{u_1(t)}}{\boldsymbol{P+h}} - \alpha_2 EC - \alpha_3 EB - \mu_5 E$$

$$\frac{dP}{dt} = \delta - \mu_7 P$$

$$C(0) = C_0 > 0, N(0) = N_0 > 0, E(0) = E_0 > 0\,, B(0) = B_0 > 0, P(0) = P_0 > 0.$$

The evolution of the tumor is given in the first equation of system (4.1). The term, $r_1 C(1 - k_1 C)$, represents the advancement of the tumor and is regarded as logistic growth at rate r_1 and a carrying capacity $\frac{1}{k_1}$. The next term models the expulsion of tumor by activated immune effector cells (activated by BCG) with elimination rate α_1, and the procedure is understood to

be distorted by the immune checkpoints where $\frac{1}{P+h}$ is regarded as the immunosuppressive term. This term suppresses/block the activities of the effector cells. The control function u_1 denotes the dosage of the immune checkpoint inhibitors that will block the activity of the immune checkpoints against the effector cells. It is applied directly in order to block the action of the immunosuppressive term, and hence, we have $\frac{u_1(t)}{P+h}$, with inhibitory parameter h.

The third term describes the destruction of normal cells by the malignant cells at rate μ_1.

The dynamics of normal cells is given in the second equation, with the first term describing their growth (logistic) at the rate r_2 and carrying capacity $\frac{1}{k_2}$. The second and third terms represents the elimination of the normal cells by the tumor and BCG (due to its toxicity) at the rate μ_2 and μ_8 respectively. The last term gives the natural death of normal cells (via apoptosis) at rate μ_4.

The third equation explains the evolution of BCG. $u_2(t)$ is the concentration of the solution (BCG) that is injected into the bladder with g being the strength of the treatment. The effector cells kill the BCG because it is considered foreign at the rate α_4 and the degradation of the BCG is given by the last term.

The second to the last equation represent the activities of the immune system, where the first and second terms gives the recruitment (which depends on the tumor mass or volume at the rate a_1) and activation of effector cells by BCG (at rate a_2) respectively. Both the recruitment and the activation are presupposed to be disrupted by checkpoints; hence, we use the immunosuppressive term to explain that. We also apply the control function to both the processes in order to inhibit the activities of the immune checkpoints explained above. The third and fourth terms describe the destruction of effector cells by the tumor and BCG respectively. While the last term states the natural degradation of effector cells.

In the final equation, the evolution of the immune checkpoints is explained. δ is their constant source and $\mu_7 P$ denotes their natural death.

The analysis of the model without treatment is given in chapter 3, hence; we will directly find the characterization of our optimal control pair.

We take our controls to be class of piecewise continuous function defined for all t such that $0 < b_1 \leq u_1(t) \leq b_2 < 1$ and $\lambda_1 \leq u_2(t) \leq \lambda_2$. Moreover,

$$\lambda_1 = 3.14 \times 10^5\ c.f.u\ (colony\ forming\ unit \text{ and } \lambda_2 = 9.14 \times 10^5\ c.f.u,$$

are values obtained to bound the BCG optimal dose (Elmouki and Saadi, 2016; Alkama et al., 2018; Elmouki and Saadi, 2016; Saad and Hincal, 2018). Therefore, we present the class of admissible controls as

$$U = \{(u_1(t), u_2(t)) : 0 < b_1 \leq u_1(t) \leq b_2 < 1, \lambda_1 \leq u_2(t) \leq \lambda_2, \forall\ t \in [0, T]\},$$

with $u_1(t)$ and $u_2(t)$ piecewise continuous.

Now, we state our objective function. We seek to minimize the activities/effects of immune checkpoints, costs of the controls, tumor size, as well as maximizing the concentration of normal cells. Thus, the objective function is defined as

$$J(u_1, u_2) = \int_0^T \left(C(t) + P(t) - N(t) + \frac{1}{2} D_1 {u_1}^2 + \frac{1}{2} D_2 {u_2}^2 \right) dt.$$

Here, we are minimizing the number of cancer cells, immune checkpoints activities, costs of controls, number of cancer cells in addition to maximizing the concentration of normal cells. D_1 and D_2 are weight factors representing benefit/cost and the level of patient's acceptance of the BCG treatment respectively.

Our goal is to find ${u_1}^*, {u_2}^*$ (optimal control pair) that will satisfy the following:

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

4.3 Necessary and sufficient conditions of optimal control pair

4.3.1 Existence of Optimal Control Pair

In this part, the investigation of conditions that guarantee the existence of an optimal control pair for state system (4.1) would be conducted. To achieve this, we need to show that solutions of system (4.1) are bounded for finite time interval $[0, T]$.

The boundedness can be proved using the notion of supersolutions $\bar{C}, \bar{N}, \bar{B}, \bar{E}$, and $\bar{P}$ satisfying

$$\frac{d\bar{C}}{dt} = r_1\bar{C}$$

$$\frac{d\bar{N}}{dt} = r_2\bar{N}$$

$$\frac{d\bar{B}}{dt} = gu_2 \qquad (4.2)$$

$$\frac{d\bar{E}}{dt} = a_1\bar{E}C_{max}u_1 + a_2\bar{E}B_{max}u_1$$

$$\frac{d\bar{P}}{dt} = \delta,$$

are bounded on a finite time interval, where $C_{max}$and B_{max} are upper bound solutions related to C and B respectively. We can apply a result demonstrated by Fleming and Rishel to establish the existence of the control pair (Fleming and Rishel, 1975).

Theorem 4.1Given the objective functional

$$J(u_1, u_2) = \int_0^T \left(C(t) + P(t) - N(t) + \frac{1}{2}D_1{u_1}^2 + \frac{1}{2}D_2{u_2}^2\right)dt,$$

where,

$$U = \{(u_1(t), u_2(t)) : 0 < b_1 \leq u_1(t) \leq b_2 < 1, \lambda_1 \leq u_2(t) \leq \lambda_2, \forall\, t \in [0, T]\},$$

with $u_1(t)$ and $u_2(t)$ piecewise continuous,

subject to state equations of (1) with $C(0) = C_0$, $N(0) = N_0$, $B(0) = B_0$, $E(0) = E_0$, and $P(0) = P_0$; then there exists an optimal control pair ${u_1}^*, {u_2}^*$ such that

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

provided the following conditions are met:

i) The class of all initial conditions with an optimal control pair u_1, u_2in the admissible control set along with each state equation being satisfied is nonempty.

ii) The admissible control set U is closed and convex.

iii) Each right hand side of the equations of system (4.1) is continouous, bounded above by a sum of the bounded control and the state, and can be written as a linear function of an optimal control pair $u_1, u_2$with coefficients depending on time and state.

iv) The integrand of $J(u_1, u_2)$is convex on $U$and bounded below by $-C_2 + C_1(|u_1|^2 + |u_2|^2)$ with $C_1 > 0$.

Proof. In order to prove i), we utilize an outcome from Lukes (Lukes, 1982) that give the existence of solutions of ordinary differential equations in system (4.1) with bounded coefficients. Since the solution of system (4.1) is bounded as established, hence, condition 1 is proved. Therefore, the set is nonempty. By definition, U is closed and convex. The right hand side of system (4.1) is continuous and can be expressed as follows:

$$f(t, \vec{X}, u) = \vec{\varphi}(t, \vec{X}) + \vec{\beta}(t, \vec{X})\vec{u}$$

$$= \begin{pmatrix} r_1 C(1 - k_1 C) - \mu_1 NC \\ r_2 N(1 - k_2 N) - \mu_2 NC - \mu_8 NB - \mu_4 N \\ -\alpha_4 EB - \mu_6 B \\ -\alpha_4 EC - \alpha_3 EB - \mu_5 E \\ \delta - \mu_7 P \end{pmatrix} + \begin{pmatrix} -\frac{\alpha_1 EC}{P+h} & 0 \\ 0 & 0 \\ 0 & 1 \\ \frac{a_1 EC}{P+h} + \frac{a_2 EB}{P+h} & 0 \\ 0 & 0 \end{pmatrix} \times \begin{pmatrix} u_1 \\ u_2 \end{pmatrix}.$$

Using the boundedness of solutions we have that

$$|f(t, \vec{X}, u)| \leq C_1(1 + |\vec{X}| + |\vec{u}|)$$

for $0 \leq t \leq T$ where $\vec{X} = \begin{pmatrix} C \\ N \\ E \\ B \\ P \end{pmatrix} \in \Re^5$, $\vec{\varphi}$and $\vec{\beta}$ are vector valued functions of $\vec{X}$, $\vec{u} \in \Re^2$, and C_1 depends on coefficients of (1). Next, we show the integrand of $J(u_1, u_2)$ is convex in U. Let $\rho \in [0,1]$ and $R(C, N, P, \vec{u}) = P(t) + C(t) - N(t) + \frac{1}{2} D_1 {u_1}^2 + \frac{1}{2} D_2 {u_2}^2$. To show the convexity of R, we have to establish the inequality

$$R(C, N, P, (1-\rho)\vec{u} + \rho\vec{v}) \leq (1-\rho)R(C, N, P, \vec{u}) + \rho R(C, N, P, \vec{v}) \text{ if and only if,}$$

$$(1-\rho)R(C, N, P, \vec{u}) + \rho R(C, N, P, \vec{v}) - R(C, N, P, (1-\rho)\vec{u} + \rho\vec{v}) \geq 0,$$

where $\vec{u} = (u_1, u_2), \vec{v} = (v_1, v_2) \in U$. Now,

$$(1-\rho)R(\,C, N, P, \vec{u}) + \rho R(\,C, N, P, \vec{v}) - R(\,C, N, P, (1-\rho)\vec{u} + \rho\vec{v})$$

$$= (1-\rho)\left[P(t) + C(t) - N(t) + \frac{D_1}{2}{u_1}^2 + \frac{D_1}{2}{u_2}^2\right]$$

$$+\rho\left[P(t) + C(t) - N(t) + \frac{D_1}{2}{v_1}^2 + \frac{D_2}{2}{v_2}^2\right]$$

$$-\left[P(t) + C(t) - N(t) + \frac{D_1}{2}\big((1-\rho)u_1 + \rho v_1\big)^2 + \frac{D_2}{2}\big((1-\rho)u_2 + \rho v_2\big)^2\right]$$

$$= (1-\rho)\frac{D_1}{2}{u_1}^2 + (1-\rho)\frac{D_2}{2}{u_2}^2 + \rho\frac{D_1}{2}{v_1}^2 + \rho\frac{D_2}{2}{v_2}^2 - \frac{D_1}{2}\big((1-\rho)u_1 + \rho v_1\big)^2$$

$$-\frac{D_2}{2}\big((1-\rho)u_2 + \rho v_2\big)^2 = \frac{D_1}{2}\left[(1-\rho){u_1}^2 + \rho{v_1}^2 - \big((1-\rho)u_1 + \rho v_1\big)^2\right]$$

$$+\frac{D_2}{2}\left[(1-\rho){u_2}^2 + \rho{v_2}^2 - \big((1-\rho)u_2 + \rho v_2\big)^2\right]$$

$$= \frac{D_1}{2}[\rho(1-\rho){u_1}^2 - 2\rho(1-\rho)u_1v_1 + \rho(1-\rho){v_1}^2]$$

$$+\frac{D_2}{2}[\rho(1-\rho){u_2}^2 - 2\rho(1-\rho)u_2v_2 + \rho(1-\rho){v_2}^2]$$

$$= \frac{D_1}{2}\rho(1-\rho)[{u_1}^2 - 2u_1v_1 + {v_1}^2] + \frac{D_2}{2}\rho(1-\rho)[{u_2}^2 - 2u_2v_2 + {v_2}^2]$$

$$= \frac{D_1}{2}\rho(1-\rho)(u_1 - v_1)^2 + \frac{D_2}{2}\rho(1-\rho)(u_2 - v_2)^2 \geq 0.$$

It holds because $D_1, D_2 > 0$ and $\rho \in [0, 1]$. Therefore the integrand of $J(u_1, u_2)$ is convex. Furthermore,

$$P(t) + C(t) - N(t) + \frac{1}{2}D_1{u_1}^2 + \frac{1}{2}D_2{u_2}^2 \geq -N(t) + \frac{1}{2}D_1{u_1}^2 + \frac{1}{2}D_2{u_2}^2$$

$$\geq -C_2 + C_1(|u_1|^2 + |u_2|^2),$$

with C_2 depending on the lower bound on E, $C_1 > 0$ because $D_1, D_2 > 0$. Thus, since all the conditions are proved, then optimal control pair exists.

4.3.2 Characterization of optimal control pair

In consideration of existence of optimal control pair that will minimize the objective function $J(u_1, u_2)$ subject to state equations in (4.1), then we use a version of Pontryagin's maximum principle to obtain the necessary conditions as well as characterization of the optimal control pair (Pontryagin et al., Garira et al., 2005; Fister et al., 1998). To achieve this, we state the Lagrangian as follows:

$$L(t, C, N, B, E, P, \sigma_1, \sigma_2, \sigma_3, \sigma_4, \sigma_5)$$

$$= H + \theta_{11}(\lambda_2 - u_2) + \theta_{12}(u_2 - \lambda_1) + \theta_{21}(u_1 - b_2) + \theta_{22}(b_1 - u_1),$$

where $\theta_{11},\ \theta_{12},\ \theta_{21},\ \theta_{22} \geq 0$ are penalty multipliers satisfying:

$$\theta_{11}(\lambda_2 - u_2) = 0, \theta_{12}(u_2 - \lambda_1) = 0 \text{ at } {u_1}^*\ \text{ and}$$

$$\theta_{21}(u_1 - b_2) = 0,\ \theta_{22}(b_1 - u_1) = 0 \text{ at } {u_2}^*,$$

while H is the Hamiltonian given by

$$H = P(t) + C(t) + -N(t) + \frac{D_1}{2}{u_1}^2 + \frac{D_2}{2}{u_2}^2 + \sigma_1(\dot{C}) + \sigma_2(\dot{N}) + \sigma_3(\dot{B}) + \sigma_4(\dot{E})$$
$$+\sigma_5(\dot{P}).$$

Therefore, the Lagrangian can now be expressed as follows;

$$L(t, C, N, B, E, P, \sigma_1, \sigma_2, \sigma_3, \sigma_4, \sigma_5)$$
$$= P(t) + C(t) + -N(t) + \frac{D_1}{2}{u_1}^2 + \frac{D_2}{2}{u_2}^2 + \sigma_1(\dot{C}) + \sigma_2(\dot{N}) + \sigma_3(\dot{B}) + \sigma_4(\dot{E})$$
$$+\sigma_5(\dot{P}) + \theta_{11}(\lambda_2 - u_2) + \theta_{12}(u_2 - \lambda_1) + \theta_{21}(u_1 - b_2) + \theta_{22}(b_1 - u_1)$$
$$= P(t) + C(t) + -N(t) + \frac{D_1}{2}{u_1}^2 + \frac{D_2}{2}{u_2}^2$$
$$+\sigma_1\left(r_1 C(1 - k_1 C) - \frac{\alpha_1 EC u_1}{P + h} - \mu_1 NC\right)$$
$$+\sigma_2(r_2 N(1 - k_2 N) - \mu_2 NC - \mu_4 N - \mu_8 BN)$$
$$+\sigma_3(gu_2 - \alpha_4 EB - \mu_6 B) + \sigma_4\left(\frac{a_1 CEu_1}{P+h} + \frac{a_2 EBu_1}{P+h} - \alpha_2 EC - \mu_5 E - \mu_9 EB\right)$$

$$+\sigma_5(\delta - \mu_7 P) + \theta_{11}(\lambda_2 - u_2) + \theta_{12}(u_2 - \lambda_1) + \theta_{21}(u_1 - b_2) + \theta_{22}(b_1 - u_1).$$

Theorem 4.2Given an optimal control pair u_1^*, u_2^* and solutions C, N, B, E, and P of the corresponding state system (1), there exists adjoint variables σ_i for$i = 1, 2, 3, 4, 5$, that satisfy the following adjoint system

$$\frac{d\sigma_1}{dt} = -1 - r_1\sigma_1 + 2r_1k_1\sigma_1 C + \frac{\alpha_1\sigma_1 E u_1}{P+h} + \mu_1\sigma_1 N + \mu_2\sigma_2 N - \frac{a_1\sigma_4 E u_1}{P+h} + \alpha_2\sigma_2 E$$
$$\frac{d\sigma_2}{dt} = 1 + \mu_1\sigma_1 C - r_2\sigma_2 + 2r_2k_2\sigma_2 N + \mu_2\sigma_2 C + \mu_4\sigma_2 + \mu_8\sigma_2 B$$
$$\frac{d\sigma_3}{dt} = \mu_8\sigma_2 N + \alpha_4\sigma_3 E + \mu_6\sigma_3 - \frac{a_2\sigma_4 E u_1}{P+h} + \alpha_3\sigma_4 E$$
$$\frac{d\sigma_4}{dt} = \frac{\alpha_1\sigma_1 C u_1}{P+h} + \alpha_4\sigma_3 B - \frac{a_1\sigma_4 C u_1}{P+h} - \frac{a_2\sigma_4 u_1 B}{P+h} + \alpha_2\sigma_4 C + \mu_5\sigma_4 - \alpha_3\sigma_4 B$$
$$\frac{d\sigma_5}{dt} = -1 + \frac{\alpha_1\sigma_1 E C u_1}{(P+h)^2} + \frac{a_1\sigma_4 E C u_1}{(P+h)^2} + \frac{a_2\sigma_4 E B u_1}{(P+h)^2} + \mu_7\sigma_5$$

with transversality conditions $\sigma_i(T) = 0$ for $i = 1, 2, 3, 4, 5$. Furthermore, the characterization is given by

$$u_1 = min\left(max\left(\frac{\alpha_1\sigma_1 EC - a_1\sigma_4 EC - a_2\sigma_4 EB}{D_1(P+h)}, b_1\right), b_2\right)$$
$$u_2 = min\left(max\left(-\frac{g\sigma_3(t)}{D_2}, \lambda_1\right), \lambda_2\right).$$

Proof. The proof is a direct implementation of the Pontryagin's maximum principle for bounded controls. The adjoint system can be found using the following:

$$\frac{d\sigma_1}{dt} = -\frac{\partial L}{\partial C}, \quad \frac{d\sigma_2}{dt} = -\frac{\partial L}{\partial N}, \quad \frac{d\sigma_3}{dt} = -\frac{\partial L}{\partial B}, \qquad \frac{d\sigma_3}{dt} = -\frac{\partial L}{\partial E}, \qquad \frac{d\sigma_5}{dt} = -\frac{\partial L}{\partial P},$$

and $\sigma_i(T) = 0$ for $i = 1, 2, 3, 4, 5$ evaluated at the optimal control and corresponding states. This gives the adjoint system and transversality conditions. Finally, to get the optimal control pair, the optimality conditions requires that

$$\frac{\partial L}{\partial u_1} = \frac{\partial L}{\partial u_2} = 0$$

for the optimal control pair $(u_1{}^*, u_2{}^*)$. Therefore,

$$u_1{}^* = \frac{\alpha_1\sigma_1 EC - a_1\sigma_4 EC - a_2\sigma_4 EB}{D_1(P+h)} - \frac{(\theta_{21} - \theta_{22})}{D_1}$$

$$and\ \ u_2{}^* = \frac{-g\sigma_3(t) - \theta_{12} + \theta_{11}}{D_2}.$$

Now, we find the representation for the control pair explicitly without penalty multipliers. For u_1, we check the following cases:

Case 1: If $0 < b_1 < u_1{}^* < b_2 < 1$, then $\theta_{21} = \theta_{22} = 0$. Hence,

$$u_1{}^* = \frac{\alpha_1\sigma_1 EC - a_1\sigma_4 EC - a_2\sigma_4 EB}{D_1(P+h)}.$$

Case 2: If$b_1 = u_1{}^*$, then $\theta_{21} = 0$. Hence,

$$b_1 = u_1{}^* = \frac{\alpha_1\sigma_1 EC - a_1\sigma_4 EC - a_2\sigma_4 EB}{D_1(P+h)} + \frac{\theta_{22}}{D_1}.$$

Then, $\theta_{22} = D_1 b_1 - \frac{\alpha_1\sigma_1 EC - a_1\sigma_4 EC - a_2\sigma_4 EB}{(P+h)} \geq 0$ since $\theta_{22} \geq 0$. Therefore,

$$b_1 = u_1{}^* \geq \frac{\alpha_1\sigma_1 EC - a_1\sigma_4 EC - a_2\sigma_4 EB}{D_1(P+h)}.$$

Case 3: If$b_2 = u_1{}^*$, then $\theta_{22} = 0$. Thus,

$$b_2 = u_1{}^* = \frac{\alpha_1\sigma_1 EC - a_1\sigma_4 EC - a_2\sigma_4 EB}{(P+h)} - \frac{\theta_{21}}{D_1}.$$

Now, $\theta_{21} = \frac{\alpha_1\sigma_1 EC - a_1\sigma_4 EC - a_2\sigma_4 EB}{(P+h)} - D_1 b_2 \geq 0$ because $\theta_{22} \geq 0$. Thence,

$$\frac{\alpha_1\sigma_1 EC - a_1\sigma_4 EC - a_2\sigma_4 EB}{D_1(P+h)} \geq b_2 = u_1{}^*.$$

In conclusion, putting the cases together yields

$$u_1{}^*(t)$$

$$= \begin{cases} \dfrac{\alpha_1\sigma_1 EC - a_1\sigma_4 EC - a_2\sigma_4 EB}{D_1(P+h)}, & if \;\; b_1 < \dfrac{\alpha_1\sigma_1 EC - a_1\sigma_4 EC - a_2\sigma_4 EB}{D_1(P+h)} < b_2 \\ b_1, & if \;\; \dfrac{\alpha_1\sigma_1 EC - a_1\sigma_4 EC - a_2\sigma_4 EB}{D_1(P+h)} \leq b_1 \\ b_2, & if \;\; \dfrac{\alpha_1\sigma_1 EC - a_1\sigma_4 EC - a_2\sigma_4 EB}{D_1(P+h)} \geq b_2 \end{cases}$$

Alternatively, $u_1{}^*$ can be expressed in compact form as

$$u_2{}^* = min\left(max\left(\frac{\alpha_1\sigma_1 EC - a_1\sigma_4 EC - a_2\sigma_4 EB}{D_1(P+h)}, b_1\right), b_2\right).$$

In similar fashion, $u_1{}^*$ can be characterize as follows

$$u_2{}^*(t) = \begin{cases} -\dfrac{g\sigma_3(t)}{D}, & if \;\; \lambda_1 < -\dfrac{g\sigma_3(t)}{D_2} < \lambda_2 \\ \lambda_1, & if \;\; -\dfrac{g\sigma_3(t)}{D_2} \leq \lambda_1 \\ \lambda_2, & if \;\; -\dfrac{g\sigma_3(t)}{D_2} \geq \lambda_2 \end{cases}$$

In compact form we have,

$$u_2{}^* = min\left(max\left(-\frac{g\sigma_3(t)}{D_2}, \lambda_1\right), \lambda_2\right).$$

Hence, the theorem is proved.

4.3.3 Optimality System

We now present the optimality system and prove the uniqueness theorem of its solutions. It constitutes the state equations and their initial conditions coupled with the adjoint system and transversality conditions. It is given by:

$$\frac{\boldsymbol{dC}}{\boldsymbol{dt}} = r_1 C(1 - k_1 C) - \frac{\alpha_1 EC\left\{min\left(max\left(\frac{\alpha_1\sigma_1 EC - a_1\sigma_4 EC - a_2\sigma_4 EB}{D_1(P+h)}, b_1\right), b_2\right)\right\}}{\boldsymbol{P+h}}$$

$$-\mu_1 NC,$$

$$\frac{\boldsymbol{dN}}{\boldsymbol{dt}} = r_2 N(1 - k_2 N) - \mu_2 NC - \mu_8 NB - \mu_4 N,$$

$$\frac{\boldsymbol{dB}}{\boldsymbol{dt}} = g\left\{min\left(max\left(-\frac{s\sigma_3(t)}{D_2}, \lambda_1\right), \lambda_2\right)\right\} - \alpha_4 EB - \mu_6 B,$$

$$\frac{\boldsymbol{dE}}{\boldsymbol{dt}} = \frac{a_1 CE\left\{min\left(max\left(\frac{\alpha_1\sigma_1 EC - a_1\sigma_4 EC - a_2\sigma_4 EB}{D_1(P+h)}, b_1\right), b_2\right)\right\}}{\boldsymbol{P + h}}$$

$$\frac{\boldsymbol{dP}}{\boldsymbol{dt}} = \delta - \mu_7 P$$

$$+\frac{a_2 BE\left\{min\left(max\left(\frac{\alpha_1\sigma_1 EC - a_1\sigma_4 EC - a_2\sigma_4 EB}{D_1(P+h)}, b_1\right), b_2\right)\right\}}{\boldsymbol{P + h}} - \alpha_2 EC - \alpha_3 EB$$

$$-\mu_5 E,$$

$$\frac{\boldsymbol{d\sigma_1}}{\boldsymbol{dt}} = -1 - r_1\sigma_1 + 2r_1 k_1\sigma_1 C + \mu_1\sigma_1 N + \mu_2\sigma_2 N + \alpha_2\sigma_2 E$$
$$+\frac{\alpha_1\sigma_1 E\left\{min\left(max\left(\frac{\alpha_1\sigma_1 EC - a_1\sigma_4 EC - a_2\sigma_4 EB}{D_1(P+h)}, b_1\right), b_2\right)\right\}}{P + h}$$
$$-\frac{a_1\sigma_4 E\left\{min\left(max\left(\frac{\alpha_1\sigma_1 EC - a_1\sigma_4 EC - a_2\sigma_4 EB}{D_1(P+h)}, b_1\right), b_2\right)\right\}}{P + h},$$

$$\frac{\boldsymbol{d\sigma_2}}{\boldsymbol{dt}} = 1 + \mu_1\sigma_1 C - r_2\sigma_2 + 2r_2 k_2\sigma_2 N + \mu_2\sigma_2 C + \mu_4\sigma_2 + \mu_8\sigma_2 B$$

$$\frac{\boldsymbol{d\sigma_3}}{\boldsymbol{dt}} = \mu_8\sigma_2 N + \alpha_4\sigma_3 E + \mu_6\sigma_3 + \alpha_3\sigma_4 E$$
$$-\frac{a_2\sigma_4 E\left\{min\left(max\left(\frac{\alpha_1\sigma_1 EC - a_1\sigma_4 EC - a_2\sigma_4 EB}{D_1(P+h)}, b_1\right), b_2\right)\right\}}{P + h},$$

$$\frac{\boldsymbol{d\sigma_4}}{\boldsymbol{dt}} = \frac{\alpha_1\sigma_1 C\left\{min\left(max\left(\frac{\alpha_1\sigma_1 EC - a_1\sigma_4 EC - a_2\sigma_4 EB}{D_1(P+h)}, b_1\right), b_2\right)\right\}}{P + h} + \alpha_4\sigma_3 B$$
$$-\frac{a_1\sigma_4 C\left\{min\left(max\left(\frac{\alpha_1\sigma_1 EC - a_1\sigma_4 EC - a_2\sigma_4 EB}{D_1(P+h)}, b_1\right), b_2\right)\right\}}{P + h}$$
$$-\frac{a_2\sigma_4 B\left\{min\left(max\left(\frac{\alpha_1\sigma_1 EC - a_1\sigma_4 EC - a_2\sigma_4 EB}{D_1(P+h)}, b_1\right), b_2\right)\right\}}{P + h}$$

$$+\alpha_2\sigma_4 C + \mu_5\sigma_4 - \alpha_3\sigma_4 B,$$

$$\frac{\boldsymbol{d\sigma_5}}{\boldsymbol{dt}} = -1 + \frac{\alpha_1\sigma_1 EC\left\{min\left(max\left(\frac{\alpha_1\sigma_1 EC - a_1\sigma_4 EC - a_2\sigma_4 EB}{D_1(P+h)}, b_1\right), b_2\right)\right\}}{(P+h)^2}$$

$$+\frac{a_1\sigma_4 EC\left\{min\left(max\left(\frac{\alpha_1\sigma_1 EC - a_1\sigma_4 EC - a_2\sigma_4 EB}{D_1(P+h)}, b_1\right), b_2\right)\right\}}{(P+h)^2}$$

$$+\frac{a_2\sigma_4 EB\left\{min\left(max\left(\frac{\alpha_1\sigma_1 EC - a_1\sigma_4 EC - a_2\sigma_4 EB}{D_1(P+h)}, b_1\right), b_2\right)\right\}}{(P+h)^2} + \mu_7\sigma_5$$

$C(0) = C_0, N(0) = N_0,\ E(0) = E_0,\ B(0) = B_0,\ P(0) = P_0$ and $\sigma_i(T) = 0$ for $i = 1, 2, 3, 4, 5$.

We then state the theorems for the uniqueness of the optimality system.

Theorem 4.3The function given by $u(z) = \{min(max(z, y), x)\}$ is Lipschitz continuous in z, with $x < y$ being positive parameters.

Proof**.** (Garira et al., 2005).

Theorem 4.4. The bounded solutions of the optimality system above are unique for a sufficiently small time T.

Proof. Assume for the sake of contradiction that there are two different solutions of the optimality system viz. $(C, N, B, E, P, \sigma_1, \sigma_2, \sigma_3, \sigma_4, \sigma_5)$ and $(\bar{C}, \bar{N}, \bar{B}, \bar{E}, \bar{P}, \bar{\sigma}_1, \bar{\sigma}_2, \bar{\sigma}_3, \bar{\sigma}_4, \bar{\sigma}_5)$. We now make the following change of variables:

$C = e^{rt}x,\ N = e^{rt}y,\ B = e^{rt}z,\ E = e^{rt}w,\ P = e^{rt}v,\ \sigma_1 = e^{-rt}q,\ \sigma_2 = e^{-rt}s,$ $\sigma_3 = e^{-rt}l, \sigma_4 = e^{-rt}m, \sigma_5 = e^{-rt}n$ and

$\bar{C} = e^{rt}\bar{x},\ \bar{N} = e^{rt}\bar{y},\ \bar{B} = e^{rt}\bar{z},\ \bar{E} = e^{rt}\bar{w},\ \bar{P} = e^{rt}\bar{v},\ \bar{\sigma}_1 = e^{-rt}\bar{q},\ \bar{\sigma}_2 = e^{-rt}\bar{s},$ $\bar{\sigma}_3 = e^{-rt}\bar{l}, \bar{\sigma}_4 = e^{-rt}\bar{m}, \bar{\sigma}_5 = e^{-rt}\bar{n}$where $r > 0$ is chosen.

Furthermore, we let

$$u_1 = min\left(max\left(\frac{\alpha_1 qwxe^{rt} - a_1 mxwe^{rt} - a_2 mzwe^{rt}}{D_1(e^{rt}v + h)}, b_1\right), b_2\right)$$

and

$$\bar{u}_1 = min\left(max\left(\frac{\alpha_1\bar{q}\bar{w}\bar{x}e^{rt} - a_1\bar{m}\bar{w}\bar{x}e^{rt} - a_2\bar{m}\bar{z}\bar{w}e^{rt}}{D_1(e^{rt}\bar{v}+h)}, b_1\right), b_2\right),$$

$$u_2 = min\left(max\left(-\frac{gle^{-rt}}{D_2}, \lambda_1\right), \lambda_2\right)$$

and

$$\bar{u}_2 = min\left(max\left(-\frac{g\bar{l}e^{-rt}}{D_2}, \lambda_1\right), \lambda_2\right).$$

Observe that from theorem 4.3 we have,

$$u_1 - \bar{u}_1 \leq \frac{1}{D_1}\left(\frac{\alpha_1 qwxe^{rt} - a_1 mxwe^{rt} - a_2 mzwe^{rt}}{(e^{rt}v+h)}\right)$$

$$-\frac{1}{D_1}\left(\frac{\alpha_1\bar{q}\bar{w}\bar{x}e^{rt} - a_1\bar{m}\bar{w}\bar{x}e^{rt} - a_2\bar{m}\bar{z}\bar{w}e^{rt}}{(e^{rt}\bar{v}+h)}\right),$$

and $u_2 - \bar{u}_2 \leq \frac{ge^{-rt}}{D_2}(l - \bar{l})$. Substituting $C = e^{rt}x$, $\bar{C} = e^{rt}\bar{x}$ and $\sigma_1 = e^{-rt}q$, $\bar{\sigma}_1 = e^{-rt}\bar{q}$ into the first and sixth equations of the optimality system respectively we have:

$$\dot{x} + rx = r_1 x(1 - k_1 xe^{rt}) - \frac{\alpha_1 wxu_1 e^{rt}}{ve^{rt}+h} - \mu_1 xye^{rt},$$

$$\dot{\bar{x}} + r\bar{x} = r_1\bar{x}(1 - k_1\bar{x}e^{rt}) - \frac{\alpha_1\bar{w}\bar{x}\bar{u}_1 e^{rt}}{\bar{v}e^{rt}+h} - \mu_1\bar{x}\bar{y}e^{rt}$$

and

$$\dot{q} - rq = -e^{rt} - q + 2r_1 k_1 qxe^{rt} + \frac{\alpha_1 qwe^{rt}}{ve^{rt}+h} - \mu_1 qye^{rt} + \mu_2 sye^{rt} - \frac{a_1 mwu_1 e^{rt}}{ve^{rt}+h}$$

$$+\alpha_1 swe^{rt},$$

$$\dot{\bar{q}} - r\bar{q} = -e^{rt} - \bar{q} + 2r_1 k_1\bar{q}\bar{x}e^{rt} + \frac{\alpha_1\bar{q}\bar{w}e^{rt}}{\bar{v}e^{rt}+h} - \mu_1\bar{q}\bar{y}e^{rt} + \mu_2\bar{s}\bar{y}e^{rt} - \frac{a_1\bar{m}\bar{w}\bar{u}_1 e^{rt}}{\bar{v}e^{rt}+h}$$

$$+\alpha_1\bar{s}\bar{w}e^{rt}.$$

Now, we take the difference between equations for x and $\bar{x}$, q and $\bar{q}$, and the result is then multiplied by $x-\bar{x}$ and $q-\bar{q}$ and further integrated from 0 to T respectively.

$$\frac{1}{2}\left(x(T)-\bar{x}(T)\right)^2+(r-r_1)\int_0^T(x-\bar{x})^2dt=-r_1k_1\int_0^T e^{rt}(x^2-\bar{x}^2)(x-\bar{x})dt$$

$$-\alpha_1\int_0^T e^{rt}\left(\frac{wxu_1}{ve^{rt}+h}-\frac{\bar{w}\bar{x}\bar{u}_1}{\bar{v}e^{rt}+h}\right)(x-\bar{x})dt-\mu_1\int_0^T e^{rt}(xy-\bar{x}\bar{y})(x-\bar{x})dt, \tag{4.3}$$

$$\frac{1}{2}\left(q(0)-\bar{q}(0)\right)^2+(1-r)\int_0^T(q-\bar{q})^2dt=2r_1k_1\int_0^T e^{rt}(qx-\bar{q}\bar{x})(q-\bar{q})dt$$

$$+\alpha_1\int_0^T e^{rt}\left(\frac{qw}{ve^{rt}+h}-\frac{\bar{q}\bar{w}}{\bar{v}e^{rt}+h}\right)(q-\bar{q})dt+\mu_1\int_0^T e^{rt}(qy-\bar{q}\bar{y})(q-\bar{q})dt$$

$$+\mu_2\int_0^T e^{rt}(sy-\bar{s}\bar{y})(q-\bar{q})dt-a_1\int_0^T e^{rt}\left(\frac{mwu_1}{ve^{rt}+h}-\frac{\bar{m}\bar{w}\bar{u}_1}{\bar{v}e^{rt}+h}\right)(q-\bar{q})dt$$

$$+\alpha_2\int_0^T e^{rt}(sw-\bar{s}\bar{w})(q-\bar{q})dt. \tag{4.4}$$

We obtain similar equations for N and $\bar{N}$, B and $\bar{B}$, E and $\bar{E}$, P and $\bar{P}$, σ_2 and $\bar{\sigma}_2$, σ_3 and $\bar{\sigma}_3$, σ_4 and $\bar{\sigma}_4$, and σ_5 and $\bar{\sigma}_5$. Next, we find upper bounds or estimates on the right-hand sides of all the ten integral equations obtained. Moreover, we separate terms that involve powers, squares, several multiplied terms and quotients. For example, from equation (4.3), we have

$$\frac{1}{2}\left(x(T)-\bar{x}(T)\right)^2+(r-r_1)\int_0^T(x-\bar{x})^2dt=-r_1k_1\int_0^T e^{rt}(x^2-\bar{x}^2)(x-\bar{x})dt$$

$$-\alpha_1\int_0^T e^{rt}\left(\frac{wxu_1}{ve^{rt}+h}-\frac{\bar{w}\bar{x}\bar{u}_1}{\bar{v}e^{rt}+h}\right)(x-\bar{x})dt-\mu_1\int_0^T e^{rt}(xy-\bar{x}\bar{y})(x-\bar{x})dt$$

$$\leq R_1e^{rT}\int_0^T(x-\bar{x})^2dt$$

$$+R_2e^{rT}\int_0^T((x-\bar{x})^2+(w-\bar{w})^2+(v-\bar{v})^2+(u_1-\bar{u}_1)^2)dt$$

$$+R_3e^{rT}\int_0^T((x-\bar{x})^2+(y-\bar{y})^2)dt,$$

where R_1, R_2, and R_3 are dependent on the coefficients and the appropriate bounds on solutions variables x, y, w, v, m, q, and z. Similarly, from equation (4.4) we have the following estimates;

$$\frac{1}{2}\big(q(0)-\bar{q}(0)\big)^2+(1-r)\int_0^T(q-\bar{q})^2dt=2r_1k_1\int_0^T e^{rt}(qx-\bar{q}\bar{x})(q-\bar{q})dt$$

$$+\alpha_1\int_0^T e^{rt}\left(\frac{qw}{ve^{rt}+h}-\frac{\bar{q}\bar{w}}{\bar{v}e^{rt}+h}\right)(q-\bar{q})dt+\mu_1\int_0^T e^{rt}(qy-\bar{q}\bar{y})(q-\bar{q})dt$$

$$+\mu_2\int_0^T e^{rt}(sy-\bar{s}\bar{y})(q-\bar{q})dt-a_1\int_0^T e^{rt}\left(\frac{mwu_1}{ve^{rt}+h}-\frac{\bar{m}\bar{w}\bar{u}_1}{\bar{v}e^{rt}+h}\right)(q-\bar{q})dt$$

$$+\alpha_2\int_0^T e^{rt}(sw-\bar{s}\bar{w})(q-\bar{q})dt$$

$$\leq R_4e^{rT}\int_0^T((x-\bar{x})^2+(q-\bar{q})^2)dt$$

$$+R_5e^{rT}\int_0^T((q-\bar{q})^2+(w-\bar{w})^2+(v-\bar{v})^2)dt$$

$$+R_6e^{rT}\int_0^T((q-\bar{q})^2+(y-\bar{y})^2)dt+R_7e^{rT}\int_0^T((q-\bar{q})^2+(s-s)^2+(y-\bar{y})^2)dt$$

$$+R_8e^{rT}\int_0^T((m-\bar{m})^2+(w-\bar{w})^2+(v-\bar{v})^2+(x-x)^2+(z-\bar{z})^2+(q-\bar{q})^2)dt$$

$$+R_9 e^{rT}\int_0^T((q-\bar{q})^2+(s-\bar{s})^2+(w-\bar{w})^2)dt,$$

where $R_i's$, $i=4,\dots,9$, depends on the coefficients and appropriate bounds on solutions. The remaining eight integral equations are obtained in a similar manner. To prove the uniqueness, all the ten integral equations of $(x-\bar{x}),(y-\bar{y}),(z-\bar{z}),(q-\bar{q}),(m-\bar{m}),(s-\bar{s}),(w-\bar{w})$, $(v-\bar{v}),\left(l-\bar{l}\right)$, and $(n-\bar{n})$ are combined. This yields the following:

$$\frac{1}{2}\left(x(T)-\bar{x}(T)\right)^2+\frac{1}{2}\left(y(T)-\bar{y}(T)\right)^2+\frac{1}{2}\left(z(T)-\bar{z}(T)\right)^2+\frac{1}{2}\left(w(T)-\bar{w}(T)\right)^2$$

$$+\frac{1}{2}\left(v(T)-\bar{v}(T)\right)^2+\frac{1}{2}\left(q(0)-\bar{q}(0)\right)^2+\frac{1}{2}\left(s(0)-\bar{s}(0)\right)^2+\frac{1}{2}\left(l(0)-\bar{l}(0)\right)^2$$

$$+\frac{1}{2}\left(m(0)-\bar{m}(0)\right)^2+\frac{1}{2}\left(n(0)-\bar{n}(0)\right)^2+(r-r_1)\int_0^T(x-\bar{x})^2\,dt$$

$$+(1-r)\int_0^T(q-\bar{q})^2\,dt+(r-r_2)\int_0^T(y-\bar{y})^2\,dt+(r_2-r-\mu_4)\int_0^T(s-\bar{s})^2\,dt$$

$$+(r+\mu_6)\int_0^T(z-\bar{z})^2\,dt+(\mu_6-r)\int_0^T\left(l-\bar{l}\right)^2dt+(r+\mu_5)\int_0^T(w-\bar{w})^2\,dt$$

$$+(\mu_5-r)\int_0^T(m-\bar{m})^2\,dt+(r+\mu_7)\int_0^T(v-\bar{v})^2\,dt+(\mu_7-r)\int_0^T(n-\bar{n})^2\,dt$$

$$\leq\tilde{R}_1 e^{rT}\int_0^T((x-\bar{x})^2+(y-\bar{y})^2+(q-\bar{q})^2+(w-\bar{w})^2)\,dt$$

$$+\tilde{R}_1 e^{rT}\int_0^T((m-\bar{m})^2+(v-\bar{v})^2+(z-\bar{z})^2)\,dt$$

$$+\tilde{R}_2\int_0^T(x-\bar{x})^2\,dt+\tilde{R}_3\int_0^T((q-\bar{q})^2+(w-\bar{w})^2+(v-\bar{v})^2)dt$$

$$+\tilde{R}_4 e^{rT} \int_0^T ((x-\bar{x})^2 + (y-\bar{y})^2 + (z-\bar{z})^2)dt$$

$$+\tilde{R}_5 e^{rT} \int_0^T ((x-\bar{x})^2 + (y-\bar{y})^2 + (z-\bar{z})^2 + (q-\bar{q})^2 + (s-\bar{s})^2)dt$$

$$+\tilde{R}_6 e^{rT} \int_0^T \left(\left(l-\bar{l}\right)^2 + (w-\bar{w})^2 + (z-\bar{z})^2\right) dt$$

$$+\tilde{R}_7 e^{rT} \int_0^T \left((s-\bar{s})^2 + \left(l-\bar{l}\right)^2 + (y-\bar{y})^2 + (m-\bar{m})^2 + (w-\bar{w})^2\right) dt$$

$$+\tilde{R}_7 e^{rT} \int_0^T ((z-\bar{z})^2 + (x-\bar{x})^2 + (v-\bar{v})^2 + (q-\bar{q})^2)\, dt$$

$$+\tilde{R}_8 e^{rT} \int_0^T \left(\left(l-\bar{l}\right)^2 + (m-\bar{m})^2 + (w-\bar{w})^2 + (z-\bar{z})^2\right) dt,$$

$$+\tilde{R}_8 e^{rT} \int_0^T ((x-\bar{x})^2 + (v-\bar{v})^2 + (q-\bar{q})^2)dt$$

$$+\tilde{R}_9 e^{2rT} \int_0^T ((n-\bar{n})^2 + (m-\bar{m})^2 + (w-\bar{w})^2 + (z-\bar{z})^2)dt$$

$$+\tilde{R}_9 e^{2rT} \int_0^T ((x-\bar{x})^2 + (v-\bar{v})^2 + (q-\bar{q})^2)dt,$$

where $\tilde{R}_i's$, $i = 1, \ldots, 9$, depends on the coefficients and appropriate bounds. Applying the positivity of solutions of the variable expressions computed at both the initial and final time, and further simplifying the above inequality is restored to the following:

$$\left(r - R - \tilde{R}e^{2rT}\right)\int_0^T \Big\{(x-\bar{x})^2 + (y-\bar{y})^2 + (z-\bar{z})^2 + (q-\bar{q})^2 + (w-\bar{w})^2$$
$$+ (m-\bar{m})^2 + \left(l-\bar{l}\right)^2 + (s-\bar{s})^2 + (v-\bar{v})^2 + +(n-\bar{n})^2\Big\}dt \leq 0,$$

with R and $\tilde{R}$ depending on all the coefficients and upper bounds on all variable solutions $x, y, z, q, w, m, l, s, v, n$. If we select r such that $r - R - \tilde{R}e^{2rT} > 0$, then (4.5) holds if the integrand is identically zero. Thus, due to the fact that the natural logarithm function has an increasing property, then $ln\left(\frac{r-R}{\tilde{R}}\right) > 2rT$ provided $r > R + \tilde{R}$. This implies that $T < \frac{1}{2r} ln\left(\frac{r-R}{\tilde{R}}\right)$. Therefore, $x = \bar{x}, y = \bar{y}$, $z = \bar{z}$, $q = \bar{q}$, $w = \bar{w}$, $m = \bar{m}$, $l = \bar{l}$, $s = \bar{s}$, $v = \bar{v}$, and $n = \bar{n}$. Thus, the solution of the optimality system is unique for small time.

Table 4.1: Values of the parameters

Parameter	Values and units
r_1	$0.000000009\ day^{-1}$
k_1	$0.00886\ cells^{-1}$
μ_1	$0.05\ cell\ day^{-1}$
α_1	$0.99\ day^{-1}$
r_2	$0.09 day^{-1}$
k_2	$0.0089 cells^{-1}$
μ_2	$0.00008\ cell\ day^{-1}$
μ_8	$0.0091\ cell\ day^{-1}$
α_4	$9.1 \times 10^{-14} cells^{-1} day^{-1}$
μ_4	$0.00066 day^{-1}$
μ_6	$5.2 \times 10^{-15} day^{-1}$
a_1	$0.025\ cells^{-1} day^{-1}$
a_2	$0.052 cells^{-1} day^{-1}$
α_2	$0.345 cells^{-1} day^{-1}$
μ_5	$9.0 \times 10^{-8} day^{-1}$
μ_7	$0.14 day^{-1}$
d	2.0×10^{-10}

Table 4.1 Continued

Parameter	Values and units
h	0.5

4.4 Numerical Simulations

The optimality system obtained in section 4.3 is a two-point boundary value problem, where the initial conditions of the state system are given and final conditions of the adjoint system are also specified. It is solved via an iterative method with RK-4 scheme using parameter values from Table 4.1. An initial guess for the controls is first assumed. So, the state optimality system is solved forward in time by using the guessed values of controls via RK-4 algorithm with initial conditions of state system used. Next, the new solutions of state system obtained are applied to solve the adjoint system backward in time using RK-4 schemes with the terminal conditions used. We then compute new values of the controls from our characterization by using the new solutions of the state and adjoint systems. We repeat these iterations from the beginning with the new values of the optimal control pair until convergence (Garira et al., 2005). It is important to note that both systems above are solved with MATLAB version 2017b.

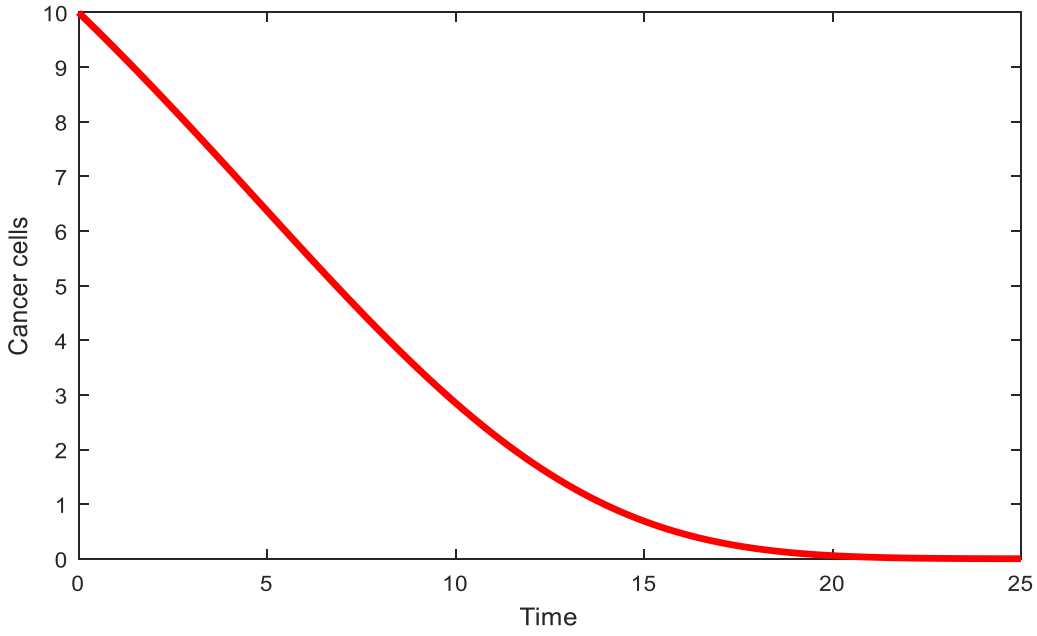

Figure 4.1: Cancer cells with optimal control pair

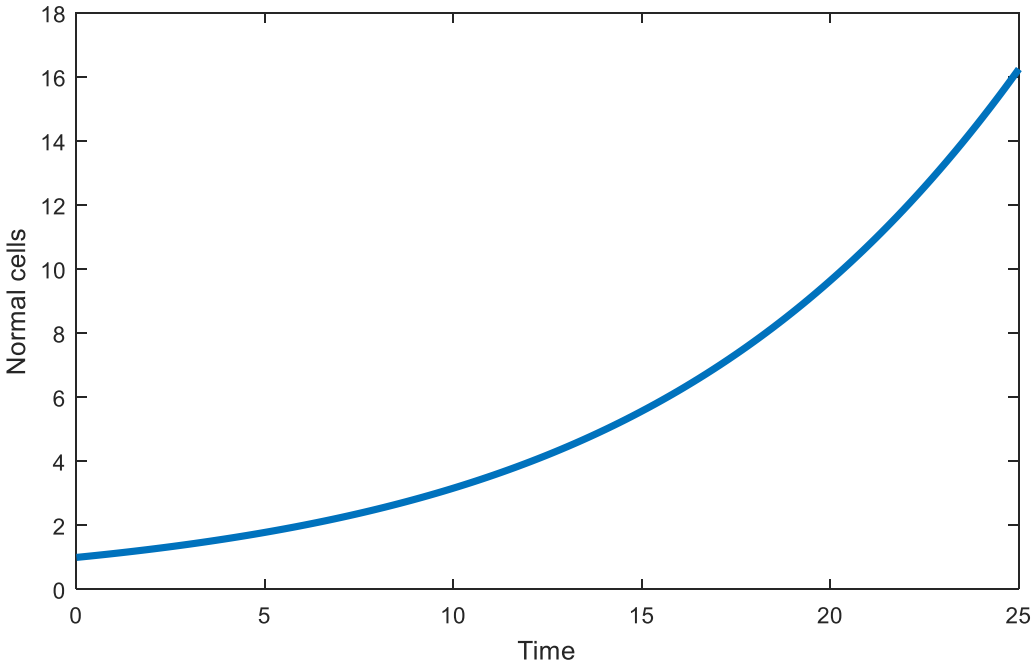

Figure 4.2: Normal cells with optimal control pair

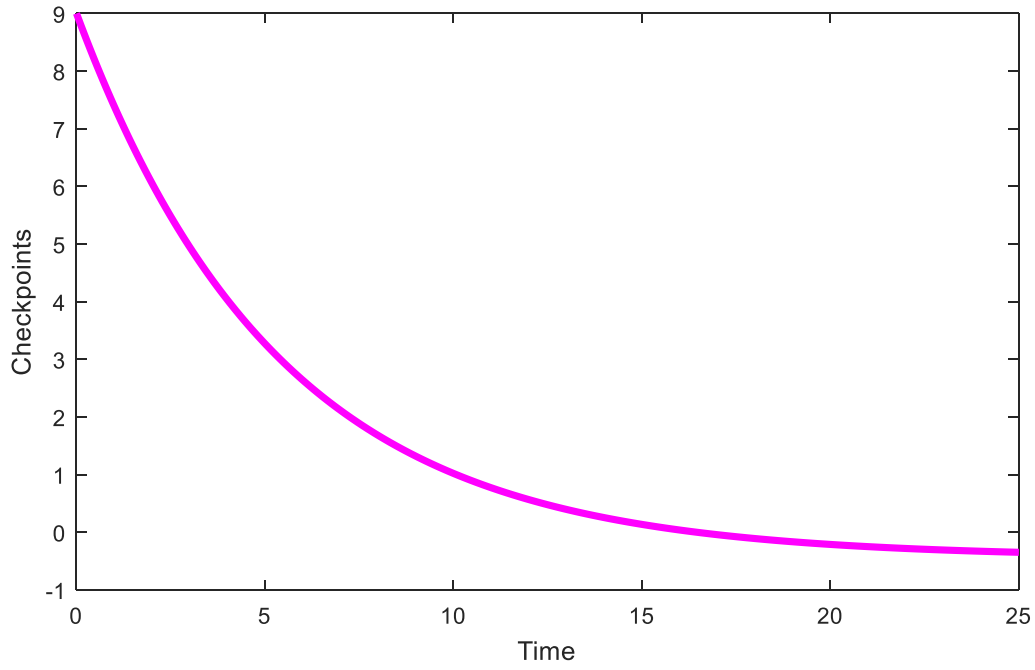

Figure 4.3: Immune checkpoints with optimal control pair

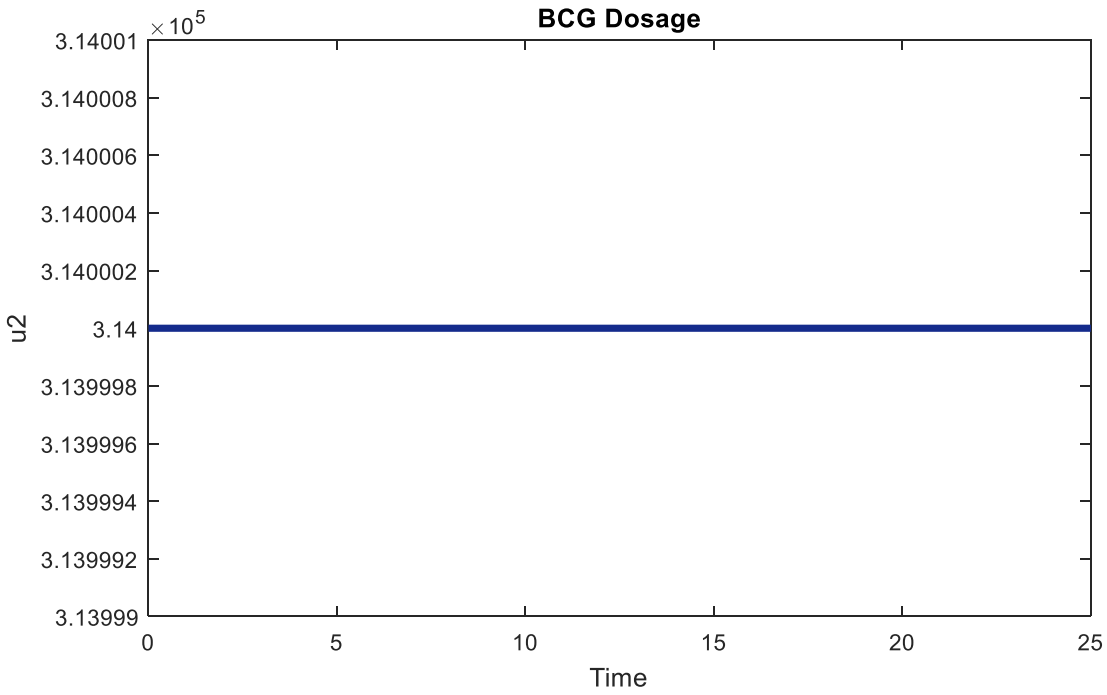

Figure 4.4: BCG dose (Second control function)

Figure 4.5: Immune checkpoint inhibitors dosage **(**First control function)

The results of the numerical simulations using parameter values from Table 4.1 are presented in Figures 4.1 through 4.5. In Figure 4.1, we can observe that the tumor is minimized and eventually eradicated when the two controls are applied. On the contrary, Figure 4.2 showed

that the concentration of normal cells is maximized after the application of the controls. The activities of the immune checkpoints are minimized after introducing the controls to the model and this can be seen in Figure 4.3. Figure 4.4 and 4.5 explains how the controls should be applied in order to achieve the desired aim (objective functional). From Figure 4.4, we can observe that the BCG dose should be $3.14 \times 10^5\ c.f.u$, and this amount must be administered throughout the period of the treatment so as to achieve the desired outcome. This amount is enough to trigger an immune response and at the same time is less toxic to the normal cells.

Moreover, from Figure 4.5, we can see that the maximum dose of the immune checkpoints inhibitors should be administered for a period of around two weeks, and then later on reduced to the minimum dose (of the checkpoint inhibitors) for the remaining duration of the treatment. Therefore, this treatment schedule for the checkpoint inhibitors will stop/block the activities of the checkpoints on the immune cells, thus, the effector cells can move freely, spread, locate, fight, and kill the tumor. Conclusively, the two controls are effective because they are able to minimize the objective functional viz. minimize the tumor volume, activities of the checkpoints, cost of controls, along with maximizing the concentration of normal cells.

4.5 Discussions and Conclusion

We presented a model of BCG immunotherapy for bladder cancer along with disturbance and suppression of immune system by the immune checkpoints. Two control functions u_1, u_2were introducedinto the model; the former block the activity of checkpoints on the immune effector cells while the latter triggers the immune system. Existence theorem of optimal control pair required to minimize the objective functional $J(u_1, u_2)$was stated and proved. The objective function minimizes the tumor concentration, activities of immune checkpoints, and cost of controls, in addition to maximizing the concentration of normal cells inside the bladder.

Pontryagin's maximum principle was followed in characterizing the nature of the optimal control pair. Coupling state system with its initial conditions and the adjoint system together with transversality conditions gave the optimality system; which is a two-point boundary value problem. The solution of the optimality system was shown to be unique for a sufficiently small time T. The forward-backward sweep method was applied to find numerical solutions of the optimality system. The solutions were displayed in Figures 4.1 to 4.5. In Figure 4.1 and 4.3, we observed that the number of cancer cells were minimized and eliminated eventually, and

the activities of the immune checkpoints were reduced as well, respectively. Figure 4.2 showed that the concentration of normal cells was maximized. The control functions required to do this was given in Figure 4.4 and 4.5; we can see the nature of our optimal control pair. When the BCG constant amount of $3.14 \times 10^5\ c.f.u$ is administered throughout the duration of the therapy *combined* with a maximum dose of checkpoint inhibitors at the early stage of the treatment (approximately two weeks), and so later reduced to a minimum dose of the checkpoint inhibitors for the period of the treatment, then, the immune system will successfully be triggered and the checkpoints will also be effectively blocked. Hence, the activated immune system will gain limitless freedom to wander about, detect, locate and rigorously attack and kill the cancer cells. Thus, the cancer will be successfully eliminated.

In conclusion, our control functions are effective in neutralizing the tumor. We recommend the combination of BCG immunotherapy and immune checkpoint inhibitors in combating this deadly disease.

CHAPTER 5

CONCLUSION

5.1 Conclusion

In conclusion, this thesis studied a deterministic model on BCG immunotherapy of bladder cancer with special consideration on the activities of immune checkpoints against the immune system. The first part of this thesis established mathematically the effects of the checkpoints on the immune system which leads to the failure of the entire treatment.

The second part deals with finding the BCG optimal dose needed to activate the immune system regardless of the actions of checkpoints. Moreover, the optimal dose is required to reduce the toxicity to normal cells. Optimal control theory is implemented via Pontryagin's maximum principle in order to find the characterization for the control function (BCG optimal dose). The control function effectively minimize the stated objective functional, because the cancer cells are minimized and eradicated eventually, activity of checkpoints is reduced as well, and the normal cells are maximized attaining some threshold.

The third part of this thesis is related to the emergence of new categories of drugs that are recently approved by the FDA named as checkpoint inhibitors – they block the activities of the immune checkpoints on the immune cells. We incorporate two control functions into the model we formulated in the second part. The first control function mimics the optimal dose of a checkpoint inhibitor, while the second control describes the BCG optimal dose. This implies that the second control gives the optimal BCG dose required to activate the immune system, whereas the first control blocks the activity of the checkpoints, so that the activated immune system move freely and kill the tumor. Pontryagin's principle was used to characterize the optimal control pair. The two control functions effectively minimize the objective function.

Thus, the medical practitioners should consider the single therapy suggested in chapter three, or combination therapy presented in chapter four. This is because all the two studies achieve the desired aim – minimizing and eventually eliminating the cancer cells.

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CURRICULUM VITAE

PERSONAL INFORMATION

Surname, Name : Saad, Farouk

Nationality : Nigerian

Date and Place of Birth : 6 April 1988, Kano

Marital Status : Single

EDUCATION

Degree	Institution	Year of Graduation
M.Sc.	AUST, Department of Mathematics	2013
B.Sc.	BUK, Department of Mathematics	2010

WORK EXPERIENCE

Year	Place	Enrollment
June, 2016 – Present	NEU, Department of Mathematics	Lecturer
Dec, 2013 – Present	Yusuf Maitama Sule University, Kano	Lecturer II
Feb, 2013 – Dec, 2013	Federal University, Kashere, Gombe	Assistant Lecturer

FOREIGN LANGUAGES

- English, fluently spoken and written.
- Arabic, speaks a little, and can write very well.

HONORS AND AWARDS

- Young researcher award, NEU, 2017.
- AUST Scholarship award, 2011.

PUBLICATIONS IN INTERNATIONAL REFERRED JOURNALS (IN COVERAGE OF SCI/SCI-EXPANDED):

- Saad, F.T., & Hincal, E. (2018). An optimal control approach for the interaction of immune checkpoints, immune system, and BCG in the treatment of superficial bladder cancer. *European Physical Journal Plus*, 133-241.

- Saad, F.T., Hincal, E., & Kaymakamzade, B. (2017). Dynamics of immune checkpoints, immune system, and BCG in the treatment of superficial bladder cancer. *Computational and Mathematical Methods in Medicine*, *2017*(1), 3573082.

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PUBLICATIONS IN INTERNATIONAL REFERRED JOURNALS (IN COVERAGE OF WEB OF SCIENCE AND SCOPUS):

- Saad, F.T., Şanlıdağ, T., Hıncal, E., Sayan, M., Baba, İ.B., & Kaymakamzade, B. (2019). Global stability analysis of HIV+ model. *In book: 13th International Conference on Theory and Application of Fuzzy Systems and Soft Computing — ICAFS-2018, doi: 10.1007/978-3-030-04164-9_109*
- Hıncal, E., Şanlıdağ, T., Saad, F.T., Suer, K., Baba, İ.B., Sayan, M., Kaymakamzade, B., & Sultanoglu, N. (2019). Dynamics and control of HIV/AIDS in Cyprus using real data. *In book: 13th International Conference on Theory and Application of Fuzzy Systems and Soft Computing — ICAFS-2018, doi: 10.1007/978-3-030-04164-9_24*
- Hincal, E., Saad, F.T., & Baba İ.B. (2018). A mathematical cancer model with BCG immunotherapy combined with immune checkpoints inhibitors: an optimal control approach. : *AIP Conference Proceedings 1997, 020003, doi: 10.1063/1.5048997.*
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THESISES

Master

- Saad, F.T. (2013). *Pricing of Compound Options.* Unpublished Master Thesis, African University of Science and Technology, Department of Mathematics, Mathematics Institute, Abuja, Nigeria.

Lisans

- Saad, F.T. (2010). *The Mathematics of Polyhedra.* Undergraduate project (B.Sc.), Bayero University, Kano, Department of Mathematics, Faculty of Science, Kano, Nigeria.

COURSES GIVEN

Undergraduate:

- Elementary Mathematics I
- Elementary Mathematics II
- Probability and Statistics
- Linear Algebra
- Mathematical Analysis
- Differential Equations
- Calculus I
- Calculus II
- Numerical Analysis I
- Numerical Analysis II
- Statistics I
- Statistics II
- Real Analysis
- Linear Algebra II

- Mathematics for Business and Economics I
- Mathematics for Business and Economics II

HOBBIES

Reading and Football