A MATHEMATICAL MODEL FOR THE EFFECTS OF INCUBATION AND CHEMOTHERAPY ON THE DYNAMICS OF TUMOR GROWTH

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DECLARATION AND APPROVAL

Declaration

This thesis is my original work and has not been presented for the conferment of a degree or award of any diploma in this or any other University.

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DEDICATION

I dedicate this thesis to my dear wife Esther Mbinya Ogidi, my jovial son Maxwell Odhiambo Ogidi and my lovely daughter Huldah Achieng' Ogidi. Not forgetting my parents Richard Wandugu Anyango and Hulda Atieno Wandugu.

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ABSTRACT

The application of mathematical models in simulating processes that are biological in nature has been in effect for a long time. A great number of mathematical, Computational, Engineering and Physical approaches have been administered to several aspects of cancerous tumour development , with a view of appreciating how cancer cell population responds to medical intervention. In most of these models however, no much attention was given to the effects of incubation in the presence of chemotherapy on the dynamics of tumour growth. This research therefore considered a mathematical model for the consequences of incubation and Chemotherapy on cancerous tumour growth dynamics by formulating a deterministic S (susceptible), E (exposed), I (infectious), R (removed) model using Delay differential equations. The delay or incubation in this case accounted for the duration between the exposure of a cell to cancer causing viruses and the onset of disease symptoms. Reproduction number (R_0) of the model was ascertained using next generation matrix approach. The stability analysis of Cancer Free Equilibrium Point (CFEP) and Cancer Endemic Equilibrium Point (CEEP) of the model were also investigated. MATLAB software was used for numerical simulations to validate the analytic results. The investigation and analysis of the consequences of incubation and Chemotherapy on the stability of the equilibrium points was also done. From the numerical findings it was found that R_0 at CFEP was obtained at 0.6667 and at 1.1037 the CEEP was stable. This study of tumour growth dynamics was significant in that it helps establish the stage and the extent of cancer spread within the body cells. It shall also help develop a better drug administration procedure as well as provide mechanistic insights. Parameter values used were mostly hypothetical values.

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LIST OF ABBREVIATIONS

DDEs   Delay Differential Equations

CEEP   Cancer Endemic Equilibrium Point

CFEP   Cancer Free Equilibrium Point

ODE   Ordinary Differential Equation

PDE   Partial Differential Equation

IVP   Initial Value Problem

ICs   Initial Conditions

HIV   Human Immunodeficiency Virus

NGM   Next Generation Matrix

IARC   International Agency for Research on Cancer

WHO   World Health Organization

ECM   Extracellular Matrix

SPVF   Singular Perturbed Vector Field

LIST OF SYMBOLS

S   Susceptible cells

I   Infectious cells

R   Removed cells

E   Exposed cells

τ Time delay

t   Time at which the tumor is considered

R_0 Cancer cell Reproduction number at the CFEP

R_1 Cancer cell Reproduction number at the CEEP

ϕ History function

μ Coefficient of Natural mortality rate

Λ Constant influx rate of new susceptible cells

N   Total Cell population

α Natural removal rate of symptomatic infected cells

β Rate at which the exposed cells become infectious

γ Probability that Susceptible cells become exposed by one infectious cell per contact time

η Removal rate of symptomatic cells due to chemotherapy

σ Removal rate of exposed cells due to autoimmunity

DEFINITIONS

Incubation - This is the phase in the development of an infection between the time a pathogen enters the body of an organism and the time the first symptoms appear

Chemotherapy - This a method of cancer treatment that makes use drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing and attacking the adjacent cells.

Dynamics - Growth dynamics refer to the changes in the cell population or organisms over time

A mathematical Model - This is an abstract description or representation of a concrete system using mathematical concepts and language.

Biopsy - This is a medical procedure where a small sample of tissue is taken from the body for examination under a microscope.

CHAPTER ONE

INTRODUCTION

1.1 Overview

The chapter provides foundation knowledge on cancer modeling. Definition of cancer and types of tumors are illustrated including a brief discussion on cancer statistics and its methods of treatment. The definition of Delay Differential Equations, types of Delay Differential Equations, simulations of delay differential equations and their analytic solutions are also discussed. Finally, the problem statement for the research, the objectives of the research, both general and specific objectives and the significance of the research are also given attention.

1.2 Background information

Incubation is the phase in the development of an infection between the time a pathogen enters the body of an organism and the time the first symptoms appear while chemotherapy is a method of cancer treatment in which drugs are used to stop the growth of cancer cells or to stop them from dividing and attacking the adjacent cells. Upon admission of chemotherapy, the cancerous cells are killed by the drug and therefore removed from the rest of the cells , this informed the use of the model SEIR where "R" represents the cells that have been killed or removed by the drug or by natural immunity.

Growth dynamics refers to the changes in the cell population or organisms over time. A mathematical model is an abstract description or representation of a concrete system using mathematical concepts and language, a process which is referred to as mathematical modeling. On the other hand, biopsy is a medical procedure where a small sample of tissue is taken from the body for examination under a microscope. Mathematical modeling of biological processes especially on cancer has in recent times received much attention. This coupled with associated numerical simulation has reduced the complicated and costly experimental procedures (Nyarko et al. 2020). It has been adopted by

several epidemiologists as one of the approaches to study non-communicable diseases such as chronic respiratory disease, diabetes, stroke among others.

According to World Health Organization (2018) cancer is rated second as a main cause of mortality after heart diseases . Cancerous tumour growth, spread to the adjacent tissues and treatment have been explained by various mathematical models in the past. Terminal illnesses or diseases are conditions which cannot be cured hence leads to the death of the affected persons. Examples of terminal diseases are Liver disease, HIV, Lung disease, advanced heart disease, advanced cancer among others. According to World Health Organization (2020), breast, lung, colon, rectum and prostate cancers are the most common ones. Since cancer cases has been on an upward trajectory, this is a clear indication that most of the measures put in place to address this issue has not been very effective. In this study we examine how mathematical models can be used to imitate tumour growth as well as cancer medication.

According to Sinha (2018) tumour is an abnormal mass of tissue which may be solid inside or filled with fluid. There are three tumor types, namely, benign, premalignant and malignant tumours. When the development of tumour cells are restricted to the location of emergence, does not spread to other sites of the body, grows slowly and have distinct borders, then they are said to be benign tumours. Such tumours are non-cancerous. Premalignant tumours are those in which cells are not yet cancerous but have the potential of becoming cancerous. Finally, when the cells are unusual, grow rapidly and can proliferate to other sections of the body, then they are referred to as malignant tumours or cancerous cells.To establish if a tumor is cancerous or benign, a fragment of the cells is taken through a biopsy procedure by a doctor and then examined. A pathologist then analyzes the biopsy under a microscope in a lab to make a diagnosis. On the other hand, cancer is a genetic malady caused by changes to genes that control the way the body cells function, how they grow and how they fractionate.

Cancer cells diverge from the other cells in different ways. For example, their growth takes place even in the absence of the signal initiating their growth, continues growing despite the signals stopping their growth. They also attack the surrounding cells of the body among others (Sinha, 2018). According to Das et al. (2022) cancer is regarded as one of the most exhausting illness to treat and hence leads to more deaths than most diseases and that combating cancer is crucial for public health. Over the years several methods of cancer treatment have been used, these include hormone therapy, surgery, radiotherapy, immune therapy and chemotherapy among others. Mathematical epidemiology has

contributed to a more in-depth understanding of cancerous tumor growth as a terminal ailment, its effect and possible future forecast about its spread in the body and the mechanism of its control and treatment.

1.3 Delay Differential Equations

Delay Differential Equations (DDEs) are a framework of Ordinary Differential Equations (ODEs) in which derivatives are dependent on previous states or past history. Many processes depend on past history hence the choice of delay differential equations. There are two classes of Delay Differential Equations, namely, Constant Delay Differential Equations and Variable Delay Differential Equations. The Delay Differential Equation takes the form

$$x^{'}(t) = f(t, x(t), x(t - \tau)) \qquad \forall x \in \mathfrak{R}^n \quad and \quad \tau > 0 \tag{1.1}$$

where

t is the time

$x(t)$ is the current cancer stage and

$x(t - \tau)$ is the tumor stage at a past time $(t - \tau)$.

If τ is constant, then Equation (1.1) is referred to as Constant Delay Differential Equation otherwise Variable Delay Differential Equations. In this study, Constant Delay Differential Equation as opposed to variable delay differential equations were considered since the time delay $,\tau$, cannot be zero or less for this research.

At time, t , the evolution of the Equation (1.1) depends on the current time, t, current status, $x(t)$, of the tumor and at some different time $\tau > 0$ in the past. Since the time delays are constant and after several time delays, Equation (1.1) becomes,

$$x^{'}(t) = f(t, x(t), x(t - \tau_1), \dots, x(t - \tau_n)) \tag{1.2}$$

If the derivatives at the time delays are incorporated into Equation (1.2), it then yields

$$x^{'}(t) = f(t, x(t), x(t - \tau_i), x^{'}(t - \tau_j)), i = 1, \dots, n, j = n + 1, \dots, m \tag{1.3}$$

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in which $x^{'}(t - \tau_j)$ is the derivative as the time delays.

At time, t, the evolution of the Equation (1.3) is dependent on the present time, t, current status, $x(t)$, of the system and status of the system, $x(t - \tau)$, that was for latest units of time.

$$x^{'}(t) = f(t, x(t), \int_{t-\tau}^{t} \phi(x(s)ds) \tag{1.4}$$

where

$\int_{t-\tau}^{t} \phi(x(s)ds)$ is the continuous version of DDEs and

ϕ is the history function

1.3.1 Simulating Delay Differential Equations

Initial Value Problem (IVP) for the Delay Differential Equation (DDE) is generally expressed in the form

$$x^{'}(t) = f(t, x(t), x(t - \tau_i)), i = 1, \ldots, n, t \geq t_0 \tag{1.5}$$

The Initial Conditions (ICs) or History function is

$$x(t) = x_0(t), t \leq t_0 \tag{1.6}$$

where

$x_0(t)$ is known as history function or Initial function.

For instance.

For

$$x^{'}(t) = f(t, x(t), x(t - \tau)), t \geq t_0 \tag{1.7}$$

We provide initial data on interval $[t_0 - \tau, t_0]$ $\forall t \in [t_0 - \tau, t_0]$, $\quad as \quad$ $x(t) = \phi(t)$ from equation (1.7) if f is smooth and is true for $x_0(t)$ we have

$$\lim_{t \to t_0^-} x_0(t)^{'} \neq \lim_{t \to t_0^+} x_0(t)^{'} \tag{1.8}$$

that is, there exists a jump derivative discontinuity at t_0. A jump discontinuity occurs when a function leaps or steps, from one point on its curve to another, frequently dividing it into two distinct pieces.

These discontinuities spread in time. We not only get discontinuity at initial point, but also at later time points.

1.3.2 Analytical solution of Delay Differential Equations

From Equation (1.7) and the original functions on the range $[t_0 - \tau, t_0]$ in which τ is the delay term, we first examine the range $[t_0, t_0 + \tau]$ on which the Delay Differential Equation reduces to Ordinary Differential Equation. We obtain a solution legitimate on this range and then use this solution as the initial function for the next interval $[t_0 + \tau, t_0 + 2\tau]$. We then find a solution on $[t_0 + \tau, t_0 + 2\tau]$. The solution is then applied forward from one interval to another. Proceeding this way gives rise to a solution of Ordinary Differential Equations on the interval $[t_0 - \tau, \infty]$ which becomes smoother and smoother with time ,t, as t increases.

1.4 Statement of the problem

Despite several studies and discoveries aimed at suppressing cancer prevalence prevention or medication, the disease has continued to be a great problem World-wide in all populations without regard to wealth or social rank. Some of these studies recommended medication such as chemotherapy without details on the stage at which the medication is optimal. As reported by the International Agency for Research on Cancer (IARC 2020), one in every five people in the world develops cancer during their lifetime. One in eight men and one in eleven women succumb to the disease according to IARC (2020). Breast cancer accounted for one in four cancer cases diagnosed among women in 2020 worldwide. Cervical, colorectal, thyroid and lung cancers are also prevalent among women while prostate cancer and lung cancer are the most popular among men which together account for close to one-third of all male cancers. For this reason a mathematical model that explores the ramifications of incubation period and chemotherapy on the tumour growth dynamics was considered for this study. Chemotherapy unlike other methods of cancer treatment does not target non-cancerous cells while incubation period gives the duration within which the medication would be optimal.

1.5 General Objective

The general objective of the research is to develop a mathematical model for the consequences of incubation and chemotherapy on tumour growth dynamics.

1.6 Specific Objectives

The specific objectives of this study were;

(i) To formulate a SEIR mathematical model that describes the effects of incubation and chemotherapy on tumour growth dynamics.

(ii) To compute equilibrium point of the model (CFEP and CEEP) to help understand important characteristics of the model.

(iii) To examine the stability of the equilibrium points of the model so as to help determine whether the model will remain stable under various conditions and inputs.

(iv) To carry out numerical simulations of the model using MATLAB software so as to predict the behavior of the model.

1.7 Justification of the study

The deterministic SEIR model developed in this study was fundamental in addressing the cancerous tumour growth dynamics for effective treatment. It took into account the effects of time delay and chemotherapy on the cancerous tumour growth dynamics. This in addition aids in developing a better drug administration procedure as well as providing mechanistic insights. However , this study is limited to mathematical modeling at this stage and may require the services of a medical practitioner for implementation.

1.8 Significance of the study

Cancer being a major cause of fatality worldwide , more and effective treatment methods are important in addressing this challenge. Further, there is need to improve the knowledge of cancerous tumour growth dynamics and treatment options. In view of this and for optimization of treatment this study presents a method whose findings shall help improve cancer treatment.

Governments spend huge sums of money in their effort to respond to the problem of cancer treatment. the results of this study has provided insights on improved and better way to monitor cancerous tumour growth dynamics and how time delay and chemotherapy effects helps in improved treatment.

Medical practitioners in their effort to provide better medical treatment to the cancer patients , shall make use of the results of this study from the stability analysis of the CFEP to design clinical trials that are more effective in cancer treatment.

This study sought to formulate a mathematical model for the effect of incubation and chemotherapy on the dynamics of tumor growth in order to establish efficacy levels of the drugs.

CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

The chapter delineates a snapshot of prior related studies which have been done in the field of cancer research. A brief summary of the methods used, findings and limitations of such studies are outlined here. The gaps identified formed the basis and the foundations on which this study is built. The aim was to come up with a better way of managing tumor growth and treatment. The study sought to achieve this.

2.2 Review of related literature

There have been considerable number of literature on the development of mathematical models on cancerous tumour growth dynamics. A number of mortality especially in developing countries have been associated with cancer. These models have contributed to improved cancer treatment as well as post treatment care for cancer patients.

The growth kinetics of cancer cells were examined by Aliasghari et al. (2023) using a fractional derivative model. The power-law kernel of the time fractional Caputo derivative was used to depict the memory effects. To apply the suggested fractional model numerically, the trapezoidal rule was used. The new fractional model's validity and effectiveness in demonstrating the presence of the cancer growth dilemma were confirmed by some numerical studies. This phenomena demonstrated how a higher non-stem cancer cell death rate (due, for example, to medication or tumor excision) caused cancer stem cells to propagate more quickly. Even though it's unknown how cancer stem cells contribute to the disease, it was important to know that conventional treatments could eradicate non-stem cancer cells. New treatments that eliminated cancer cells and prevented tumour recurrence used medicines that were specifically aimed at cancer stem cells as opposed to therapies that were

not. Clearly, fractional differentiation could be used to simulate biological systems as a highly effective approach. In addition to these benefits, fractional-order differentiation above integer-order one also had the advantage of having unique traits like heredity, long-range memory, and long-range interactions. They discovered the effectiveness of the suggested method by contrasting the outcomes of the fractional-order derivative model with the integer-order one. The solutions of their model matched reality more closely than the results of the conventional integer-order model, proving the efficiency of the proposed method. However, less attention was given to the effect of incubation or time delay on the tumour growth dynamics an aspect which this research gave attention.

Chamani et al. (2023) used in vitro research to produce a measurement for the degree of heat damage in murine pancreatic carcinoma cell lines following exposure to temperatures in the range of 42.5^oC to 50^oC and obtained thermal injury kinetic model parameters. Their findings implied that the revised Arrhenius model integrating the time delay to address the shoulder region is best acceptable for use in moderate hyperthermia therapies up to 60 minutes of heating. When cells were exposed to time-temperature profiles resembling those expected at the edge of an ablation zone, the accuracy of the created injury predicting models was experimentally tested. They however, despite having time as a factor, they did not consider the effect of time along side medication on the dynamics of tumour growth.

A mathematical model for tumour cell growth and survival considering environmental stress level was developed by Sabrina et al. (2022). The model outlined the influence of oxygen level, nutrient saturation, drug concentrations or mechanical forces to the tumour cells all together by bringing into play the "environmental stress level". A higher stress level can reduce the growth of cells while promoting cell death hence influencing cell development. As an accreditation of the idea, they contrasted the two styles of ordinary differential equations for modeling the dynamics of tumour cells under varied nutrient concentration correspondingly taking into account the stress levels of the environment and without considering the environmental stress levels. Their research neither considered time delay nor chemotherapy as factors that could affect tumour growth.

A mathematical model that considered the reciprocal action between the cancerous cells, the body immunity and viral therapy was fronted by Ali et al. (2022). The model considered the cell population in four different sub-populations. They included uninfected cells, infective cells, immune cells and virus-

free cells. The research showed an analysis of the stochastic mathematical model for the fluctuation of cancer cell population considering viro-therapy. The outcomes of the model have re instituted the attributes of the problems biological in nature, such as dynamical coherence, boundedness and positivity. These are the requisite considerations for mathematical modeling in these areas of study. The current computational techniques, such as the Stochastic Euler method, the Euler Maruyama method together with the Stochastic Runge-Kutta method, did not rejuvenate the properties mentioned above. The research suggested a stochastic non-standard finite difference method which is efficacious, cost effective, and contains all the feasible properties desired. The current standard stochastic techniques coincide with limitations after some time. The result from the non-standard finite difference method is steady and concentrates over all time intervals. This model considered viral therapy as opposed to chemotherapy.

The changing characteristic of the nonlinear mathematical model which was initially fronted by De Pillis et al. (2003) was advanced by Das et al. (2022) in a mathematical model for cancer analysis considering time delay by introducing the delay component in the relationship between the tumour cell itself and the body's defense system. This was done in an effort to ensure that the model is more practical. The investigation of the mathematical model showed that, the elimination of the tumour cells entailed a joint effort of both normal cells and the immune system without the drug administration. However it was also shown that the immune system of the body did not acknowledge the tumour cells immediately so as to give enough feedback time (i.e., the time delay was prolonged), the growth rate of the tumour increased hence the system's immune stability was lost and finally drifted away from the tumour-free steady point. As a consequence, the immune–normal cell failed to effect the destruction of the tumour burden. Despite an introduction of time delay, they did not include chemotherapy for treatment instead they depended on the immunity of the body.

The investigation in a mathematical model for chemo-immunotherapy, which is a combination of chemotherapy and immunotherapy for brain cancer by Nave (2022) depended mostly on the time interval between treatment and dosage. The system of equations used included nonlinear first-order ODEs. The mathematical model considered the interaction of immune system with cancer cells and the treatment. The dynamic variables of the system are immature dendritic cells, immunogenic dendritic cells, tolerogenic dendritic cells, naive T-cells, cytotoxic T-cells, proliferating cytotoxic T-cells, cancer cells, and chemotherapy medicine. They proposed a new treatment protocol, which was essentially a

new analytical function that depended on the time interval between treatment and dosage. To investigate the stability of the equilibrium points, it was necessary to solve the nonlinear algebraic equation related to the mathematical model, which, in this case, was impossible analytically. Hence, they applied the Singular Perturbed Vector Field (SPVF) algorithm to transfer the mathematical model to a new coordinate with an explicit hierarchy and divided it into fast and slow subsystems. This procedure enabled them to investigate only the fast subsystem, without losing the biological information of the original model. They determined all equilibrium points of the model in the new coordinates and their stability. The equilibrium points had no biological meaning in the new coordinates; hence, they inversely transformed only the stable equilibrium points into the original coordinates of the model. They investigated the mathematical model with their proposed treatment protocol, with constant dosage and different time intervals between treatments, that is, 7, 14, 28, and 56 days. Thereafter, they compared their analysis results with experimental (clinical) data. The optimal treatment was found to correspond to the protocol with a 7 day interval between treatments. The next step involved the application of the protocol with different dosages and time intervals simultaneously. They examined the behaviour of cancer cells when the initial conditions were changed. All results were identified to reach a state of equilibrium at approximately the same time. Indeed, this was dependent on the treatment, which had been determined to vary in terms of dosage and time.

The development of a model with random noise on the dynamical behaviour of the tumour and the immune system by Fathalla et al. (2021) assimilated the consequence of noise into a model for tumour-immune system with Holling type III response functions to cater for the alterations in cell dynamics. It made use of a stochastic Lyapunov function together with Ito's formula, to provide enough constrain for establishing the existing stationary distribution results, weak persistence, and elimination of tumour cells. The stochastic model for tumour-immune interaction was used. The research also showed that the growth of tumour can be reduced by increasing the intensity of the noise as a fundamental factor in the existence of immune effectors.

In their mathematical model which considered the analysis of cancer, Dehingia et al.(2021) included the time-delay in the interactivity amidst the tumour cells and the immune system of the body and their stimulation processes. It analyzed and observed the model dynamics together with changes of crucial restrictions and the effect of time delay on anti-tumour immune reaction. The delay term was included in the model. As a consequence, the modified model demonstrated that the system was able to

bring about varying responses even with the delay term included. In addition, it demonstrated that the oscillations were continuous and couldn't be eliminated through the addition of the delay term. The numerical simulations and bifurcation analysis indicated that a "careful" consideration of the model's framework has to be determined so that the fixed-state becomes less stable. It was shown that the time delay was not a requirement to originate oscillations since such oscillations could be generated even in the absence of the delay term.

Arvind et al. (2021) established a model for tumour cells population growth with the human body's metastasis process and approved by the use of Rough set method in uncertain conditions. The study used an ODE model to address tumour development and expectations about the sufficiency of growth medication. This model was pivoted on the amount of tumour cells and the carrying capability. It was found that the amount of cells increased with increase in time. The number of tumour cells reached a constant state called the carrying capacity after some specific time of growth. It was also shown that, if Tumor cells' growth reaches the carrying capacity, then a few cells from the Tumor leave and make another tumour. The rate of tumour cell growth would be proportional to the present cell population in an event there are no dead tumour cells.

In order to analyze the behavior of the tumour-immune interaction system, Pal et al. (2021) used conformable fractional derivatives. While working with biological systems, the approach did not encounter any of the problems that other fractional order derivatives do. In order to explain the behavior of tumour-immune models, it was preferable to use the conformable fractional order derivative, which incorporated the idea of long run memory. It was demonstrated that both systems had distinct dynamical behaviors by a graphic time series analysis of the data. The results of the time series analysis revealed that the population growth of tumour cells originally grew suddenly, but as time passed, it then started to decline and eventually became steady. The conformable fractional derivative may also be used with tumour models that exhibit more complicated behaviors. By taking into account the proliferation of other effector cells, particularly macrophages, and employing conformable fractional derivatives, the behavior of tumour-immune interaction may also be investigated. The effectiveness of immunotherapy in the model is established by the observations of stable dynamics of all cell populations in the fractional order tumour model, where effector cells increase, tumour cells decay to zero, and immunotherapy cells remain within a fixed range for all values of the fractional order parameter. They draw the conclusion that following discretization, change in the external source of effector cells had no impact

on the dynamics of tumour cells or immunotherapy cells, only on effector cells. The fact that tumour cells disappeared with the same decay rate for all sigma values demonstrated the efficiency of the system that was then offered for halting the growth of tumour cells in all kinds of systems.

Singh (2021) studied a mathematical model with mixed chemotherapy on tumour cells in two different stages under depression effect. The research established that the rate of tumour growth is lower in primary stage than secondary stage. They showed that the tumour growth depends on a decrease of immune cells. The results of the model demonstrated that depression reduces the amount of immune cells while increasing the tumour cell numbers. Depression in the primary stage did not affect both immune cells and tumour cells in anyway because in the primary stage the patient does not know that he has cancer. But as soon as he comes to know, the effect of depression affects the patient. As a result, the depressions increases, the patient loses immune capability, leading to increased tumour cells. When the effect of depression increases, the tumour cells increases greatly, due to which the effect of chemotherapy is very low, almost inactive and the patient can die from depression.

The use of virotherapy as a treatment for cancer was developed by Zachary et al. (2020) in which a system of four nonlinear differential equations was used . The model described interactions among infected tumor cells, uninfected tumour cells, effector T-cells, and virions. It established that when the virotherapy protocol is not strong enough to ensure tumour eradication, the model gives two possibilities. The first possibility is a stable cancer persistence state where the tumour may shrink, but is never eradicated. In such a case, the model predicts that virotherapy could be useful as a neoadjuvant therapy in preparation for surgery or radiotherapy treatment. The second possibility is periodic cancer recurrence that may indicate further progression of the tumour or metastasis. While Kim et al. (2015) found that the most important factors in controlling short term tumour growth were the immune response and the virus burst size, this model suggested that the virotherapy dosage and the infection rate of the virus are key parameters to ensure long term tumour eradication.

Nyarko et al. (2020) fronted an advection-reaction-diffusion system of partial deferential equations (PDEs) to explain interactions between tumour cells and extracellular matrix (ECM) at the macroscopic level. They used a set of common differential equations to simulate the interaction between proteolytic enzymes and the ECM at the subcellular level (ODEs). The macroscopic and microscopic events were coupled together using a contractivity function. Their model included an addition that supplied

nutrients from the underlying tissue. The PDE-ODE sets of equations modeled the beginning of tumour cell infiltration of the host extracellular matrix. Several time and geographical scales at the macroscopic and microscopic levels were taken into consideration by the model. The numerical solution for the system of equations indicated roughly three separate strata of proliferative, quiescent, and necrotic cell densities. This research contributed the following advances to the mathematical models already in use for tumour invasion of host tissues. Several spatial and temporal scales were present in subcellular, microscopic, and macroscale events. A contractivity function connected the two time scales. As a result, scientists were able to identify how biochemical dynamics at the subcellular level affected the toughness and motility of tumour cells. The model took into consideration how the tumor microenvironments may restrict quiescent and proliferative cells through interaction.

Global stability analysis to control growth of tumour in an immune-tumour normal cell model with drug administration in the form of chemotherapy by Paul et al. (2019) determined a range for the drug administration rate so that the tumour free equilibrium can be made globally stable by constructing a simple quadratic Lyapunov function. It was assumed that the administration of drug in the form of chemotherapy followed the logistic growth law with a per capita decay rate of the drug once it has been injected. Further it was assumed that the drug kills all types of cells.

Kozowska et al. (2018) established in their work that the primary cause of cancer-related mortality is resistance to chemotherapies. They also noted that in order to increase patient survival, a greater comprehension of the prevalence and dynamics of active resistance mechanisms is required. The study put out the idea that employing extensive clinical data in mathematical modeling and simulation, it is possible to accurately assess the worth of preclinical drugs in virtual cohorts. This method enables efficient and affordable assessment of the additional value of combination medicines, which may be challenging or expensive to evaluate in vivo or in patients. Sensitivity analysis revealed that the percentage of cells eliminated after surgery was the most crucial parameter. Debulking surgery has been proven to be a highly effective method of reducing the amount of tumour tissue present, and, unlike chemotherapy, it is capable of removing a large portion of chemotherapy-resistant cells, hence lowering the likelihood of resistance. Some clinical research showed that adequate cytoreduction produced a considerable survival benefit which helped highlight the importance of surgery. Chemotherapy efficiently destroys cancer cells that are sensitive to drugs, but it also gives resistant cells a selection advantage since they can proliferate with less restrictions on resources and space. Additionally, it

was determined that combination therapy had been recommended as a successful way to deal with therapy failures in advanced solid tumors. To achieve a large and long-lasting survival advantage, it was not generally recognized how many medications should be combined. The findings of this study suggested that at the time of diagnosis, some tumor cells already had up to five resistance mechanisms functioning. Throughout their analysis, they made the supposition that a targeted medication would kill cancer cells with the corresponding active resistance mechanism just as well as platinum would kill cancer cells with a platinum-sensitive resistance mechanism. Although each therapy's effectiveness varied, combining therapies can have beneficial synergistic benefits. Theoretical support for a therapy paradigm based on their findings was offered, with the aim of maximizing the impact of platinum on cancer cells while also overcoming resistance mechanisms with specific medications.

Yoichi et al. (2015) developed a kinetic model of tumour growth and its radiation response with an application to Gamma Knife stereotactic radiosurgery to simulate the growth of tumour volume. This was formulated using nonlinear Ordinary Differential Equation. It was established that tumour volume consists of cancer cells that rapidly increases in number and the non-dividing cells. When subjected to radio therapy, the multiplying cells die off gradually over a fixed period of time. The dead cells are then cleared away with cell clearance time.

In the study, Delay Differential Model for tumour-Immune Response with Chemoimmunotherapy and Optimal Control which was fronted by Rihan et al. (2014), developed a delay differential model with exceptional control that illustrates the interactions of the tumour cells and the immune response cells with external therapy. The intracellular delay was introduced into the model to account for the duration required to stimulate the effector cells. The research showed that the performance of a combination of therapy protocol of immunochemo therapy is better than the standard protocol of chemotherapy alone. While for their study they looked at the time delay for intracellular cells to account for the duration required to stimulate the effector cells. For this study , this duration is extracellular and accounts for the duration between the exposure of a cell to cancer causing viruses and the onset of the disease symptoms. This sets this research a head of the former as the performance of the chemotherapy is better. In addition their study was however limited to the patients whose immune systems are strong since one of the key parameters was immune cells thereby restricting the method.

In simulating the evolution of the total tumour cell number over time ,Heiko et al.(2014) used both

partial differential equations (PDEs) and ordinary differential equations (ODEs) in their models. Partial differential equation (PDE) model was used because the ordinary differential equation (ODE) model lacked the spatial consideration. The infiltration of cancer and the metastatic diffusion are two vital and fundamentally spatial procedures hence can be simulated using partial differential equations (PDEs) models. The study took into account the total suppression of the volume of tumour by initiating cell death in proliferating cancer cells, or by reducing the tumour support via decrease of the carrying capability. The two forms of cancer medication could be included in differential equation models.

Rihan et al. (2012) developed a mathematical model for the interaction between the growth of tumour cells and the immune system. In this study the interactions between the tumour-growth dynamics and the immunotherapy was done using ordinary differential equations and delay differential equations. It established that the elimination of tumour cells is dependent greatly on the intensity of medication.

The nonlinear mathematical model for the analysis of tumour treatment with Oncolytic Virus which was advanced by Manju et al. (2011) was used to study the interconnection between Oncolytic virus and the tumour cells. The analysis of model was done using the stability theory of the differential equations. Runge-Kutta method was also used for numerical simulation of the model which up-held the theoretical findings. It was established that both the infected and non-infected tumour cells and hence tumour burden can be eradicated in the long run and that complete cure is possible through the use of virus therapy, if the following requirements were accomplished. One, that when the Oncolytic virus attacks and destroys cancer cells by direct eradication of the tumor cells, and, two, that, if altered, as vectors permitting gene expressing anticancer proteins are delivered specifically to the tumour site.

In their research work, Ramis-Conde et al. (2008) presented a hybrid discrete-continuum mathematical model for the invasion of cancer. In an effort to simulate adhesion forces, cancer cells were considered as distinct entities that interacted with one another. In reaction to chemical and matrix gradients, cancer cells move in a coordinated manner while multiplying and secreting enzymes that break down the matrix. The chemoattractant gradients' significance in the invasion process was underlined by the model. A few cancer cells' local invasion methods may be accurately reconstructed by computational simulations of the model. The output of continuum models was in contrast to this.

2.3   The Knowledge Gap

Most of the above mentioned studies did not take into consideration the effects of incubation or time delay in their models. However, Dehingia et al. (2021) included the time delay in their study though they did not consider chemotherapy as a treatment for tumour growth while, Rihan et al. (2014) used delay differential equations to model the relationship between tumor cell growth and immune system. Their study was however limited to those patients whose immune systems are strong since one of the key parameters was immune cells thereby restricting the method. This study thus formulated a SEIR deterministic mathematical model with delay differential equations (DDE) for the investigation of the effects of incubation and chemotherapy on tumour growth dynamics.

CHAPTER THREE

RESEARCH METHODOLOGY

3.1 Introduction

Presented in this chapter are the definition and significance of basic reproduction number. The methods of solution to achieve the objectives of the study and a discussion on some different types of epidemiological models. Secondly, the approaches used to achieve the objectives of the study , the illustrations of the SEIR model for the tumour dynamics, model assumptions and equations are also outlined. In addition the model preliminary analysis, the calculation of the basic reproduction number, computation of the Equilibrium points for both Cancer Free Equilibrium point and Cancer Endemic Equilibrium point and the stability analysis of the equilibrium points for both local and global are also given. Finally, a discussion of the sensitivity analysis of the basic reproduction number is also discussed.

3.2 Methods of Solution

The mathematical model that describes the dynamics of tumour growth was formulated using a compartmental SEIR model whose governing equations were Delay Differential Equations. The Delay Differential Equations were preferred since they accounted for the incubation or period. The delay or incubation period accounted for the duration from when a cell is exposed to cancer causing virus and when the symptoms are observable. Again cause and effect does not happen at the same time, hence the choice of these equations. Chemotherapy, compared to other methods of cancer treatments, is more effective, has more advantages and is preferred as a support to other methods for example if one has chemotherapy treatment after surgery, this may reduce the chances of the cancer coming back. The equilibrium points of the system were established. The two stable states established were, the Cancer Free Equilibrium point and the Cancer Endemic Equilibrium point. A system has an equilibrium point

if there is no change in the system at all the time, (Widyaningsih et al. 2018). It is the stable-state values of the model. At the infection-free stable state , Cancer Free Equilibrium Point ,$E = I = R = 0$, hence $S = N$ while at the Cancer Endemic Equilibrium Point all the S, E, I and R are all non-zero, that is ,$S > 0, E > 0, I > 0$ and $R > 0$.

The stability of the Cancer Free Equilibrium Point and Cancer Endemic Equilibrium Point were determined by constructing the next-generation matrix. This was done by first forming two Jacobian matrices F and V from the diseased classes of the model equations. The Jacobian matrix is the first partial derivative of the differential equations deduced from the compartmental diagram. The next generation matrix is then computed from the matrices F and V. Where, F is the matrix for the new cancer cells while V is the matrix of the transfers of infections from one compartment to another. The matrix FV^{-1} is the next generation matrix. The most dominant Eigen value (spectral radius) of FV^{-1} is equivalent to the basic reproductive number of the model.

For instance, for a SEIR model from whose model equations are $(3.1), (3.2), (3.3)$ and (3.4) as shown below, the reproduction number can be calculated as follows,

$$\frac{dS}{dt} = \Theta - \Psi S - \Pi SI \tag{3.1}$$

$$\frac{dE}{dt} = \Pi SI - (\Psi + e)E \tag{3.2}$$

$$\frac{dI}{dt} = eE - (\Psi + \Phi)I \tag{3.3}$$

$$\frac{dR}{dt} = \quad \Phi I - \Psi R \tag{3.4}$$

where

Θ - is the Recruitment rate of the Susceptible class, Ψ- is the Natural death rate, Π - is the infection contact rate, e - is the infection rate of Exposed class and Φ - is the Recovery rate of the Infective class

$$f = \begin{bmatrix} \Pi SI \\ 0 \end{bmatrix} \qquad \text{and} \qquad v = \begin{bmatrix} (\Phi + e)E \\ -eE + (\Phi + \Psi)I \end{bmatrix}$$

where f and v are the vectors for the new infection rate and for the transfer of infections respectively, which when partially differentiated gives the matrices F and V as

$$F = \begin{bmatrix} 0 & \Pi S \\ 0 & 0 \end{bmatrix} \quad and \quad V = \begin{bmatrix} (\Psi + e) & 0 \\ -e & (\Psi + \Phi) \end{bmatrix} \tag{3.5}$$

The inverse of V is given as

$$V^{-1} = \frac{1}{(\Psi + e)(\Psi + \Phi)} \begin{bmatrix} (\Psi + \Phi) & 0 \\ e & (\Psi + e) \end{bmatrix}$$

which reduces to

$$V^{-1} = \begin{bmatrix} \frac{1}{(\Psi + e)} & 0 \\ \frac{e}{(\Psi + e)(\Psi + \Phi)} & \frac{1}{(\Psi + \Phi)} \end{bmatrix} \tag{3.6}$$

The next generation matrix FV^{-1} is then given by

$$FV^{-1} = \begin{bmatrix} 0 & \Pi S \\ 0 & 0 \end{bmatrix} \begin{bmatrix} \frac{1}{(\Psi + e)} & 0 \\ \frac{e}{(\Psi + e)(\Psi + \Phi)} & \frac{1}{(\Psi + \Phi)} \end{bmatrix} \tag{3.7}$$

$$\begin{bmatrix} \frac{\Pi S e}{(\Psi + e)(\Psi + \Phi)} & \frac{\Pi S}{(\Psi + \Phi)} \\ 0 & 0 \end{bmatrix} \tag{3.8}$$

The reproduction number R_0 is then given as

$$R_0 = \rho(FV^{-1}) = \frac{\Pi S e}{(\Psi + e)(\Psi + \Phi)} \tag{3.9}$$

where ρ represents the spectral radius of the constructed next generation matrix.

But from equation (3.1), if $\frac{dS}{dt} = 0$ and I=0 we have

$\Theta - \Psi S = 0$

hence

$S = \frac{\Theta}{\Psi}$ at the Cancer Free Equilibrium point

Now Equation (3.9) reduces to

$$R_0 = \frac{\Theta \Pi e}{\Psi(\Psi + e)(\Psi + \Phi)} \tag{3.10}$$

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From equation (3.10), the Cancer Free Equilibrium point (CFEP) is locally asymptotically stable if $R_0 < 1$, that is $\Theta \Pi e < \Psi(\Psi + e)(\Psi + \Phi)$, otherwise unstable if $R_0 > 1$. While the Cancer Endemic Equilibrium Point (CEEP) is locally asymptotically stable if $R_0 > 1$ and unstable if $R_0 < 1$. The global stability of the Cancer Free Equilibrium point and Cancer Endemic Equilibrium Point were checked using Lyapunov function method. From the Lyapunov function, the CFEP is globally asymptotically stable when $R_0 \leq 1$ and unstable when $R_0 > 1$ while the CEEP is globally asymptotically stable when $R_0 > 1$ otherwise unstable. The simulations of the model to establish the effects of variations of the model's parameters on its stability was done using the MATLAB computer program.

3.3 Types of Epidemiological Models

Stochastic (random) and deterministic or compartmental models are the two primary categories of epidemiological models. The stochastic models account for variance due to chance in dynamics, including exposure risk and the infectious vector itself. A deterministic model is one in which the emergence of potential future states of the system is not susceptible to randomness. Most of these models have been used by a number of researchers. The Susceptible-Infective-Susceptible (SIS) and Susceptible-Infective-Recovered (SIR) models are among the frequently utilized models. These models are widely used for understanding the transmission mechanisms and control of infectious diseases.

In this research, SEIR Mathematical model is formulated for the effects of incubation and chemotherapy on the dynamics of tumor growth. A SEIR model is appropriate for the study of a disease where there is a considerable post-infection incubation period in which the exposed is not yet infectious (Jones, 2007). In the model, the cells in the population, N(t), at time, t, are divided into four compartments. These compartments include the susceptible S(t) which refers to the healthy cells which have not yet come into contact with the cancerous cells. The exposed E(t) are the cells which have come into contact with the cancerous cells but are not yet infective or infectious. The infective I(t) are those that have become infected and are now cancerous and the removed R(t) are those that have been killed or removed from the cell population due to chemotherapy. Hence for the cell population we have

$$N(t) = S(t) + E(t) + I(t) + R(t) \tag{3.11}$$

The SEIR model is preferred over other models as it takes into account the latent period i.e exposed sub population which is left out in other models such as SIS or SIR. Also it is amenable and can easily be generalized to other models with more compartments. The transfer diagram is depicted in the following Figure 3.1.

The Schematic illustration of the SEIR Model
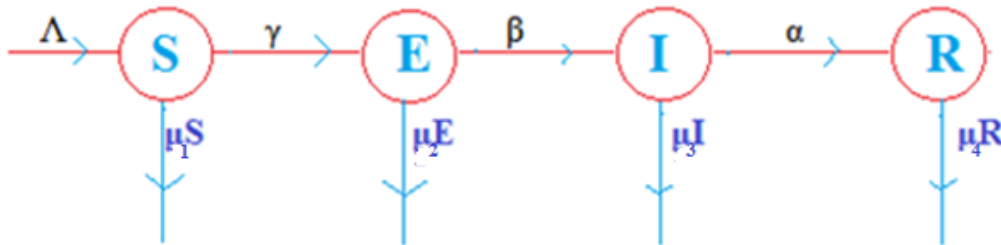
where

μ_1 S - Natural mortality rate of susceptible cells

μ_2 E - Natural mortality rate of Exposed cells

μ_3 I - Natural mortality rate of Infective cells

μ_4 R - Rate at which the cancerous cells are removed

and $\mu_1 < \mu_4 < \mu_2 < \mu_3$

Compartmental models are important in predicting properties of how diseases spread or the duration of an epidemic in a population. It also allows for in-depth understanding of how different situations may influence the aftermath of the epidemic for example, the most appropriate way of administering meager number of medications in a population of cells.

3.4 SEIR Model for Tumor Dynamics

In a SEIR model the individuals in a population are divided into four sub-populations or compartments. These compartments are the susceptible (S), which refers to the healthy cells which have not yet come into contact with the cancer cells. The exposed (E) are the cells which have come into contact with the Cancer cells but are not yet infective or infectious. The infective (I) are those that have become infected with the cancer cells and are infectious and the removed (R) are those that have been removed from the cell population upon application of chemotherapy drug which kills the cells.The Figure 3.2 below gives the SEIR model flow diagram.

SEIR Model Flow diagram
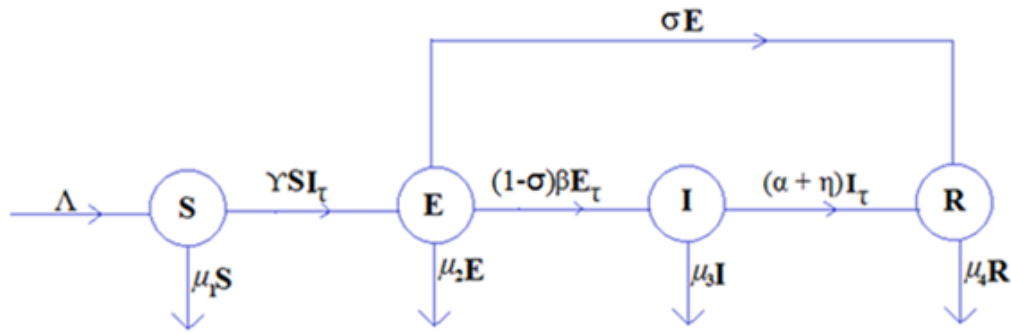
where μ_i i=1, 2...4 is the coefficient of natural mortality.

3.5 Model Assumptions

For the derivation of the model, the following important assumptions were taken into account.

i) There is uniform interaction of cells in the cell population which means that each and every cell has an equal opportunity of being infected provided it comes into contact with the infected cell.

ii) The cell population under study is a closed population, the number of cells remains constant.

iii) There is removal of cancerous cells upon administration of chemotherapy

iv) Some cells are removed naturally due to immunotherapy hence does not transit to the next stage of the SEIR model or after chemotherapy treatment.

v) There is an incubation period i.e. the time between the exposures of a cell to cancer causing viruses to the onset of symptomatic disease.

vi) The recovered cells are assumed to acquire permanent immunity meaning there is no transfer from the Recovered class back to the Susceptible class.

vii) The rate of mortality is higher in infective cells followed by exposed cells, then the removed cells and lowest in susceptible cells i.e. $\mu_1 < \mu_4 < \mu_2 < \mu_3$

The rate at which the cells transit from one sub population to another are expressed mathematically as derivatives with time lags i.e. delay differential equations. The model is therefore formulated using delay differential equations. In formulating the model, the assumption is that the size of cell population

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in each sub population is a differential function of time. In the SEIR model the total cell population N(t) at a time t is given by Equation (3.11)

3.6   Model Equations

From the flow diagram, the parameters and the model assumptions the tumor dynamics was modeled using the following delay differential equations.

$$\frac{dS}{dt} = \Lambda - \gamma SI_\tau - \mu_1 S \tag{3.12}$$

$$\frac{dE}{dt} = \gamma SI_\tau - \mu_2 E - \sigma E - (1-\sigma)\beta E_\tau \tag{3.13}$$

$$\frac{dI}{dt} = (1-\sigma)\beta E_\tau - \mu_3 I - (\alpha + \eta)I_\tau \tag{3.14}$$

$$\frac{dR}{dt} = (\alpha + \eta)I_\tau + \sigma E - \mu_4 R \tag{3.15}$$

The total cell population N, was given as $N = S + E + I + R$.

3.7   Model Preliminary Analysis

The preliminary analysis of the formulated model is given in this subsection. The analysis includes positivity and boundedness of the model solution, calculation of the basic reproductive number, determination and the stability analysis of the equilibrium points. Finally, the sensitivity analysis of the basic reproductive number was also done. Positivity and boundedness are therefore essential features of an epidemiological study as discussed below.

3.7.1   Positivity of the Solution of the Model

The model monitors the cell population in tumor dynamics, so all its associated parameters must be non-negative. Positivity of the solution is one of the important features of an epidemiological model. It is therefore important to prove that all state variables are non-negative for all time $t \geq 0$. Further any solution with positive initial values will remain positive for all the values of time $t \geq 0$. Biologically, positivity implies that the population will survive for a long time. Therefore to check how biologically valid the proposed model is, the positivity of the proposed model was as shown.

Theorem 1

Let $S(0) \geq 0, E(0) \geq 0, I(0) \geq 0$ and $R(0) \geq 0$, then it implies that all the variables of the model $S(t), E(t), I(t)$ and $R(t)$ will all remain positive for all solutions of the model equations for $t > 0$

The closed region $\sum = \{(S, E, I, R) \in \Re_+^4 \; ; \text{ such that } 0 < N \leq \frac{\Lambda}{\mu_1}\}$ is positively invariant set for the model equations (3.12), (3.13), (3.14) and (3.15)

Proof

From the model equation (3.12)

$$\frac{dS}{dt} = \Lambda - (\gamma I_\tau + \mu_1)S$$

$$\frac{dS}{dt} + (\gamma I_\tau + \mu_1)S = \Lambda$$

Letting $(\gamma I_\tau + \mu_1) = A$, the equation above becomes

$$\frac{dS}{dt} + AS = \Lambda$$

The integrating factor for the above Ordinary Differential Equation is given as $e^{\int A \, dt} = e^{At}$

$$e^{At}\frac{dS}{dt} + ASe^{At} = \Lambda e^{At}$$

$$\frac{d}{dt}(Se^{At}) = \Lambda e^{At}$$

Integrating the above equation and substituting the limits yields

$$S(t)e^{At} - S(0)e^{A(o)} = \Lambda e^{At} - \Lambda e^{A(0)}$$

$$S(t) = S(0)e^{-(\gamma I_\tau + \mu_1)t} + \Lambda - \Lambda e^{-(\gamma I_\tau + \mu_1)t} \tag{3.16}$$

as $t \to \infty$, $S(t) = \Lambda > 0$ implying that $S(t)$ is positive

From equation (3.13), (3.14) and (3.15) we can similarly show respectively that

$$E(t) = E(0)e^{-\int_0^t (\mu_2 + \sigma) + (1-\sigma)\beta E(k-\tau)d\xi} + \int_0^t (\gamma S I_\tau)e^{-\int_w^t (\mu_2 + \sigma) + (1-\sigma)\beta E(k-\tau)d\xi} dw \tag{3.17}$$

$$I(t) = I(0)e^{-\int_0^t \mu_3 + (\alpha + \eta)I(k-\tau)d\xi} + \int_0^t [(1-\sigma)\beta E(k-\tau)]e^{-\int_w^t \mu_3 + (\alpha + \eta)I(k-\tau)d\xi} dw \tag{3.18}$$

$$R(t) = R(0)e^{-\int_0^t \mu_4 d\xi} + \int_0^t [(\alpha + \eta)I(k-\tau) + \sigma E]e^{-\int_0^t \mu_4 d\xi} dw \tag{3.19}$$

From the equations (3.16), (3.17), (3.18) and (3.19), since $S(t) > 0, E(t) > 0, I(t) > 0$ and $R(t) > 0$, it implies that the region $\sum$ is positively invariant and so it is sufficient to consider solution of the model equations.

3.7.2   Boundedness of the solution of the Model

Boundedness refers to the behavior of solutions over a given time. Solutions should not grow indefinitely but should remain within certain limits for example, population carrying capacity. In this subsection a proof for boundedness of the solutions of the model equations is given. Since the model deals with the cell population, it follows that at any time, t, the sum of the cell population of all the compartments must not be greater than the whole cell population.

Theorem 2

Let the closed region $\Sigma = \{(S, E, I, R) \in \mathfrak{R}_+^4 \; ; \text{ be such that } 0 \leq N \leq \frac{\Lambda}{\mu_1}\}$ is bounded for the model equations (3.12), (3.13), (3.14) and (3.15)

Proof

$$Let \quad N(t) = S(t) + E(t) + I(t) + R(t) \tag{3.20}$$

Differentiating (3.20) with respect to t gives

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dE}{dt} + \frac{dI}{dt} + \frac{dR}{dt} \tag{3.21}$$

Substituting (3.12), (3.13), (3.14) and (3.15) into (3.21) yields

$$\frac{dN}{dt} = \Lambda - \gamma SI_\tau - \mu_1 S + \gamma SI_\tau - \mu_2 E - \sigma E - \beta E_\tau + \sigma \beta E_\tau + \beta E_\tau - \sigma \beta E_\tau - \mu_3 I - \alpha I_\tau - \eta I_\tau + \alpha I_\tau + $$
$$\eta I_\tau + \sigma E - \mu_4 R$$

$$= \Lambda - \mu_1 S - \mu_2 E - \mu_3 I - \mu_4 R$$

$$\frac{dN}{dt} \leq \Lambda - (S + E + I + R)\mu \text{ Where } \mu = \text{ is the mean of } \mu_1, \mu_2, \mu_3 \text{ and } \mu_4$$

Letting $N = S + E + I + R$ yields

$$\frac{dN}{dt} \leq \Lambda - \mu N$$

$$\frac{dN}{\mu N - \Lambda} \leq -dt \tag{3.22}$$

Integrating equation (3.22) gives

$$\int_{N_0}^{N} \frac{dN}{\mu N - \Lambda} \leq \int_{t_0}^{t} -dt$$

$$\ln(\mu N - \Lambda) - \ln(\mu N_0 - \Lambda) \leq -t - (-t_0)$$

$$\ln \left(\frac{\mu N - \Lambda}{\mu N_0 - \Lambda}\right) \leq t_0 - t$$

$$N(t) \leq \frac{\Lambda}{\mu} + \frac{(\mu N_0 - \Lambda)e^{t_0}e^{-t}}{\mu} \tag{3.23}$$

$$\lim_{t \to \infty} N(t) \leq \lim_{t \to \infty} \frac{(\mu N_0 - \Lambda)e^{t_0}e^{-t}}{\mu} \leq \frac{\Lambda}{\mu}$$

Hence $N(t) \leq \frac{\Lambda}{\mu}$ which implies that $0 \leq N(t) \leq \frac{\Lambda}{\mu}$, therefore $N(t)$ is bounded and so are S(t),E(t),I(t) and R(t) of the model in the region $\sum$.

3.8   Equilibrium points of the Model and their Stability Analysis.

In epidemiology, equilibrium points play a crucial role in understanding disease dynamics .There are at least two types of equilibrium points; the disease free equilibrium point and the endemic equilibrium point. At the Disease-Free Equilibrium Point, the infected population (I) is zero and represents a situation where the disease is not spreading while the Endemic Equilibrium Point is a point that corresponds to a non-zero infected population. It occurs when the disease persists in the population.

The existence of equilibrium points depends on stability conditions, specifically when I > 0. The Understanding these equilibrium points helps researchers analyze disease transmission and develop strategies to control outbreaks.For this study, the two points are Cancer Free Equilibrium Point (CFEP) and the Cancer Endemic Equilibrium Point (CEEP). The Cancer Free Equilibrium Point occurs when there is absence of cancer while at the Cancer Endemic Equilibrium Point there is presence of cancer within the cells. The equilibrium points are obtained by equating the model Equations (3.12),(3.13),(3.14) and (3.15) to zero then solving. The stability of the model is then studied around the equilibrium points. A system is said to be stable if all the eigenvalues obtained becomes linear around the fixed points.

3.8.1   Cancer Free Equilibrium Point

The Cancer Free Equilibrium Point $\varepsilon_o=(S_0, E_0, I_0, R_0)$ occurs when the infective class is absent and consequently the recoveries. It is found by equating the model equations to zero then evaluating. At the Cancer Free Equilibrium

$$\frac{dS(t)}{dt} = \frac{dE(t)}{dt} = \frac{dI(t)}{dt} = \frac{dR(t)}{dt} = 0 \tag{3.24}$$

By substituting Equation (3.24) into the model equations (3.12), (3.13), (3.14) and (3.15) gives

$$\Lambda - \gamma S I_\tau - \mu_1 S = 0 \tag{3.25}$$

$$\gamma S I_\tau - \mu_2 E - \sigma E - (1-\sigma)\beta E_\tau = 0 \tag{3.26}$$

$$(1-\sigma)\beta E_\tau - \mu_3 I - (\alpha + \eta)I_\tau = 0 \tag{3.27}$$

$$(\alpha + \eta)I_\tau + \sigma E - \mu_4 R = 0 \tag{3.28}$$

If we let $I_\tau = 0$, Equation (3.25) becomes $\Lambda - \mu_1 S = 0$ and so

$$S = \frac{\Lambda}{\mu_1} \tag{3.29}$$

Equations (3.26), (3.27) and (3.29) reduces to zero since all the infectious, exposed and the recovered sub-populations are all equal to zero i.e. $I = E = R = 0$

Therefore, the Cancer Free Equilibrium Point of the SEIR model is then given by

$$\varepsilon_o = (S_0, E_0, I_0, R_0) = (\frac{\Lambda}{\mu_1}, 0, 0, 0)$$

3.8.2 Cancer Endemic Equilibrium Point

This is the point where cancer is persistent in the body cells. The Cancer Endemic Equilibrium Point $\varepsilon_1 = (S^*, E^*, I^*, R^*)$ exist when $S^* > 0, E^* > 0, I^* > 0$ and $R^* > 0$

The model equations (3.12), (3.13), (3.14) and (3.15) are then evaluated for S^*, E^*, I^* and R^* as follows

Letting $S = S^*$, Equation (3.25) becomes

$$\Lambda - \gamma S^* I_\tau - \mu_1 S^* = 0$$

And so

$$S^* = \frac{\Lambda}{(\gamma I_\tau + \mu_1)} \tag{3.30}$$

From equation (3.26), letting $S = S^*$ and $E = E^*$, we obtain

$$\gamma S^* I_\tau - \mu_2 E^* - \sigma E^* (1-\sigma)\beta E_\tau = 0 \tag{3.31}$$

$$(\mu_2 + \sigma)E^* = \gamma S^* I_\tau (1-\sigma)\beta E_\tau$$

$$E^* = \frac{\gamma I_\tau S^*}{(\mu_2 + \sigma)} \frac{(1 - \sigma)\beta E_\tau}{(\mu_2 + \sigma)} \tag{3.32}$$

It follows from (3.30), equation (3.32) becomes

$$\frac{\gamma I_\tau}{(\mu_2 + \sigma)} \frac{\Lambda}{(\gamma I_\tau + \mu_1)} - \frac{(1 - \sigma)\beta E_\tau}{(\mu_2 + \sigma)}$$

$$E^* = \frac{\gamma I_\tau \Lambda - (\gamma I_\tau + \mu_1)(\beta E_\tau - \sigma \beta E_\tau)}{(\mu_2 + \sigma)(\gamma I_\tau + \mu_1)} \tag{3.33}$$

From Equation (3.27), letting $I = I^*$, we obtain

$$\mu_3 I^* = \beta E_\tau - \sigma \beta E_\tau - \sigma I_\tau - \eta I_\tau$$

$$I^* = \frac{\beta E_\tau - \sigma \beta E_\tau - \sigma I_\tau - \eta I_\tau}{\mu_3} \tag{3.34}$$

From equation (3.28), letting $E = E^*$, and $R = R^*$, we obtain

$$(\alpha + \eta)I_\tau + \sigma E^* - \mu_4 R^* = 0$$

$$\mu_4 R^* = (\alpha + \eta)I_\tau + \sigma E^*$$

$$R^* = \frac{(\alpha + \eta)I_\tau}{\mu_4} + \frac{\sigma}{\mu_4} E^* \tag{3.35}$$

Substituting (3.33) into Equation (3.35) above gives

$$R^* = \frac{(\alpha + \eta)I_\tau}{\mu_4} + \frac{\sigma}{\mu_4} \left[\frac{\gamma I_\tau \Lambda - (\gamma I_\tau + \mu_1)(\beta E_\tau - \sigma \beta E_\tau)}{(\mu_2 + \sigma)(\gamma I_\tau + \mu_1)} \right]$$

$$R^* = \frac{(\alpha + \eta)I_\tau}{\mu_4} + \frac{\sigma \gamma I_\tau \Lambda - \sigma(\gamma I_\tau + \mu_1)(\beta E_\tau - \sigma \beta E_\tau)}{\mu_4(\mu_2 + \sigma)(\gamma I_\tau + \mu_1)}$$

$$R^* = \frac{(\mu_2 + \sigma)(\gamma I_\tau + \mu_1)(\alpha + \eta)I_\tau + \sigma \gamma I_\tau \Lambda - \sigma(\gamma I_\tau + \mu_1)(\beta E_\tau - \sigma \beta E_\tau)}{\mu_4(\mu_2 + \sigma)(\gamma I_\tau + \mu_1)} \tag{3.36}$$

Hence the cancer Endemic Equilibrium Point is

$$\varepsilon_1 = \begin{bmatrix} S^* \\ E^* \\ I^* \\ R^* \end{bmatrix} = \begin{bmatrix} \frac{\Lambda}{(\gamma I_\tau + \mu_1)} \\ \frac{\gamma I_\tau \Lambda - (\gamma I_\tau + \mu_1)(\beta E_\tau - \sigma \beta E_\tau)}{(\mu_2 + \sigma)(\gamma I_\tau + \mu_1)} \\ \frac{\beta E_\tau - \sigma \beta E_\tau - \sigma I_\tau - \eta I_\tau}{\mu_3} \\ \frac{(\mu_2 + \sigma)(\gamma I_\tau + \mu_1)(\alpha + \eta)I_\tau + \sigma \gamma I_\tau \Lambda - \sigma(\gamma I_\tau + \mu_1)(\beta E_\tau - \sigma \beta E_\tau)}{\mu_4(\mu_2 + \sigma)(\gamma I_\tau + \mu_1)} \end{bmatrix} \tag{3.37}$$

3.9 Determination of the basic reproductive number

The basic reproduction number denoted by R_0 is the most significant quantity in disease modeling. It is defined as the number of new infection incidences emanating from one infection known as the primary infection case in a completely vulnerable population. The reproduction number provides an overall measure of the potential for the spread of an infection within a completely susceptible population. Reproduction number also gives an elementary and explicit elucidation for the growth and decomposition of an endemic disease. The parameter is dependent not only on the transmission coefficient but also on the average duration of the infection of the disease.

A higher value of the reproduction number (R_0) may be interpreted to mean a higher therapeutic intervention needed. Such intervention is to reduce the advancement and in the long run do away with the disease from the population under study. When $R_0 < 1$ the spread of cancer within the cells will reduce and finally die off while when $R_0 > 1$ the infection will persist. To determine the reproductive number, the dominant or maximum eigenvalue of the next generation matrix is computed. The spectral radius of the matrix FV^{-1} gives the reproduction number that is, $R_0 = \rho(FV^{-1})$ where ρ is the spectral radius of the next generation matrix, F is the matrix for the new cancer cells while V is the matrix of the transfers of infections from one compartment to another.

The vectors for the infected class and the uninfected class are then identified. The infected classes are E and I which are represented by $X = [E, I]^T$ while the uninfected class are represented by vector $Y = [S, R]^T$. The vector for the new infection rate is,

$$f = \begin{bmatrix} \gamma S I_\tau \\ 0 \end{bmatrix}$$

This is the vector for new infections from the susceptible sub-population into the exposed sub-population. The vector for other infections from compartment to another is given as

$$v = \begin{bmatrix} (\mu_2 + \sigma)E + (1 - \sigma)\beta E_\tau \\ -(1 - \sigma)\beta E_\tau + \mu_3 I + (\alpha + \eta)I_\tau \end{bmatrix}$$

The product of F and V^{-1} gives the next generation matrix

The matrix $F = (\frac{\partial f}{\partial X}|_{\varepsilon_0})$ is formed by partial derivative of the vector of new infection rates evaluated at the Cancer Free Equilibrium Point while the matrix $V = (\frac{\partial v}{\partial X}|_{\varepsilon_0})$ is formed from the partial derivative of the vector of other rates which are not new infections evaluated at the Cancer Free Equilibrium Point. Therefore

$$
F = \begin{bmatrix} \frac{\partial f}{\partial E} & \frac{\partial f}{\partial I} \\ \frac{\partial f}{\partial E} & \frac{\partial f}{\partial I} \end{bmatrix} \quad and \quad V = \begin{bmatrix} \frac{\partial v}{\partial E} & \frac{\partial v}{\partial I} \\ \frac{\partial v}{\partial E} & \frac{\partial v}{\partial I} \end{bmatrix}
$$

Hence

$$
F = \begin{bmatrix} 0 & \gamma S e^{-\lambda \tau} \\ 0 & 0 \end{bmatrix} \quad and \quad V = \begin{bmatrix} (\mu_2 + \sigma) + (1-\sigma)\beta e^{-\lambda \tau} & 0 \\ -(1-\sigma)\beta e^{-\lambda \tau} & (\mu_3 + (\alpha+\eta)e^{-\lambda \tau}) \end{bmatrix}
$$

The inverse V^{-1} of V is given as

$$
= \frac{1}{(\mu_2 + \sigma + \beta e^{-\lambda \tau} - \sigma\beta e^{-\lambda \tau})(\mu_3 + \alpha e^{-\lambda \tau} + \eta e^{-\lambda \tau})} \begin{bmatrix} (\mu_3 + \alpha e^{-\lambda \tau} + \eta e^{-\lambda \tau}) & 0 \\ \beta e^{-\lambda \tau} - \sigma\beta e^{-\lambda \tau} & \mu_2 + \sigma + \beta e^{-\lambda \tau} - \sigma\beta e^{-\lambda \tau} \end{bmatrix}
$$

$$
= \begin{bmatrix} \frac{1}{\mu_2 + \sigma + \beta e^{-\lambda \tau} - \sigma\beta e^{-\lambda \tau}} & 0 \\ \frac{\beta e^{-\lambda \tau} - \sigma\beta e^{-\lambda \tau}}{(\mu_2 + \sigma + \beta e^{-\lambda \tau} - \sigma\beta e^{-\lambda \tau})(\mu_3 + \alpha e^{-\lambda \tau} + \eta e^{-\lambda \tau})} & \frac{1}{(\mu_3 + \alpha e^{-\lambda \tau} + \eta e^{-\lambda \tau})} \end{bmatrix}
$$

Therefore FV^{-1} reduces to

$$
\begin{bmatrix} 0 & \gamma S e^{-\lambda \tau} \\ 0 & 0 \end{bmatrix} \begin{bmatrix} \frac{1}{\mu_2 + \sigma + \beta e^{-\lambda \tau} - \sigma\beta e^{-\lambda \tau}} & 0 \\ \frac{\beta e^{-\lambda \tau} - \sigma\beta e^{-\lambda \tau}}{(\mu_2 + \sigma + \beta e^{-\lambda \tau} - \sigma\beta e^{-\lambda \tau})(\mu_3 + \alpha e^{-\lambda \tau} + \eta e^{-\lambda \tau})} & \frac{1}{(\mu_3 + \alpha e^{-\lambda \tau} + \eta e^{-\lambda \tau})} \end{bmatrix}
$$

$$
= \begin{bmatrix} \frac{\gamma S e^{-\lambda \tau}(\beta e^{-\lambda \tau} - \sigma\beta e^{-\lambda \tau})}{(\mu_2 + \sigma + \beta e^{-\lambda \tau} - \sigma\beta e^{-\lambda \tau})(\mu_3 + \alpha e^{-\lambda \tau} + \eta e^{-\lambda \tau})} & \frac{\gamma S e^{-\lambda \tau}}{(\mu_3 + \alpha e^{-\lambda \tau} + \eta e^{-\lambda \tau})} \\ 0 & 0 \end{bmatrix}
$$

And so

$$R_0 = \frac{\gamma S e^{-\lambda_\tau}(\beta e^{-\lambda_\tau} - \sigma \beta e^{-\lambda_\tau})}{(\mu_2 + \sigma + \beta e^{-\lambda_\tau} - \sigma \beta e^{-\lambda_\tau})(\mu_3 + \alpha e^{-\lambda_\tau} + \eta e^{-\lambda_\tau})} \tag{3.38}$$

substituting equation (3.38) into equation (3.29), we obtain the following

$$R_0 = \frac{\beta \Lambda \gamma e^{-2\lambda_\tau}(1 - \sigma)}{\mu_1(\mu_2 + \sigma + \beta e^{-\lambda_\tau} - \sigma \beta e^{-\lambda_\tau})(\mu_3 + \alpha e^{-\lambda_\tau} + \eta e^{-\lambda_\tau})} \tag{3.39}$$

3.10 Determination of the Stability of the Equilibrium Points

The study of the stability of the equilibrium points considers the linearization of the model Equations about both the Cancer Free Equilibrium Point and the Cancer Endemic Equilibrium Point by taking the Jacobian Matrix of the model equations.

3.10.1 Local Stability of the Cancer Free Equilibrium Point

Local stability refers to the behavior of a system near an equilibrium point (also known as a fixed point). An equilibrium point (Z_0) is considered locally stable if, for any neighborhood (W) of (Z_0), there exists another neighborhood (W_0) such that if the initial state (Z) is within (W_0), the system trajectory remains within (W) for all time. In other words, nearby trajectories converge to the equilibrium point. The local stability of the Cancer Free Equilibrium Point therefore is the point where if the system is put nearby the equilibrium point, then it will converge to the equilibrium point in some time.

Theorem 3

The Cancer Free Equilibrium Point ε_0 is locally stable if $R_0 < 1$ whereas ε_0 is unstable if $R_0 > 1$.

Proof

The Jacobian matrix at the Cancer Free Equilibrium Point is computed by differentiating each of the equations (3.12), (3.13), (3.14) and (3.15) with respect to S, E, I and R and letting $E = I = R = 0$. The matrix is then defined as,

$$J_{\varepsilon_0} = \begin{bmatrix} -\mu_1 & 0 & -\gamma S e^{-\lambda\tau} & 0 \\ 0 & -(\mu_2+\sigma+\beta e^{-\lambda\tau}-\sigma\beta e^{-\lambda\tau}) & \gamma S e^{-\lambda\tau} & 0 \\ 0 & \beta e^{-\lambda\tau}-\sigma\beta e^{-\lambda\tau} & -(\mu_3+\alpha e^{-\lambda\tau}+\eta e^{-\lambda\tau}) & 0 \\ 0 & \sigma & \alpha e^{-\lambda\tau}+\eta e^{-\lambda\tau} & -\mu_4 \end{bmatrix} \qquad (3.40)$$

And the associated polynomial is given as $\mid J_{\varepsilon_0} - \lambda I \mid = 0$ at the Cancer Free Equilibrium Point. Applying (3.29) in (3.40) we get

$$\begin{vmatrix} -\mu_1-\lambda & 0 & -\frac{\gamma\Lambda e^{-\lambda\tau}}{\mu_1} & 0 \\ 0 & -(\mu_2+\sigma+\beta e^{-\lambda\tau}-\sigma\beta e^{-\lambda\tau})-\lambda & \frac{\gamma\Lambda e^{-\lambda\tau}}{\mu_1} & 0 \\ 0 & \beta e^{-\lambda\tau}-\sigma\beta e^{-\lambda\tau} & -(\mu_3+\alpha e^{-\lambda\tau}+\eta e^{-\lambda\tau})-\lambda & 0 \\ 0 & \sigma & \alpha e^{-\lambda\tau}+\eta e^{-\lambda\tau} & -\mu_4-\lambda \end{vmatrix} = 0$$
$$\qquad (3.41)$$

Letting A=-μ_1, B= $-\frac{\gamma\Lambda e^{-\lambda\tau}}{\lambda_1}$, C= -$(\mu_2+\sigma+\beta e^{-\lambda\tau}-\sigma\beta e^{-\lambda\tau})$, D= $\frac{\gamma\Lambda e^{-\lambda\tau}}{\mu_1}$, Y= $\beta e^{-\lambda\tau}-\sigma\beta e^{-\lambda\tau}$, F= -$(\mu_3+\alpha e^{-\lambda\tau}+\eta e^{-\lambda\tau})$, G=$\sigma$, H= $\alpha e^{-\lambda\tau}+\eta e^{-\lambda\tau}$ and Z= -μ_4

Equation (3.41) reduces to

$$\begin{vmatrix} A-\lambda & 0 & B & 0 \\ 0 & C-\lambda & D & 0 \\ 0 & Y & F-\lambda & 0 \\ 0 & G & H & Z-\lambda \end{vmatrix} = 0$$

On solving we obtain the values of $\lambda_1, \lambda_2, \lambda_3$ and λ_4 as follows

$$\lambda_1 = A , \lambda_2 = Z$$

$$\lambda_3 = \frac{(C+F)+\sqrt{C^2+F^2-2CF+4DY}}{2}$$

and

$$\lambda_4 = \frac{(C+F)-\sqrt{C^2+F^2-2CF+4DY}}{2}$$

The Cancer Free Equilibrium point ε_0 in the model equations is asymptotically stable if $\lambda_1, \lambda_2, \lambda_3, \lambda_4 <$ 0 and unstable if at least one of the $\lambda_1, \lambda_2, \lambda_3, \lambda_4$ is greater than zero for all $\mu_1, \mu_2, \mu_3, \mu_4, \sigma, \beta, \eta, \alpha, \Lambda$

and γ being positive. The first two eigenvalues $\lambda_1 = -\mu_1$ and $\lambda_2 = -\mu_4$, which are real negative values, are a sufficient condition for local stability. It is also clear that λ_4 is less dominant compared to λ_3 because of the subtraction sign in the numerator. λ_3 is therefore the most dorminant eigenvalue.

$$\frac{(C+F)+\sqrt{C^2+F^2-2CF+4DY}}{2} < 0$$

for the stability of the Cancer Free Equilibrium point

$$DY < CF$$

$$\left(\frac{\Lambda\gamma e^{-\lambda\tau}}{\mu_1}\right)(\beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau}) < (\mu_2 + \sigma + \beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau})(\mu_3 + \alpha e^{-\lambda\tau} + \eta e^{-\lambda\tau})$$

$$\frac{\Lambda\gamma e^{-\lambda\tau}(\beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau})}{\mu_1(\mu_2 + \sigma + \beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau})(\mu_3 + \alpha e^{-\lambda\tau} + \eta e^{-\lambda\tau})} < 1$$

$R_0 < 1$. Hence the Cancer Free Equilibrium is stable whenever $R_0 < 1$.

3.10.2 Local Stability of the Cancer Endemic Equilibrium Point

Theorem 4

The Cancer Endemic Equilibrium Point ε_1 of the model Equations (3.12), (3.13), (3.14) and (3.15) is locally stable in the feasible region of the model Equations if $R_0 > 1$

Proof

We first construct the Jacobian matrix by taking the derivatives of the model equations at the Cancer Endemic Equilibrium Point with respect to S^*, E^*, I^* and R^* from which we obtain the following matrix.

$$J_{\varepsilon_1} = \begin{bmatrix} -(\gamma I_\tau + \mu_1) & 0 & -\gamma S^* e^{-\lambda\tau} & 0 \\ \gamma I_\tau & -(\mu_2 + \sigma + \beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau}) & \gamma S^* e^{-\lambda\tau} & 0 \\ 0 & \beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau} & -(\mu_3 + \alpha e^{-\lambda\tau} + \eta e^{-\lambda\tau}) & 0 \\ 0 & \sigma & \alpha e^{-\lambda\tau} + \eta e^{-\lambda\tau} & -\mu_4 \end{bmatrix}$$

And the associated polynomial is given as $|J_{\varepsilon_1} - \lambda I| = 0$ as follows

$$\begin{bmatrix} -(\gamma I_\tau + \mu_1) - \lambda & 0 & -\gamma S^* e^{-\lambda\tau} & 0 \\ \gamma I_\tau & -(\mu_2 + \sigma + \beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau}) - \lambda & \gamma S^* e^{-\lambda\tau} & 0 \\ 0 & \beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau} & -(\mu_3 + \alpha e^{-\lambda\tau} + \eta e^{-\lambda\tau}) - \lambda & 0 \\ 0 & \sigma & \alpha e^{-\lambda\tau} + \eta e^{-\lambda\tau} & -\mu_4 - \lambda \end{bmatrix} = 0$$

$$(3.42)$$

The characteristic equation is obtained by finding the determinant of the above matrix and equating to zero.

Letting $J=-(\gamma I_\tau + \mu_1), K = -\gamma S^* e^{-\lambda_\tau}, L = \gamma I_\tau, M = -(\mu_2 + \sigma + \beta e^{-\lambda_\tau} - \sigma\beta e^{-\lambda_\tau}), P = \gamma S^* e^{-\lambda_\tau}, Q = \beta e^{-\lambda_\tau} - \sigma\beta e^{-\lambda_\tau}, T = -(\mu_3 + \alpha e^{-\lambda_\tau} + \eta e^{-\lambda_\tau}), U = \sigma, V = \alpha e^{-\lambda_\tau} + \eta e^{-\lambda_\tau}$ and $W = -\mu_4$, equation (3.42) becomes

$$
\begin{vmatrix}
J-\lambda & 0 & K & 0 \\
L & M-\lambda & P & 0 \\
0 & Q & T-\lambda & 0 \\
0 & U & V & W-\lambda
\end{vmatrix} = 0
$$

On solving we obtain the values of λ_1, λ_2 , λ_3 and λ_4 as follows

$$\lambda_1 = J , \lambda_2 = W$$

$$\lambda_3 = \frac{(M+T)+\sqrt{M^2+T^2-2MT+4PQ-4KLQ}}{2}$$

and

$$\lambda_4 = \frac{(M+T)-\sqrt{M^2+T^2-2MT+4PQ-4KLQ}}{2}$$

For Cancer Endemic Equilibrium point to be stable at least one of the λ_1, λ_2 , λ_3 , λ_4 is greater than zero. It is clear that both $\lambda_1 = -(\gamma I_\tau + \mu)$ and $\lambda_2 = -\mu_4$ are negative real values. While λ_4 is less dominant compared to λ_3 . This leaves λ_3 as the most dominant Eigen value.

For

$$\frac{(M+T)+\sqrt{M^2+T^2-2MT+4PQ-4KLQ}}{2} > 0$$

$$PQ - KLQ > MT$$

which gives

$$\frac{\Lambda \gamma e^{-\lambda_\tau}(\beta e^{-\lambda_\tau} - \sigma\beta e^{-\lambda_\tau})}{\mu_1(\mu_2+\sigma+\beta e^{-\lambda_\tau}-\sigma\beta e^{-\lambda_\tau})(\mu_3+\alpha e^{-\lambda_\tau}+\eta e^{-\lambda_\tau})} > \frac{(\mu_1+\gamma I_\tau)}{(1+\gamma I_\tau)}$$

$R_0 > \frac{(\mu_1+\gamma I_\tau)}{(1+\gamma I_\tau)}$, when $(\mu_1 + \gamma I_\tau) > (1 + \gamma I_\tau)$ since μ_1, γ and I_τ are all positive, a condition for the persistence of the Cancer Endemic Equilibrium point.

3.10.3   Global Stability of the Cancer Free Equilibrium Point

In this subsection, a proof of the global stability of the Cancer Free Equilibrium Point ε_0 is given. The global stability of the ε_0 was done by constructing the Lyapunov function for the Cancer Free Equilibrium point.

Theorem 5

If $R_0 \leq 1$ then the Cancer Free Equilibrium Point ε_0 of the model equations is globally asymptotically stable, otherwise unstable if $R_0 > 1$.

Proof

$$V(S,E,I,R) = (S - S^0)^2 + (E - 0)^2 + (I - 0)^2 + (R - 0)^2$$

$$= (S - S^o)^2 + E^2 + I^2 + R^2 \tag{3.43}$$

From equation (3.12) $S = \frac{\Lambda}{\gamma I_\tau - \mu_1}$ Implying that $S > 0$ hense positive .It follows that equations (3.13), (3.14) and (3.15) would also give $E = I = R > 0$.

The time derivative of equation is (3.43)

$$\frac{dV}{dt}(S,E,I,R) = 2(S - S^o)\frac{dS}{dt} + 2E\frac{dE}{dt} + 2I\frac{dI}{dt} + 2R\frac{dR}{dt}$$

$$\frac{dV}{dt}(S,E,I,R) = 2(S - S^o)(\Lambda - \gamma SI_\tau - \mu_1 S) + 2E(\gamma SI_\tau - \mu_2 E - \sigma E - \beta E_\tau + \sigma\beta E_\tau) + 2I(\beta E_\tau - \sigma\beta E_\tau - \mu_3 I - \alpha I_\tau - \eta I_\tau) + 2R(\alpha I_\tau + \eta I_\tau + \sigma E - \mu_4 R)$$

$$= 2S - 2S^o + 2E\Lambda - 2E\gamma SI_\tau - 2E\mu_1 S + 2I\gamma SI_\tau - 2I\mu_2 E - 2I\sigma E - 2I\beta E_\tau + 2I\sigma\beta E_\tau + 2R\sigma I_\tau - 2R\eta I_\tau + 2R\sigma E - 2\mu_4 R^2$$

$$= 2S + 2E\Lambda + 2I\gamma SI_\tau + 2I\sigma\beta E_\tau + 2R\alpha I_\tau + 2R\sigma E - 2S^o - 2E\gamma SI_\tau - 2E\mu_1 S - 2I\mu_2 E - 2I\sigma E - 2I\beta E_\tau - 2R\eta I_\tau - 2\mu_4 R^2$$

At Cancer Free Equilibrium Point ε_0 , $E = I = R = 0$ hence the equation above becomes

$\dot{V} = 2(S - S^o)$

For global stability $S < S^o$ so that $\dot{V} < 0$ .If $S \leq S^o$ then $\dot{V} \leq 0$ implying that $R_0 \leq 1$ hence the Cancer Free Equilibrium Point is globally stable

3.10.4 Global Stability of the Cancer Endemic Equilibrium Point

In this subsection we prove the global stability of the Cancer Endemic Equilibrium Point ε_1 by constructing the Lyapunov function.

Theorem 6

If $R_0 > 1$ then the Cancer Endemic Equilibrium Point ε_1 of the model is globally asymptotically stable otherwise unstable when $R_0 < 1$.

Proof

Consider the following Lyapunov function $V : \{(S,E,I,R) \in \Omega : S,E,I,R > 0\} \to R$ is given by

$$V(S,E,I,R) = \tfrac{1}{2}[(S-S^*)^2 + (E-E^*)^2 + (I-I^*)^2 + (R-R^*)^2]$$

Differentiating V with respect to t, we get,

$$\dot{V}(S,E,I,R) = (S-S^*)\,\dot{S} + (E-E^*)\,\dot{E} + (I-I^*)\dot{I} + (R-R^*)\,\dot{R}$$

$$= (1-\tfrac{S^*}{S})\dot{S} + (1-\tfrac{E^*}{E})\dot{E} + (1-\tfrac{I^*}{I})\dot{I} + (1-\tfrac{R^*}{R})\dot{R}$$

$$= (1-\tfrac{S^*}{S})(\Lambda - \gamma SI_\tau - \mu_1 S) + (1-\tfrac{E^*}{E})(\gamma SI_\tau - \mu_2 E - \sigma E - \beta E_\tau + \sigma\beta E_\tau) + (1-\tfrac{I^*}{I})$$

$$(\beta E_\tau - \sigma\beta E_\tau - \mu_3 I - \alpha I_\tau - \eta I_\tau) + (1-\frac{R^*}{R})(\alpha I_\tau + \eta I_\tau + \sigma E - \mu_4 R) \qquad (3.44)$$

By considering the model equations (3.12), (3.13), (3.14) and (3.15) at the Cancer Endemic Equilibrium Point, we have,

$$\Lambda = \gamma S^* I_\tau + \mu_1 S^*$$

$$\gamma S^* I_\tau = \mu_2 E^* - \sigma E - \beta E^*_\tau + \sigma\beta E_\tau$$

$$\beta E_\tau - \sigma\beta E_\tau = \mu_3 I^* - \alpha I_\tau - \eta I_\tau$$

$$\alpha I_\tau + \eta I_\tau = \mu_4 R^* - \sigma E^*$$

Substituting the values of $\Lambda, \gamma S^* I_\tau, \beta E_\tau - \sigma\beta E_\tau$ and $\sigma I_\tau + \eta I_\tau$ into (3.43) and simplifying ,we have

$$= (1-\tfrac{S^*}{S})(\mu_2 E^* + \sigma E^* + \mu_3 I^* + \sigma I_\tau + \eta I_\tau + \mu_1 S^* - \gamma SI_\tau - \mu_1 S) +$$

$$(1-\tfrac{E^*}{E})(\gamma SI_\tau - \mu_2 E - \sigma E^{\smallsmile}\mu_3 I^* - \sigma I_\tau - \eta I_\tau) + (1-\tfrac{I^*}{I})(\mu_3 I^* - \mu_3 I) +$$

$$(1-\tfrac{R^*}{R})(\mu_4 R^* - \sigma E^* + \sigma E - \mu_4 R)$$

Here $\dot{V}=0$ when $(S,E,I,R) = (S^*,E^*,I^*,R^*)$ otherwise $\dot{V} > 0$. Therefore the greatest compact invariant set in $\{(S,E,I,R) \in \Omega : \dot{V} > 0 \}$ is the singleton $\{\varepsilon_1\}$, where ε_1 is the endemic equilibrium point . It then implies that ε_1 is globally asymptotically stable in the interior of the compact set (Ω).

CHAPTER FOUR

RESULTS AND DISCUSSION

4.1   Introduction

In this chapter, using MATLAB software, the numerical simulations were done. The chapter also has a detailed discussion of the results obtained from the numerical simulation using MATLAB software. This was done to verify the analytic results obtained in chapter Three. The parameter values used in this chapter were mostly hypothetical values to help understand the dynamics of the tumour growth. The analytic solutions in the chapter three were explained using illustrations of analytic results with particular numerical examples.

4.2   Numerical Simulations and Discussions

The numerical simulations of the equations of the model were determined using the parameters and their estimated values shown in Table 4.1

Table 4.1 Table of parameters and values

Parameter	Description	Value
S(0)	Susceptible Population	$1000/mm^3$
E(0)	Exposed population	$1000 /mm^3$
I(0)	Infected population	$500 /mm^3$
R(0)	Removed population	$100 /mm^3$
N(0)	Total population	$2600 /mm^3$
γ	Rate at which Susceptible cells become exposed by one infectious cell per contact time	$0.500 \, mm^3$/day
β	Rate at which the exposed cells become infectious	$0.020 \, mm^3$/day
σ	Removal rate of exposed cells due to autoimmunity	$0.030 \, mm^3$/day
η	Removal rate of symptomatic cells due to chemotherapy	$0.010 \, mm^3$/day
Λ	Constant influx rate of new susceptible cells	$0.020 \, mm^3$/day
μ_1	Coefficient of Natural mortality rate of Susceptible cells	0.005 /day
μ_2	Natural mortality rate of Exposed cells	0.020 /day
μ_3	Natural mortality rate of Infective cells	0.050 /day
μ_4	Rate of mortality of the cancerous cells	0.010 /day
α	Natural removal rate of symptomatic infected cells	$0.020 \, mm^3$/day
τ	Time Delay	To be determined

Figure 4.1 shows a plot of reproduction number against the previously infected tumour cells at the Cancer Endemic Equilibrium Point (CEEP). From the figure, it can be shown that with increase in previously infected tumour cells, the viral replication also increases with increase in reproduction number.

A plot of Reproduction Number (R_1) against Previously Infected Tumour Cells (I_τ)
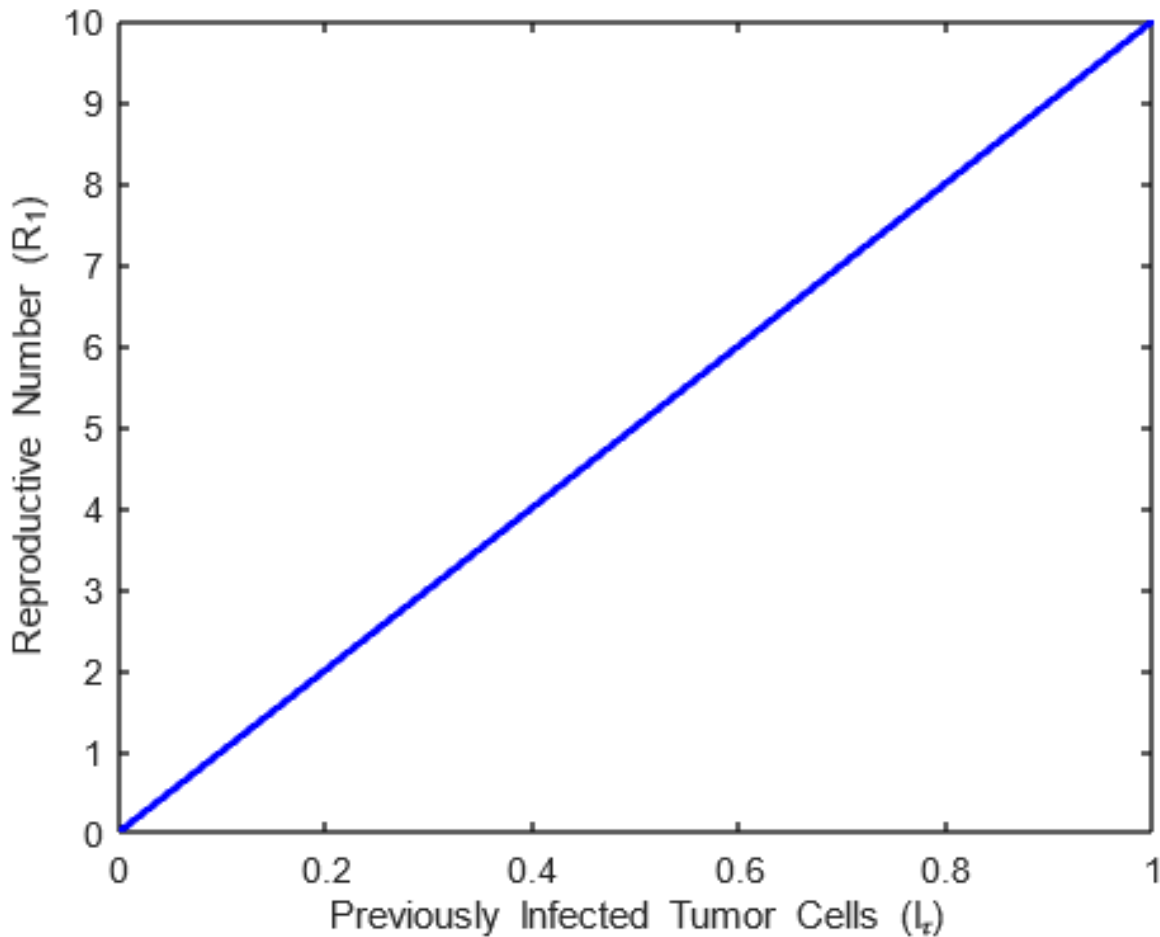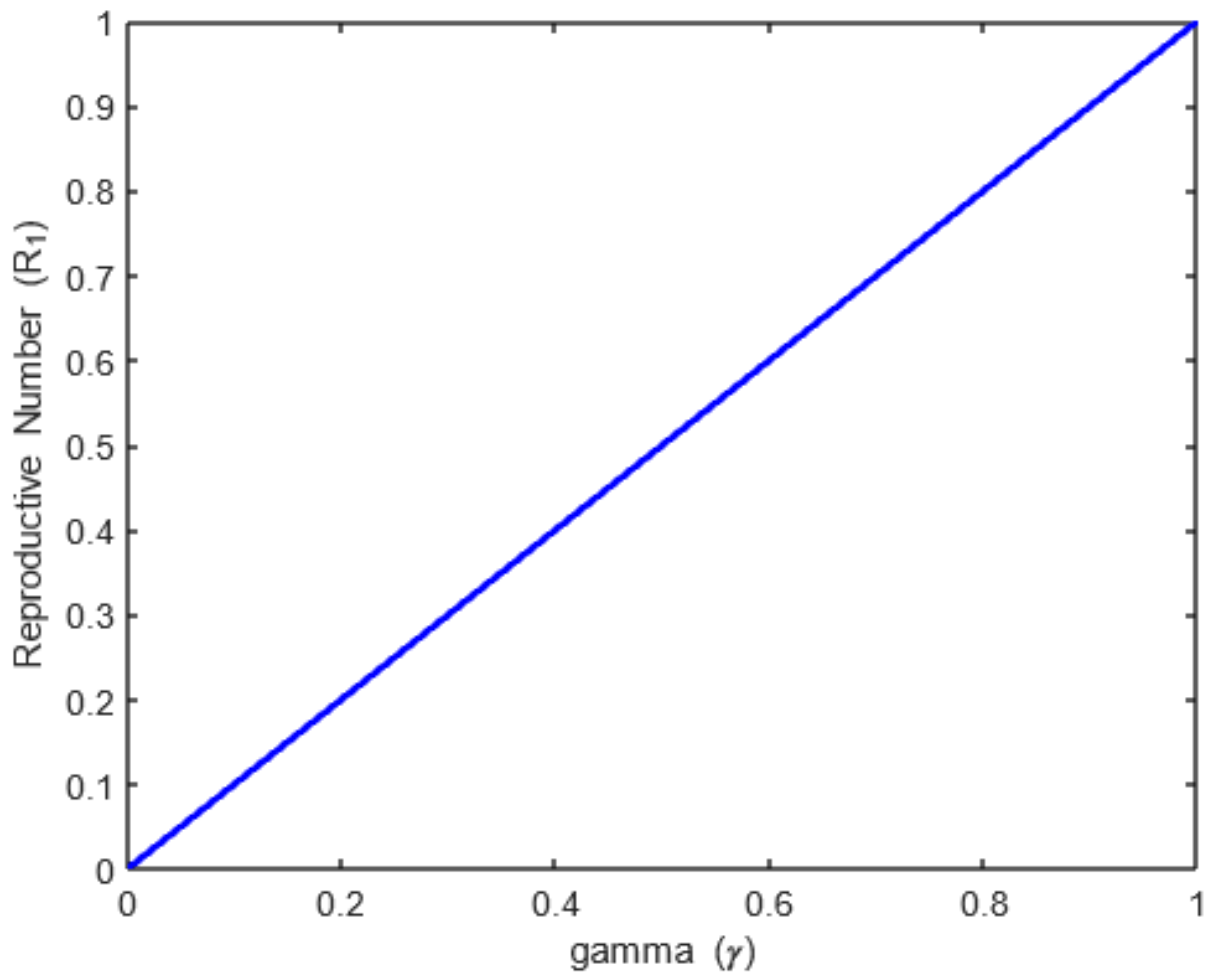

Figure 4.2 shows a plot of reproduction number at the cancer endemic equilibrium point against the rate at which the susceptible cells become exposed by one infectious cell per contact time. It can be clearly seen that the reproduction number and the rate at which the susceptible cells become exposed by one infectious cell per contact time are directly proportional.

A plot of Reproduction Number (R_1) against the probability that Susceptible Cells become exposed by one infectious cell per contact time (γ)

In Figure 4.3 the results for a plot of the reproduction number at the Cancer Endemic Equilibrium Point (CEEP) against the natural mortality rate of susceptible cells. It is shows that the rate of mortality of the susceptible cells increases as the reproduction number increases.

A plot of Reproduction Number (R_1) against Natural Mortality Rate of Susceptible Cells (μ_1)
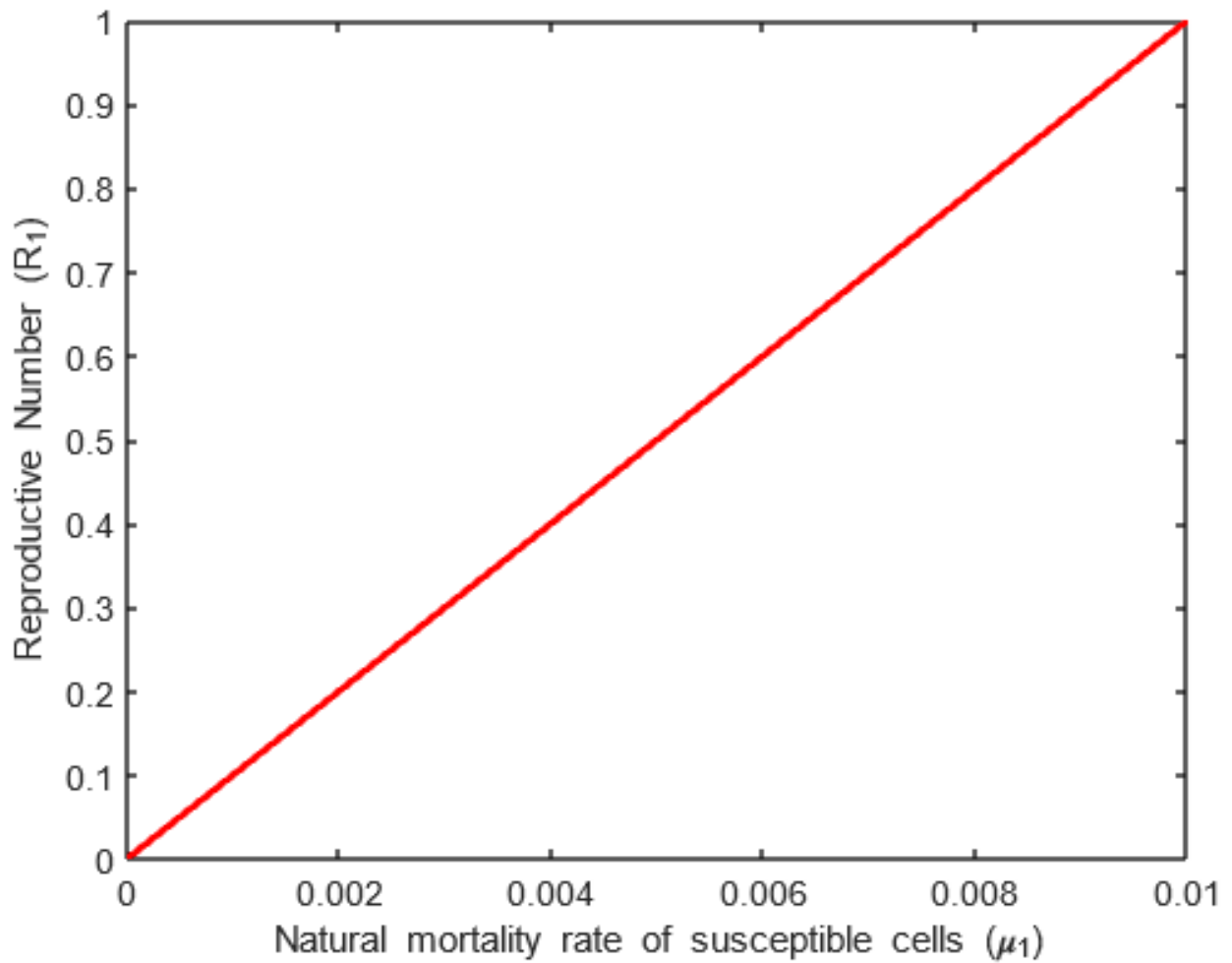
Figure 4.4 shows a plot of the Reproduction number (R_0) against the Time delay (τ) in days. From the graph it's clear that as the Time delay increases the number of new tumor cells decreases. The graph presents the comparison of the delay factor and reproduction number. An increase in the delay time reduces the number of new tumor cells.

A plot of Reproduction number (R_0) against Time Delay (τ) (days)
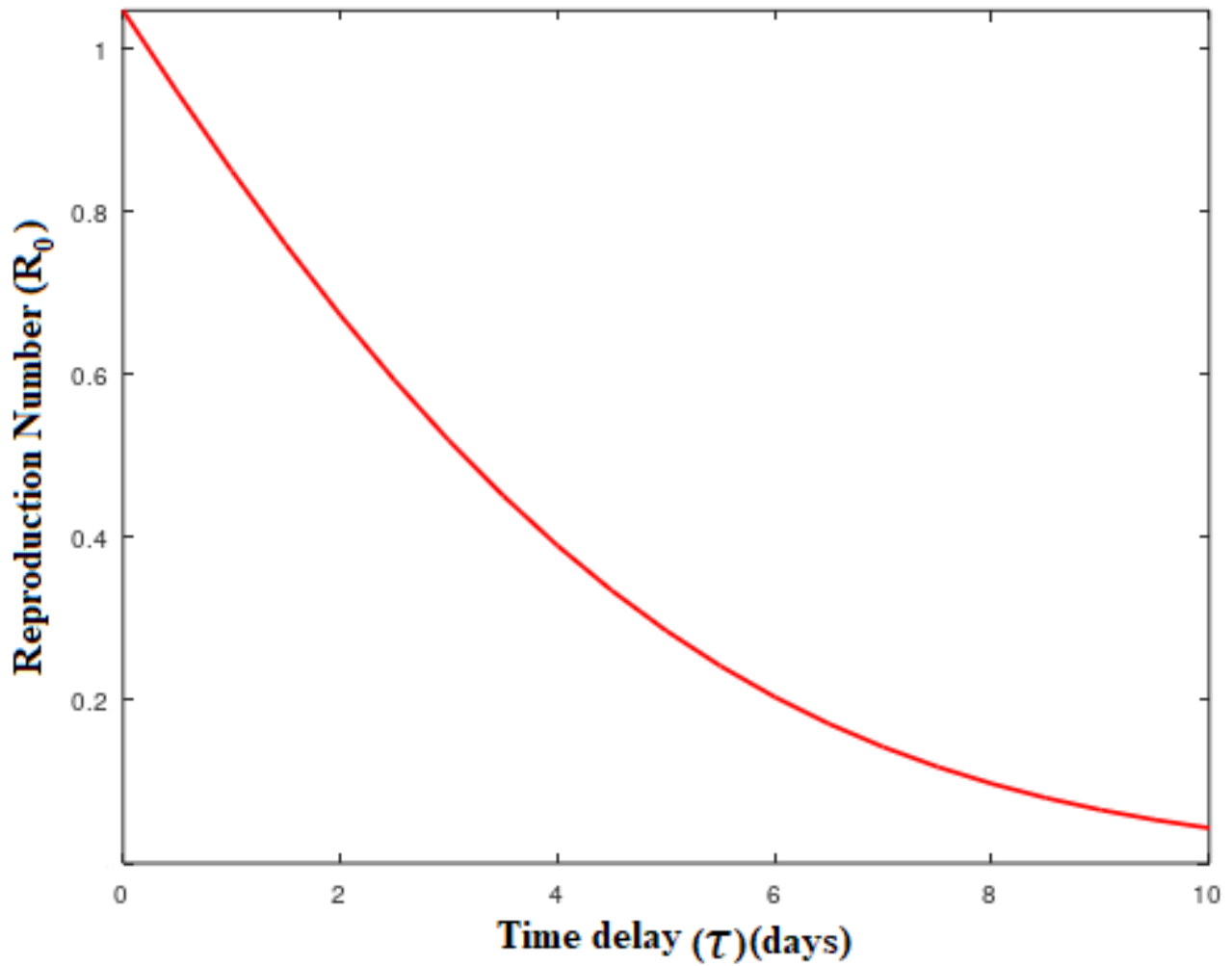
Figure 4.5 shows a plot of the Reproduction number (R_0) against the Number of Tumor Cells. From the graph it can be seen clearly that there is an increase in the amount of Tumor cells as the Reproduction Number increases. Also at low replication rate the Number of Tumor cells are lower.

A plot of the Reproduction Number (R_0) against the Number of Tumor Cells
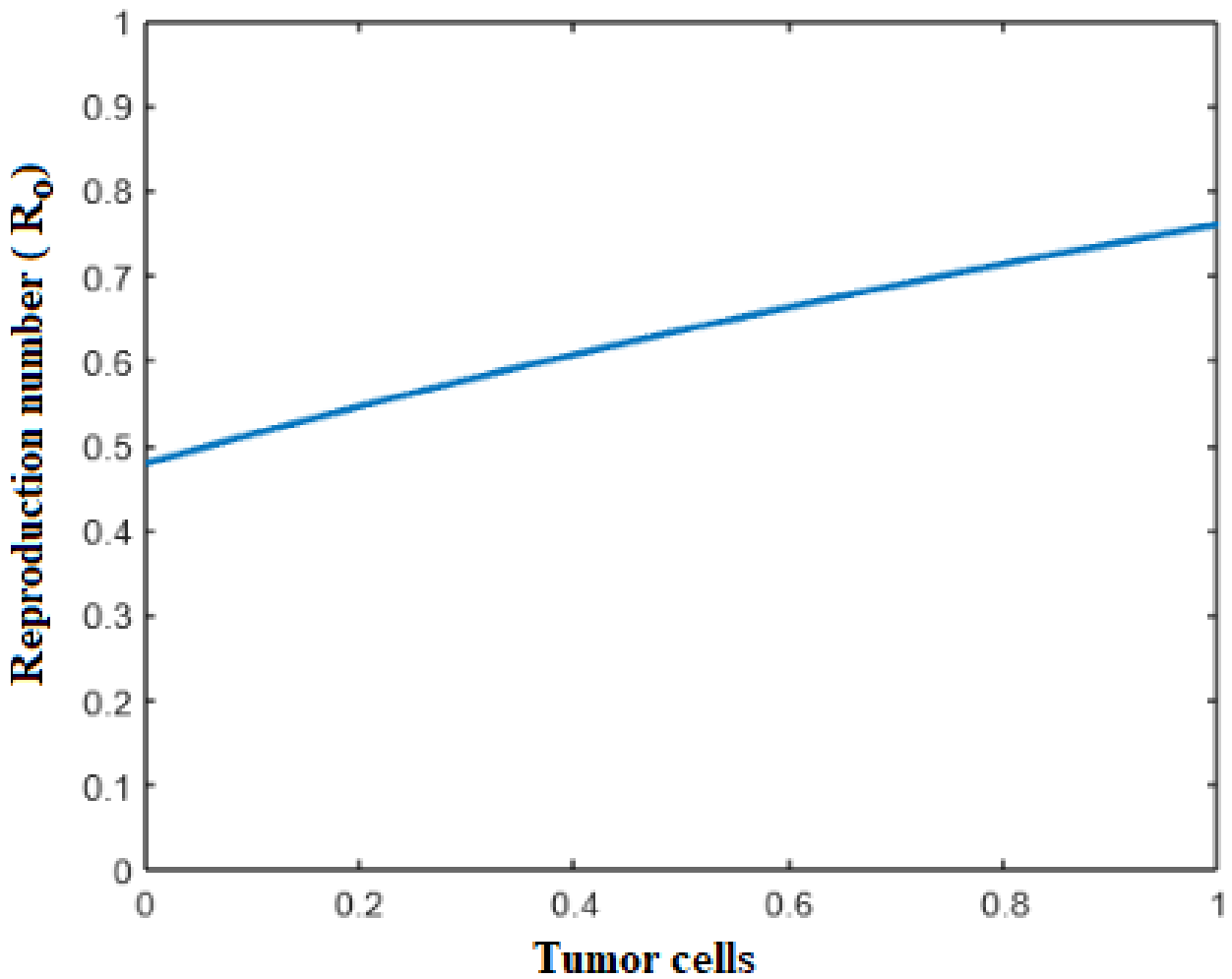
Presented in Figure 4.6 is a plot of the Reproduction number (R_0) against the Drug Efficacy. It shows that as the drug efficacy increases, the reproduction number decreases. This therefore depicts that chemotherapy plays an important role in reducing the tumour replication for stability to be attained at $R_0 < 1$.

A plot of the Reproduction number (R_0) against the Drug Efficacy
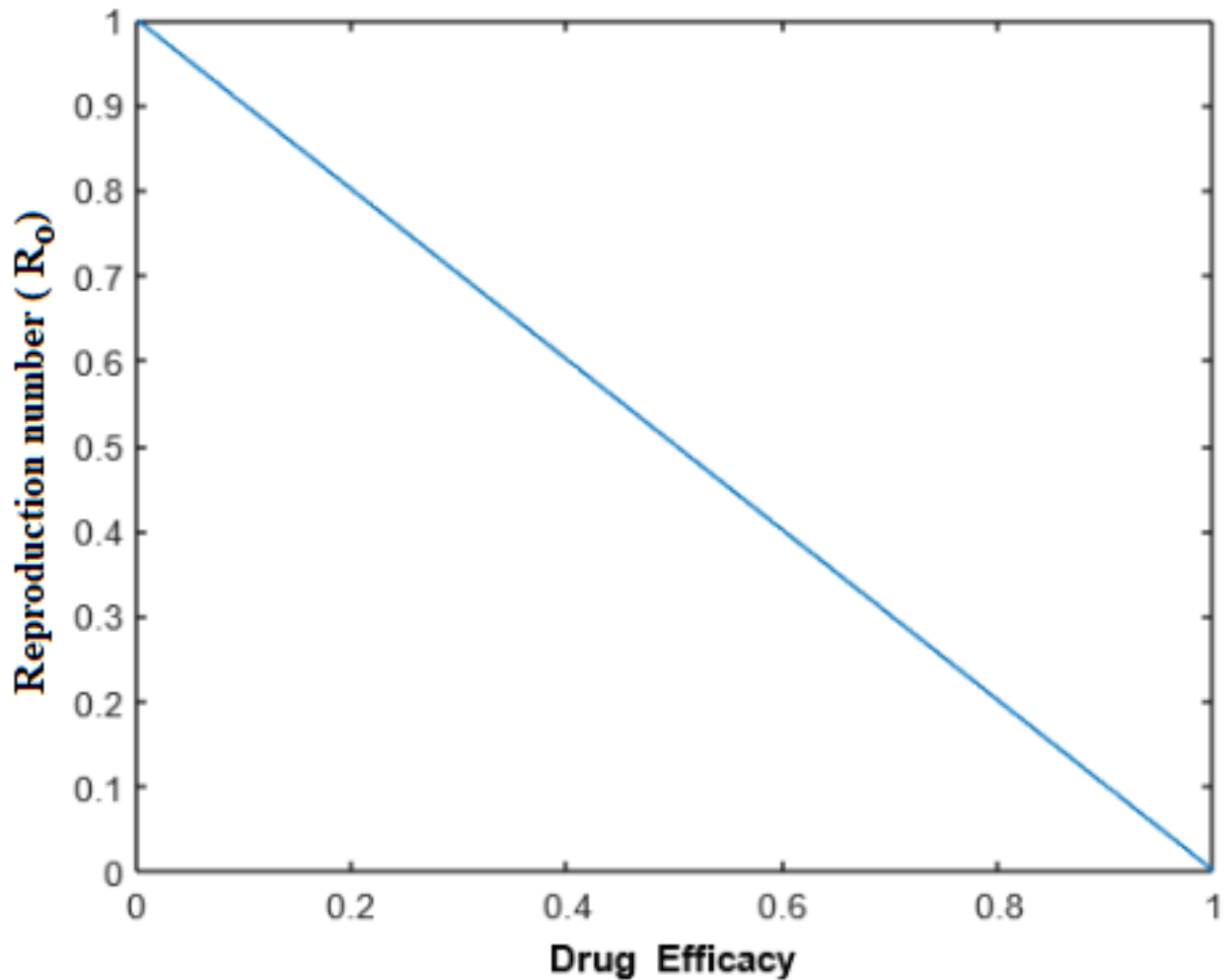
Figure 4.7 shows a plot of the Proportion of cell population against the Time in days. It gives the dynamics of the various compartments of the SEIR model with time. From the graph it's clear that the number of the susceptible cells are more than the infected cells. The number of infectious cells reduces due to chemotherapy while at the same time the number of removed cells increases. This dynamics reduces the number of exposed cells.

A plot of the Proportion of cell population against the Time in days
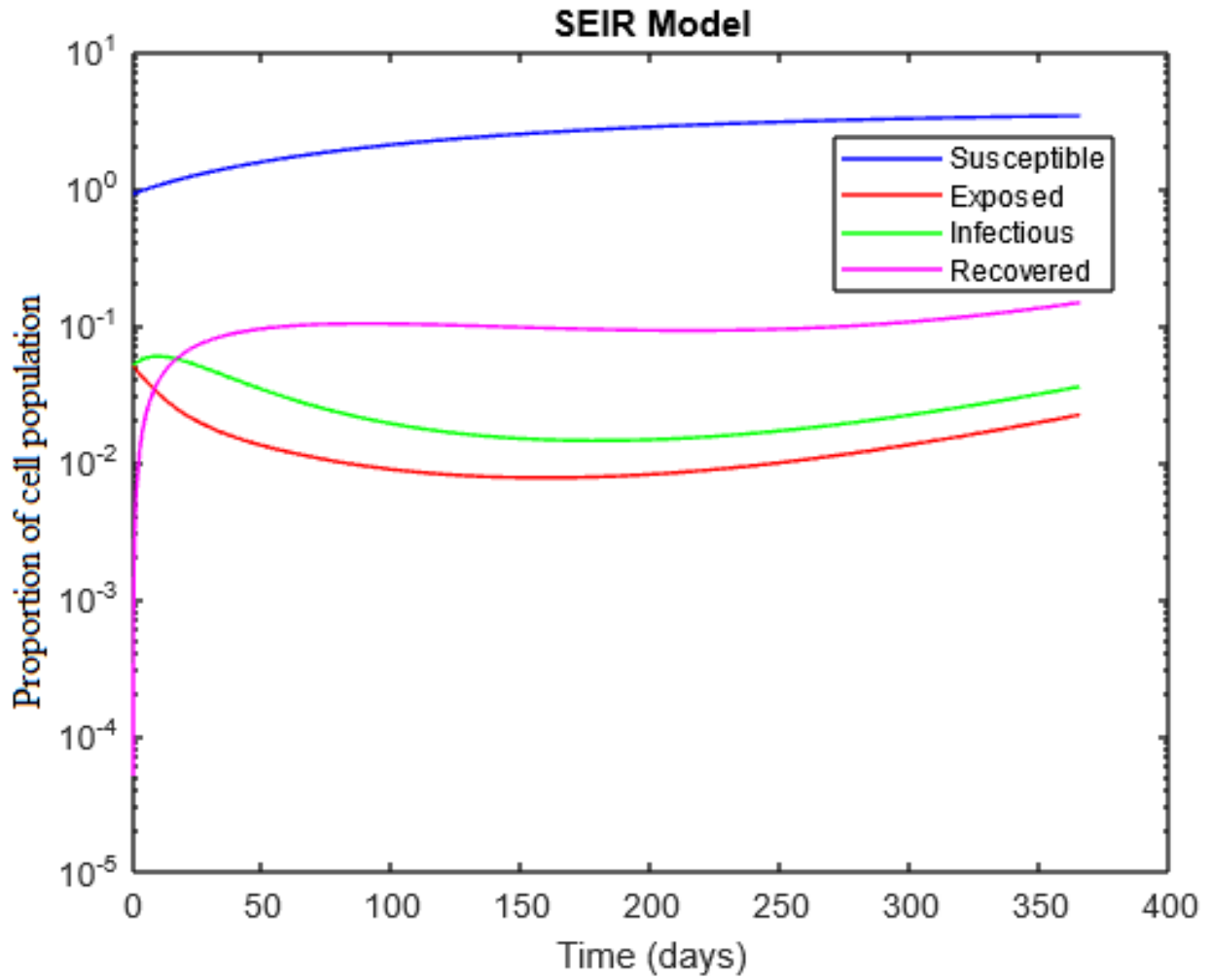
Using MATLAB Software and the hypothetical parameter values in table 4.1, the numerical simulation was done for

$$R_0 = \frac{\beta \Lambda \gamma e^{-2\lambda_\tau}(1-\sigma)}{\mu_1(\mu_2 + \sigma + \beta e^{-\lambda_\tau} - \sigma\beta e^{-\lambda_\tau})(\mu_3 + \alpha e^{-\lambda_\tau} + \eta e^{-\lambda_\tau})} \tag{4.1}$$

in which R_0 was found to be 0.6667 at the CFEP and 1.1037 at the CEEP.

4.3   Comparison with Published Related Works

In this study a delay differential model with control variables that describe the interaction of the time delay (incubation), tumor cells and chemotherapy treatment while for Rihan et al. (2014) a delay differential model with control variables that describes the interactions of immune cells , tumor cells ,

normal cells and immunochemotherapy was provided. While Rihan et al. (2014) found that the most important factors controlling tumor growth were the immune cells and normal cells in the presence of chemotherapy, our model suggests that the time delay (incubation) and timely chemotherapy are the key parameters to ensure long time tumor eradication.

CHAPTER FIVE

SUMMARY,CONCLUSIONS AND RECOMMENDATIONS

5.1 Introduction

The chapter outlines in summary the effects of incubation and chemotherapy on both the Cancer Free Equilibrium Point (CFEP) and the Cancer Endemic Equilibrium Point (CEEP). Conclusion, recommendations and suggestions for further research are also discussed.

5.2 Summary

In this research a SEIR model was formulated for tumour growth dynamics using delay differential equations for the effects of time delay and chemotherapy or drug efficacy on the stability of both the Cancer Free Equilibrium Point (CFEP) and Cancer Endemic Equilibrium Point (CEEP). These effects were numerically analyzed using MATLAB DDE23 solver. In Chapter One, an introduction of the thesis is given starting with background information of the research which is discussed by highlighting cancer modeling, definition of cancer and types of tumours are also illustrated including a summary discussion on cancer statistics and its methods of treatment. The definition of Delay Differential Equations, types of Delay Differential Equations, simulations of delay differential equations and their analytic solutions are also discussed. Finally, the problem statement for the research, the objectives of the research and the significance of the research are also given attention in this chapter.

Chapter Two outlined in details the literature review on cancer modeling, methods used, the findings and limitations of such studies. The research gaps were identified which formed the basis of this study. Chapter three, outlined the methodology of the research. The SEIR model for the tumour dynamics, the assumptions of the research and the model equations are also stated in this chapter. The model preliminary analysis, the determination of the basic reproductive number, computation of the Cancer Free Equilibrium Point and Cancer Endemic Equilibrium Point and the stability analysis of

the equilibrium points both local and global were equally discussed in chapter three. In Chapter Four, numerical simulations were obtained using MATLAB DDE23 for the verification of the analytic results derived in Chapter Three.

5.3   Conclusions

A SEIR mathematical model governed by Delay Differential Equations was formulated for the effects of incubation and chemotherapy on tumor growth dynamics.

Both the cancer endemic equilibrium point and cancer free equilibrium point of the model were computed around which the dynamics of tumor growth was studied.

In line with one of the objectives of the study,the stability of the cancer endemic equilibrium point and cancer free equilibrium point of the model was examined under medication and time delay.

The numerical simulation was done using Matlab software to establish the numerical value of the reproduction number at the equilibrium points and to validate the analytic results.For a reduced spread of infection , the disease free equilibrium point is attained when $R_0 < 1$. From the numerical simulation, CFEP was found to be stable when R_0 was 0.6667 while the CEEP was stable when R_1 is 1.1037. The reproduction number is critical in minimizing the growth of tumour.

5.4   Recommendations

The delay differential equation SEIR mathematical model formulated in this study is recommended for the study of a disease where there is a considerable post-infection incubation period in which the exposed is not yet infectious.

It is recommended that in any epidemiological study , both the disease free state and the decease endemic state be established for ease of disease control. In this study both the cancer endemic equilibrium point and the cancer free equilibrium point of the model were computed.

The stability of the cancer free equilibrium point is an indication that cancer spread within the body cell is on a decline hence effectiveness of the medical intervention whereas the stability of cancer endemic equilibrium point symbolises an upward spread which in turn means medical intervention is necessary. It is therefore recommended that for any epidemiological study, the stability of the equilibrium points

should be ascertained.

When R_0 value in greater than 0.6667, the spread of cancer within the host is increasing and therefore the type of medical intervention is either not effective or immediate treatment is required. Below this value, the spread of cancer within the host is diminishing to a possible extinction of the cancer. Numerical simulation to determine the numerical value of the reproduction number is therefore recommended.

5.5   Suggestions for Further Research

This research has not exhausted all the scientific studies on tumor growth dynamics and treatment. The effects of immune response to tumour growth dynamics were not considered as it has been studied by some researchers. The model can be extended to include reaction-diffusion effects on the tumour growth dynamics. Public knowledge through education on pre-disposing factors and early screening are also possible insights for further research work on tumour growth dynamics. An advancement for a vaccine therapy against the tumour development and growth may also be considered for future studies. The recommendation for inclusion of reaction – diffusion equations in the model is because of a possible spread of tumour cells from one point to other parts of the body.

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APPENDICES

5.6 APPENDIX I : MATLAB Code at the Cancer Free Equilibrium Point

Code for the SEIR model. . . . .

Set the parameter values

Lambda = 0.02;% constant influx rate of new susceptible cells

gamma = 0.1;% probabilty that susceptible cells infected by one infectious cell per contact time

mu1 = 0.005;% coefficient of natural mortality rate of susceptible cells

mu2 = 0.02;% coefficient of natural mortality rate of Exposed cells

mu3 = 0.05;% coefficient of natural mortality rate of Infective cells

mu4 = 0.01; % coefficient of natural mortality rate of recovered cells

sigma = 0.1; % recovery rate of exposed cells due to autoimmunity

beta = 0.4; % rate at which the exposed cells become infective

alpha = 0.02; % natural recovery rate of symptomatic infected cells

eta = 0.01; % recovery rate of symptomatic cells due to chemotherapy

tau = 1/7; % Average time spent in the infectious stage

% Set the initial conditions

S0 = 0.9; % Initial proportion of susceptible individuals

E0 = 0.05; % Initial proportion of exposed individuals

I0 = 0.05; % Initial proportion of infectious individuals

R0 = 0; % Initial proportion of recovered individuals

y0 = [S0, E0, I0, R0]; % Vector of initial conditions

% Set the time range for simulation

tspan = [0, 365]; % Simulation time range (in days)

% Define the system of differential equations

f = @(t, y) [Lambda - mu1*y(1) - gamma*y(1)*y(3)*tau; ... gamma*y(1)*y(3)*tau - mu2*y(2) - sigma*y(2) + (1 - sigma)*beta*y(2)*tau; sigma*y(2) - mu3*y(3) - (alpha + eta)*y(3)*tau; ... alpha*y(3)*tau + eta*y(3)*tau + sigma*y(2) - mu4*y(4)];

% Solve the system of differential equations numerically using ode45

[t, y] = dde23(f, tspan, y0);

```matlab
% Compute the total population N over time

N = y(:, 1) + y(:, 2) + y(:, 3) + y(:, 4);

% Plot the results with a logarithmic y-axis scale

figure;

semilogy(t, y(:, 1), 'b-', t, y(:, 2), 'r-', t, y(:, 3), 'g-', t, y(:, 4), 'm-');

xlabel('Time (days)');

ylabel('Proportion of individuals');

legend('Susceptible', 'Exposed', 'Infectious', 'Recovered');

title('SEIR Model');

%Code for the Ro vs Drug Efficacy...........................................................

function Ro vs drug efficacy()

% Define parameter values

N = 1000;%Total cell population

Lambda = 0.2; %constant influx rate of new susceptible cells

gamma = 1/14; %probabilty that susceptible cells infected by one infectious cell per contact time

sigma = 1/5.2; %recovery rate of exposed cells due to autoimmunity

alpha = 1/7; %natural recovery rate of symptomatic infected cells7;

%recovery rate of symptomatic cells due to chemotherapy

beta = 1.5; %rate at which the exposed cells become infective

% Define

eta = 1/

range of drug efficacy values to test with higher resolution

efficacy range = 0:0.01:1;

% Define array to store RO values for each drug efficacy

Ro vals = 1 - efficacy range;

% Plot RO vs drug efficacy

plot(efficacy range, Ro vals, 'LineWidth', 1);

xlabel('Drug Efficacy');

ylabel('Reproduction Number (Ro)');

title('Ro vs Drug Efficacy');
```

```matlab
grid on;

axis([0 1 0 1]);

grid off;

end
```

%Code for the Ro vs Tumor Cells. . . . .

```matlab
function Ro vs TumorCells()
% Define parameter values
Lambda = 0.03; %constant influx rate of new susceptible cells
gamma = 0.05; %probabilty that susceptible cells infected by one infectious cell per contact time
mu1=0.005;%coefficient of natural mortality rate of susceptible cells
mu2=0.01;%coefficient of natural mortality rate of Exposed cells
mu3=0.01;%coefficient of natural mortality rate of Infective cells
mu4=0.01;%coefficient of natural mortality rate of recovered cells
Sigma=0.1;%recovery rate of exposed cells due to autoimmunity
beta=0.2;%rate at which the exposed cells become infective
alpha=0.005;%natural recovery rate of symptomatic infected cells
eta=0.005;%recovery rate of symptomatic cells due to chemotherapy
% Define range of tumor cell values to test
S vals = 0:0.01:1;
% Define array to store Ro values for each tumor cell value
Ro vals = zeros(size(S vals));
% Loop over each tumor cell value
for i = 1:length(S vals)
% Calculate corresponding values for other variables
N = 1;
E = 0.1;
I = 0.1;
R = 0.8;
S = S vals(i);
beta tau = beta * (S + E + I + R);
```

```
alpha tau = alpha * (S + E + I + R);

eta tau = eta * (S + E + I + R);

lambda tau = Lambda * (S + E + I + R);

% Calculate Ro using current tumor cell value

Ro vals(i) = Ro calculation(N, beta tau, gamma, lambda tau, sigma, alpha tau, eta tau, mu1, mu2, mu3,

mu4);

end

% Plot Ro vs. tumor cells with a limit of 1 on the y-axis

plot(S vals, Ro vals, 'LineWidth', 2);

xlim([0 1]);

ylim([0 1]);

xlabel('Tumor Cells');

ylabel('Reproduction Number (Ro)');

title('Ro vs. Tumor Cells');

grid off;

end

function Ro = Ro calculation(N, beta tau, gamma, lambda tau, sigma, alpha tau, eta tau, mu1, mu2,

mu3, mu4)

% Calculate Ro using provided equation

Ro = beta tau * gamma / ((mu1 + mu2 + mu3 + mu4 + sigma) * (mu1 + mu4 + lambda tau + sigma +

alpha tau + eta tau));

end

%Code for Ro versus time delay. . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . .

% Parameters

Lambda = 0.25;

gamma = 0.05;

mu1 = 0.02;

mu2 = 0.04;

mu3 = 0.05;

mu4 = 0.02;
```

```matlab
alpha = 0.1;

eta = 0.1;

sigma = 0.3;

beta = 0.35;

% Time delay range

tau = 0:0.5:10;

% Function to calculate R0

R0 = @(tau) (beta * Lambda * gamma * exp(-2 * Lambda * tau) * (1 - sigma)) ./ ... (mu1 * (mu2

+ sigma + beta * exp(-Lambda * tau) - sigma * beta * exp(-Lambda * tau)) .* ...  (mu3 + alpha *

exp(-Lambda * tau) + eta * exp(-Lambda * tau)));

% Calculate R0 values

Ro = R0(tau);

% Find Ro values at CEEP greater than 1 and CFEP less than 1

Ro CEEP = Ro(Ro > 1);

Ro CFEP = Ro(Ro < 1);

% Find the highest values of CEEP and CFEP

max CEEP = max(Ro CEEP);

max CFEP = max(Ro CFEP);

% Print the highest values of CEEP and CFEP

fprintf('Highest value of CEEP: %.2f \ n ', max CEEP);

fprintf('Lowest value of CFEP: %.2f\ n', max CFEP);

% Plot Ro vs TIME DELAY

figure;

plot(tau, Ro,'r', 'LineWidth', 1);

xlabel('Time delay(\tau)');

ylabel('Reproduction Number(Ro)');

title('Ro versus time delay(\tau)');

grid off;

ylim([0,max(Ro)*1.0]);
```

5.7 APPENDIX II : MATLAB Code: Drug Efficacy Versus Reproductive Ratio

```
% Function Drug Efficacy Versus Reproductive Ratio
%parameters.................................................
Lambda=0.04;%constant influx rate of new susceptible cells
gamma=0.9;%probabilty that susceptible cells are infected by one infectious cell per contact time
mu1=0.009;%coefficient of natural mortality rate of susceptible cells
mu2=0.003;%coefficient of natural mortality rate of Exposed cells
mu3=0.004;%coefficient of natural mortality rate of Infective cells
mu4=0.002;%coefficient of natural mortality rate of recovered cells
Sigma=0.03;%recovery rate of exposed cells due to autoimmunity
beta=0.02;%rate at which the exposed cells become infective
alpha=0.01;%natural recovery rate of symptomatic infected cells
eta=0.05;%recovery rate of symptomatic cells due to chemotherapy
I tau=10;
%R1=(mu1-gamma*I tau)/(1-gamma*I tau);
figure;
R1=0:0.5:1;
I tau=0:5:10;
plot(R1,I tau,'b','LineWidth',1)
title('R 1 versus Previously Infected Tumor Cells (I \ tau)');
xlabel('Previously Infected Tumor Cells (I \ tau)'
ylabel('Reproductive Number (R1)')
%ylabel('Reproductive Number (R1)')
figure;
gamma=0:.5:1
R1=0:0.5:1;
plot(gamma,R1,'g','LineWidth',1);
xlabel('gamma (\ gamma)')
ylabel('Reproductive Number (R1)')
title('R1 versus gamma ( \ gamma)');
```

```
figure;

mu1=0:.005:0.01

R1=0:0.5:1;

plot(mu1,R1,'g','LineWidth',1);

xlabel('Natural mortality rate of susceptible cells (\ mu1)')

ylabel('Reproductive Number (R1)')

title('R1 versus Natural mortality rate of susceptible cells(\ mu1)');
```

5.8   APPENDIX III : Publication from the Thesis

A Mathematical Model for the Effects of Incubation and Chemotherapy on the Dynamics of Tumor Growth

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Original Research Article

Abstract

The application of Mathematical models in simulating processes that are biological in nature has been in effect for a long time. A great number of Mathematical, Computational, Engineering and Physical approaches have been administered to several aspects of development of Tumor, with a view of appreciating how cancer cell population responds to medical intervention. This research therefore considered a Mathematical model for the consequences of incubation and Chemotherapy on Tumor growth dynamics by formulating a deterministic S (susceptible), E (exposed), I (infectious), R (recovered) model using Delay differential equations. The Delay in this case accounted for the duration between the subjection of a cell to cancer virus and the onset of symptomatic disease. Reproduction number (R_0) of the model was ascertained using next generation matrix approach. The stability analysis of Cancer Free Equilibrium Point (CFEP) of the model was investigated. MATLAB computer program was used for numerical simulations to validate the analytic results. The investigation and analysis of the consequences of incubation and Chemotherapy on the stability of the

_____

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equilibrium point was also done. This study of Tumor growth dynamics is significant in that it shall help establish the stage and the extent of cancer spread within the body cells. It shall also help develop a better drug administration procedure as well as providing mechanistic insights. Parameter values used were mostly estimated values. From the numerical analysis, our findings suggest that CFEP is stable when R_0 is 0.6667 otherwise unstable.

1 Introduction

Mathematical modeling of biological processes especially on cancer has in recent times received much attention. Mathematical models of Biological processes and the associated numerical simulation has reduced the complicated and costly experimental procedures [1-3]. It has been adopted by several epidemiologists as one of the approaches to study non-communicable diseases. Worldwide, including Africa, cancer is rated second as a main cause of mortality behind heart diseases; this is according to World Health Organization (2018). Cancerous tumor growth, spread to the adjacent tissues and treatment have been explained by various Mathematical models in the past. Terminal illnesses or diseases are conditions which cannot be cured hence leads to the death of the affected person. Examples of terminal diseases are Liver disease, HIV, Lung disease, advanced heart disease, advanced cancer among others [4-6].

According to World Health Organization (WHO), 2020, breast, lung, colon, rectum and prostate cancers are the most common ones. In this study we examine how Mathematical models can be used to imitate Tumor growth as well as cancer medication.

Tumor is an abnormal mass of tissue which may be solid inside or filled with fluid. There are three Tumor types, namely benign, premalignant and malignant Tumors. When the development of Tumor cells are restricted to the location of emergence, does not spread to other sites of the body, grows slowly and have distinct borders, then they are said to be benign Tumors. Such tumors are non-cancerous. Premalignant tumors are those in which cells are not yet cancerous but have the potential of becoming cancerous. Finally, when the cells are unusual, grow rapidly and can proliferate to other sections of the body, then they are referred to as malignant tumors or cancerous cells. To establish if a tumor is cancerous or benign, a fragment of the cells is taken through a biopsy procedure by a doctor and then examined. A pathologist then analyzes the biopsy under a microscope. On the other hand, cancer is a genetic malady caused by changes to genes that control the way the body cells function, how they grow and how they fractionate. Cancer cells diverge from the other cells in different ways. For example, their growth takes place even in the absence of the signal initiating the growth, continues growing despite the signals stopping their growth. They also attack the surrounding cells of the body among others [7-9]. Cancer is regarded as one of the most exhausting illness to treat and hence leads to more deaths than most diseases. It's also noted that combating cancer is crucial for public health, [10-12]. Over the years several methods of cancer treatment have been used, these include hormone therapy, surgery, radiotherapy, immune therapy and chemotherapy among others. Mathematical epidemiology has contributed to a more in-depth understanding of cancerous Tumor growth as a terminal ailment, its effect and possible future forecast about its spread in the body and the mechanism of its control and treatment.

Advanced mathematical model for cancer analysis considering time delay was done [11, 13, 14]. The changing characteristic of the nonlinear mathematical model which was initially fronted by introducing the delay component in the relationship between the tumor cell itself and the body's defense system. This was done in an effort to ensure that the model is more practical. The investigation of the Mathematical model showed that, the elimination of the tumor cells entailed a joint effort of both normal cells and the immune system without the drug administration. However it was also shown that the immune system of the body does not acknowledge the tumor cells immediately so as to give enough feedback time (i.e., the delay term is prolonged), the growth rate of the tumor increases hence the system's immune stability is lost and finally drifts away from the tumor-free steady point. As a consequence, the immune–normal cell fails to effect the destruction of the tumor burden.

According to [3, 15, 16] they investigated a mathematical model for chemo-immunotherapy, which is a combination of chemotherapy and immunotherapy for brain cancer. The system of equations used included nonlinear first-order ODEs. The mathematical model considered the interaction of immune system cells with

cancer cells and the treatment. The dynamic variables of the system are immature dendritic cells, immunogenic dendritic cells, tolerogenic dendritic cells, naive *T*-cells, cytotoxic *T*-cells, proliferating cytotoxic *T*-cells, cancer cells, and chemotherapy medicine. They proposed a new treatment protocol, which was essentially a new analytical function that depended on the time interval between treatment and dosage. To investigate the stability of the equilibrium points, it was necessary to solve the nonlinear algebraic equation related to the mathematical model, which, in this case, was impossible analytically. Hence, they applied the SPVF algorithm to transfer the mathematical model to a new coordinate with an explicit hierarchy and divided it into fast and slow subsystems. This procedure enabled them to investigate only the fast subsystem, without losing the biological information of the original model. They determined all equilibrium points of the model in the new coordinates and their stability. The equilibrium points had no biological meaning in the new coordinates; hence, they inversely transformed only the stable equilibrium points into the original coordinates of the model. They investigated the mathematical model with our proposed treatment protocol, with constant dosage and different time intervals between treatments, that is, 7, 14, 28, and 56 days. Thereafter, they compared their analysis results with experimental (clinical) data. The optimal treatment was found to correspond to the protocol with a 7day interval between treatments. The next step involved the application of the protocol with different dosages and time intervals simultaneously. They examined the behaviour of cancer cells when the initial conditions were changed. All results were identified to reach a state of equilibrium at approximately the same time. Indeed, this was dependent on the treatment, which had been determined to vary in terms of dosage and time.

A model with random noise on the dynamical behaviour of the Tumor and the immune system was developed. The study assimilated the consequence of noise into a model for Tumor-immune system with Holling type III response functions to cater for the alterations in cell dynamics. It made use of a stochastic Lyapunov function together with Ito's formula, to provide enough constrain for establishing the existing stationary distribution results, weak persistence, and elimination of Tumor cells. The stochastic model for Tumor- immune interaction was used. The research also showed that the growth of tumor can be reduced by increasing the intensity of the noise as a fundamental factor in the existence of immune effectors [17, 18, 19].

According to [7,20,21] they considered the analysis of a cancer Mathematical model which included the time-delay in the interactivity amidst the Tumor cells and the immune system of the body and their stimulation processes. It analyzed and observed the model dynamics together with changes of crucial restrictions and the effect of time delay on anti -Tumor immune reaction. The delay term was included in the model. As a consequence, the modified model demonstrated that the system was able to bring about varying responses even with the delay term included. In addition, it demonstrated that the oscillations were continuous and couldn't be eliminated through the addition of the delay term. The numerical simulations and bifurcation analysis indicated that a "careful" consideration of the model's framework has to be determined so that the fixed-state becomes less stable. It was shown that the time delay was not a requirement to originate oscillations since such oscillations could be generated even in the absence of the delay term.

In this paper, we have formulated a SEIR deterministic mathematical model with delay differential equations (DDE) for the investigation of the effects of incubation and chemotherapy on Tumor growth dynamics. In a SEIR model the individuals in a population are divided into four sub-populations or compartments. These compartments are the susceptible **(S)**, which refers to the healthy Cells which have not yet come into contact with the cancer cells. The exposed **(E)** are the Cells which have come into contact with the Cancer cells but are not yet infective or infectious. The infective **(I)** are those that have become infected with the cancer cells and are infectious and the recovered **(R)** are those that have recovered or removed from the cell population.

2 Methods of Solution

The stability of the model has been approached from Jacobian matrix method of checking stability of Cancer Free Equilibrium Point (CFEP) and numerical simulations have been done using MATLAB to validate the analytic results.

2.1 Model equations

From the flow chart, the parameters and the model assumptions the tumor dynamics can be modeled using the following delay differential equations.

$$\frac{dS}{dt} = \Lambda - \gamma\, SI_\tau - \mu_1 S \tag{2.1}$$

$$\frac{dE}{dt} = \gamma\, SI_\tau - \mu_2 E - \sigma E - (1 - \sigma)\beta E_\tau \tag{2.2}$$

$$\frac{dI}{dt} = (1 - \sigma)\beta E_\tau - \mu_3 I - (\alpha + \eta)I_\tau \tag{2.3}$$

$$\frac{dR}{dt} = (\alpha + \eta)I_\tau + \sigma E - \mu_4 R \tag{2.4}$$

The total cell population N, is given as $N = S + E + I + R$.

2.2 Model preliminary analysis

The preliminary analysis of the formulated model is given in this section. The analysis includes positivity and boundedness of the model solution, calculation of the basic reproductive number, determination and the stability analysis of the equilibrium points. Finally, the sensitivity analysis of the basic reproductive number is also done. Positivity and boundedness are therefore essential features of an epidemiological study.

2.2.1 Positivity of the solution of the model

The model monitors the cell population in Tumor dynamics, so all its associated parameters must be non-negative. Positivity of the solution is one of the important features of an epidemiological model. It is therefore important to prove that all state variables are non-negative for all time $t \geq 0$. Further any solution with positive initial values will remain positive for all the time $t \geq 0$. Biologically, positivity implies that the population will survive a long time. Therefore to check how biologically valid the proposed model is, the positivity of the proposed model must be shown.

Theorem 1: Let $S(0) \geq 0, E(0) \geq 0, I(0) \geq 0$ and $R(0) \geq 0$, then it implies that all the variables of the model $S(t), E(t), I(t)$ and $R(t)$ will all remain positive for all solutions of the model equations for $t > 0$

The closed region $\sum = \left\{(S, E, I, R) \in \mathbb{R}^4_+ ; \text{such that } 0 < N \leq \frac{\Lambda}{\mu_1}\right\}$ is positively invariant set for the model equations (2.1), (2.2), (2.3) and (2.4)

Proof

From the model equation (2.1)

$$\frac{dS}{dt} = \Lambda - (\gamma\, I_\tau + \mu_1)S$$

Letting $(\gamma\, I_\tau + \mu_1) = A$, the equation above becomes

$$\frac{dS}{dt} + AS = \Lambda$$

The integrating factor for the above Ordinary Differential Equation is given as $e^{\int A\,dt} = e^{At}$

$$e^{At}\frac{dS}{dt} + ASe^{At} = \Lambda e^{At}$$

$$\frac{d}{dt}(Se^{At}) = \Lambda e^{At}$$

Integrating the above equation and substituting the limits yields

$$S(t)e^{At} - S(0)e^{A(0)} = \Lambda e^{At} - \Lambda e^{A(0)}$$

$$S(t) = S(0)e^{-(\gamma I_\tau + \mu_1)t} + \Lambda - \Lambda e^{-(\gamma I_\tau + \mu_1)t} \tag{2.5}$$

as $t \to \infty$, $S(t) = \Lambda > 0$ implying that S(t) is positive

From equation (2.2), (2.3) and (2.4) we can similarly show respectively that

$$E(t) = E(0)e^{-\int_0^t (\mu_2 + \sigma) + (1-\sigma)\beta E(k-\tau)d\xi} + \int_0^t (\gamma\, S\, I_\tau)e^{-\int_\omega^t (\mu_2 + \sigma) + (1-\sigma)\beta E(k-\tau)d\xi} d\omega \tag{2.6}$$

$$I(t) = I(0)e^{-\int_0^t \mu_3 + (\alpha + \eta)I(k-\tau)]d\xi} + \int_0^t [(1-\sigma)\beta E(k-\tau)]\, e^{-\int_\omega^t [\mu_3 + (\alpha + \eta)I(k-\tau)]d\xi} d\omega \tag{2.7}$$

$$R(t) = R(0)e^{-\int_0^t \mu_4 d\xi} + \int_0^t [(\alpha + \eta)I(k-\tau) + \sigma E]\, e^{-\int_0^t \mu_4 d\xi} d\omega \tag{2.8}$$

From the equations (2.5), (2.6), (2.7) and (2.8), since $S(t) > 0, E(t) > 0, I(t) > 0$ and R (t) > 0, it implies that the region $\sum$ is positively invariant and so it is sufficient to consider solution of the model equations.

2.2.2 Boundedness.

This subsection seeks to prove the boundedness of the solutions of the model equations. Since the model deals with the cell population, it follows that at any time, t the sum of the cell population of all the compartments must be greater than the whole cell population.

Theorem 2: Let the closed region $\sum = \left\{ (S, E, I, R) \in \mathbb{R}_+^4; \text{such that } 0 \le N \le \frac{\Lambda}{\mu_1} \right\}$ is bounded for the model equations (2.1), (2.2), (2.3) and (2.4)

Proof

Let $N(t) = S(t) + E(t) + I(t) + R(t)$ \hfill (2.9)

Differentiating (2.9) with respect to t gives

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dE}{dt} + \frac{dI}{dt} + \frac{dR}{dt} \tag{2.10}$$

Substituting (2.1), (2.2), (2.3) and (2.4) into (2.10) yields

$\frac{dN}{dt} = \Lambda - \gamma\, SI_\tau - \mu_1 S + \gamma\, SI_\tau - \mu_2 E - \sigma E - \beta E_\tau + \sigma\beta E_\tau + \beta E_\tau - \sigma\beta E_\tau - \mu_3 I - \alpha I_\tau - \eta I_\tau + \alpha I_\tau + \eta I_\tau + \sigma E - \mu_4 R$

$= \Lambda - \mu_1 S - \mu_2 E - \mu_3 I - \mu_4 R$

$\frac{dN}{dt} \le \Lambda - (S + E + I + R)$ Where

$\mu = $ is the mean of μ_1, μ_2, μ_3 and μ_4

Letting N = S + E + I + R yields

$$\frac{dN}{dt} \le \Lambda - \mu N$$

$$\frac{dN}{\mu N - \Lambda} \le -dt \tag{2.11}$$

Integrating equation (2.11) gives

$$\int_{N_0}^{N} \frac{dN}{\mu N - \Lambda} \le \int_{t_0}^{t} -dt$$

$$\ln(\mu N - \Lambda) - \ln(\mu N_0 - \Lambda) \le -t - \ (-t_0)$$

$$\ln \left(\frac{\mu N - \Lambda}{\mu N_0 - \Lambda} \right) \ \le t_0 - t$$

$$N(t) \le \frac{\Lambda}{\mu} + \frac{(\mu N_0 - \Lambda)e^{t_0}e^{-t}}{\mu}$$

$$\lim_{t \to \infty} N(t) \le \ \lim_{t \to \infty} \frac{(\mu N_0 - \Lambda)e^{t_0}e^{-t}}{\mu} \le \frac{\Lambda}{\mu} \tag{2.12}$$

Hence $N(t) \le \frac{\Lambda}{\mu}$

Which implies that $0 \le N(t) \le \frac{\Lambda}{\mu}$, $N(t)$ is bounded and so are $S(t), E(t), I(t)$ and $R(t)$ of the model are also bounded in the region Σ

2.3 Equilibrium point of the model.

Epidemiological processes basically exhibits two points of equilibrium, points at which there is no change in the state of the system. The two points are the disease free equilibrium point and the endemic equilibrium point. We considered the Cancer Free Equilibrium Point (CFEP) for this study. The Cancer Free Equilibrium Point occurs when there is absence of cancer within the cells. This equilibrium point was obtained by equating the model Equations (2.1), (2.2), (2.3) and (2.4) to zero then solving. The stability of the model is then studied around the equilibrium point. A system is said to be stable if all the eigenvalues obtained linearizes around the fixed points.

2.3.1 Cancer free equilibrium point

The Cancer Free Equilibrium Point $\mathcal{E}_o = (S_0, E_0, I_0, R_0)$ occurs when the infective class is absent and consequently the recoveries. It is found by equating the model equations to zero then evaluating.

At the Cancer Free Equilibrium

$$\frac{dS(t)}{dt} = \frac{dE(t)}{dt} = \frac{dI(t)}{dt} = \frac{dR(t)}{dt} = 0 \tag{2.13}$$

By substituting Equation (2.13) into the model equations (2.1), (2.2), (2.3) and (2.4) gives

$$\Lambda - \gamma SI_\tau - \mu_1 S = 0 \tag{2.14}$$

$$\gamma SI_\tau - \mu_2 E - \sigma E - (1 - \sigma)\beta E_\tau = 0 \tag{2.15}$$

$$(1 - \sigma)\beta E_\tau - \mu_3 I - (\alpha + \eta)I_\tau = 0 \tag{2.16}$$

$$(\alpha + \eta)I_\tau + \sigma E - \mu_4 R = 0 \tag{2.17}$$

If we let $I_\tau = 0$, Equation (2.14) becomes $\Lambda - \mu_1 S = 0$ and so

$$S = \frac{\Lambda}{\mu_1} \qquad (2.18)$$

Equations (2.15), (2.16) and (2.17) reduces to zero since all the infectious, exposed and the recovered sub populations are all equal to zero i.e. $I = E = R = 0$

Therefore, the Cancer Free Equilibrium Point of the SEIR model is then given by

$$\mathcal{E}_o = (S_0, E_0, I_0, R_0) = (\frac{\Lambda}{\mu_1}, 0, 0, 0)$$

2.4 Basic reproductive number

The basic reproduction number denoted by $\boldsymbol{R_0}$ is the most significant quantity in disease modeling. It is defined as the number of new infection incidences emanating from one infection known as the primary infection case in a completely vulnerable population. The reproduction number provides an overall measure of the potential for the spread of an infection within a completely susceptible population. Reproduction number also gives an elementary and explicit elucidation for the growth and decomposition of an endemic disease. The parameter is dependent not only on the transmission coefficient but also on the average duration of infectiousness of the disease. A higher value of the reproduction number ($\boldsymbol{R_0}$) may be interpreted to mean a higher therapeutic intervention needed. Such intervention is to reduce the advancement and in the long run do away with the disease from the population under study. When $R_0 < 1$ the spread of cancer within the cells will reduce and finally die off while when $R_0 > 1$ the infection will persist.

To determine the reproductive number, the dominant or maximum eigenvalue of the next generation matrix is computed. The spectral radius of the matrix FV^{-1} gives the reproduction number that is, $R_0 = \rho(FV^{-1})$ where $\boldsymbol{\rho}$ is the spectral radius of the next generation matrix, F is the matrix for the new cancer cells while V is the matrix of the transfers of infections from one compartment to another.

The vectors for the infected class and the uninfected class are then identified. The infected classes are E and I which are represented by $X = [E, I]^T$ while the uninfected class are represented by vector $Y = [S, R]^T$

The vector for the new infection rate $\mathcal{F} = \begin{bmatrix} \gamma \, SI_\tau \\ 0 \end{bmatrix}$. This is the vector for new infections from the susceptible sub-population into the exposed sub-population.

The vector for other infections from compartment to another is given as

$$\mathcal{V} = \begin{bmatrix} (\mu_2 + \sigma)E + (1 - \sigma)\beta E_\tau \\ -(1 - \sigma)\beta E_\tau + \mu_3 I + (\alpha + \eta)I_\tau \end{bmatrix}$$

The product of F and V^{-1} gives the next generation matrix

The matrix $F = \left(\frac{\partial \mathcal{F}}{\partial X}\Big|_{\mathcal{E}_0} \right)$ is the matrix formed by partial derivative of the vector of new infection rates evaluated at the Cancer Free Equilibrium Point while the matrix $V = \left(\frac{\partial \mathcal{V}}{\partial X}\Big|_{\mathcal{E}_0} \right)$ is the matrix formed from the partial derivative of the vector of other rates which are not new infections evaluated at the Cancer Free Equilibrium Point. Therefore

$$F = \begin{bmatrix} \frac{\partial \mathcal{F}}{\partial E} & \frac{\partial \mathcal{F}}{\partial I} \\ \frac{\partial \mathcal{F}}{\partial E} & \frac{\partial \mathcal{F}}{\partial I} \end{bmatrix} \quad \text{and} \quad V = \begin{bmatrix} \frac{\partial \mathcal{V}}{\partial E} & \frac{\partial \mathcal{V}}{\partial I} \\ \frac{\partial \mathcal{V}}{\partial E} & \frac{\partial \mathcal{V}}{\partial I} \end{bmatrix}$$

Hence

$$F = \begin{bmatrix} 0 & \gamma Se^{-\lambda\tau} \\ 0 & 0 \end{bmatrix} \text{ and}$$

$$V = \begin{bmatrix} (\mu_2 + \sigma) + (1-\sigma)\beta e^{-\lambda\tau} & 0 \\ -(1-\sigma)\beta e^{-\lambda\tau} & (\mu_3 + (\alpha+\eta)e^{-\lambda\tau}) \end{bmatrix}$$

The inverse V^{-1} of V is given as

$$= \frac{1}{(\mu_2 + \sigma + \beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau})(\mu_3 + \alpha e^{-\lambda\tau} + \eta e^{-\lambda\tau})} \begin{bmatrix} (\mu_3 + \alpha e^{-\lambda\tau} + \eta e^{-\lambda\tau}) & 0 \\ \beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau} & \mu_2 + \sigma + \beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau} \end{bmatrix}$$

$$= \begin{bmatrix} \dfrac{1}{\mu_2 + \sigma + \beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau}} & 0 \\ \dfrac{\beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau}}{(\mu_2 + \sigma + \beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau})(\mu_3 + \alpha e^{-\lambda\tau} + \eta e^{-\lambda\tau})} & \dfrac{1}{(\mu_3 + \alpha e^{-\lambda\tau} + \eta e^{-\lambda\tau})} \end{bmatrix}$$

Therefore FV^{-1} reduces to

$$= \begin{bmatrix} 0 & \gamma Se^{-\lambda\tau} \\ 0 & 0 \end{bmatrix} \begin{bmatrix} \dfrac{1}{\mu_2 + \sigma + \beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau}} & 0 \\ \dfrac{\beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau}}{(\mu_2 + \sigma + \beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau})(\mu_3 + \alpha e^{-\lambda\tau} + \eta e^{-\lambda\tau})} & \dfrac{1}{(\mu_3 + \alpha e^{-\lambda\tau} + \eta e^{-\lambda\tau})} \end{bmatrix}$$

$$= \begin{bmatrix} \dfrac{\gamma Se^{-\lambda\tau}(\beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau})}{(\mu_2 + \sigma + \beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau})(\mu_3 + \alpha e^{-\lambda\tau} + \eta e^{-\lambda\tau})} & \dfrac{\gamma Se^{-\lambda\tau}}{(\mu_3 + \alpha e^{-\lambda\tau} + \eta e^{-\lambda\tau})} \\ 0 & 0 \end{bmatrix}$$

And so

$$R_0 = \frac{\gamma Se^{-\lambda\tau}(\beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau})}{(\mu_2 + \sigma + \beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau})(\mu_3 + \alpha e^{-\lambda\tau} + \eta e^{-\lambda\tau})} \tag{2.19}$$

From (2.18), Equation (2.19) becomes

$$R_0 = \frac{\beta\Lambda\gamma e^{-2\lambda\tau}(1-\sigma)}{\mu_1(\mu_2 + \sigma + \beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau})(\mu_3 + \alpha e^{-\lambda\tau} + \eta e^{-\lambda\tau})}$$

2.5 Stability of the cancer free equilibrium point

The study of the stability of the equilibrium points consider the linearization of the model Equations about both the Cancer Free Equilibrium by taking the Jacobian Matrix the model equations.

2.5.1 Local stability of the cancer free equilibrium point

The local stability of the Cancer Free Equilibrium Point being the point where if the system is put somewhere nearby the equilibrium point, then it will move itself to the equilibrium point in some time.

Theorem 3: The Cancer Free Equilibrium Point $\mathcal{E}_0$ is locally stable if $R_0 < 1$ whereas $\mathcal{E}_0$ is unstable if $R_0 > 1$.

Proof

The Jacobian matrix at the Cancer Free Equilibrium Point is computed by differentiating each of the equations (2.1), (2.2), (2.3) and (2.4) with respect to S, E, I and R and letting $E = I = R = 0$. The matrix is defined as,

$$J_{\varepsilon_0} = \begin{bmatrix} -\mu_1 & 0 & -\gamma S e^{-\lambda\tau} & 0 \\ 0 & -(\mu_2 + \sigma + \beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau}) & \gamma S e^{-\lambda\tau} & 0 \\ 0 & \beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau} & -(\mu_3 + \alpha e^{-\lambda\tau} + \eta e^{-\lambda\tau}) & 0 \\ 0 & \sigma & \alpha e^{-\lambda\tau} + \eta e^{-\lambda\tau} & -\mu_4 \end{bmatrix} \tag{2.20}$$

The associated polynomial is given as $|J_{\varepsilon_0} - \lambda I| = 0$ at the Cancer Free Equilibrium Point. Applying (2.18) in (2.20) we get

$$\begin{vmatrix} -\mu_1 - \lambda & 0 & \dfrac{-\gamma\Lambda e^{-\lambda\tau}}{\mu_1} & 0 \\ 0 & -(\mu_2 + \sigma + \beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau}) - \lambda & \dfrac{\gamma\Lambda e^{-\lambda\tau}}{\mu_1} & 0 \\ 0 & \beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau} & -(\mu_3 + \alpha e^{-\lambda\tau} + \eta e^{-\lambda\tau}) - \lambda & 0 \\ 0 & \sigma & \alpha e^{-\lambda\tau} + \eta e^{-\lambda\tau} & -\mu_4 - \lambda \end{vmatrix} = 0 \tag{2.21}$$

Letting $A = -\mu_1, B = \dfrac{-\gamma\Lambda e^{-\lambda\tau}}{\mu_1}, C = -(\mu_2 + \sigma + \beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau}), D = \dfrac{\gamma\Lambda e^{-\lambda\tau}}{\mu_1}, Y = \beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau}, F = -(\mu_3 + \alpha e^{-\lambda\tau} + \eta e^{-\lambda\tau}), G = \sigma, H = \alpha e^{-\lambda\tau} + \eta e^{-\lambda\tau},$ and $Z = -\mu_4$

Equation (2.21) reduces to,

$$\begin{vmatrix} A - \lambda & 0 & B & 0 \\ 0 & C - \lambda & D & 0 \\ 0 & Y & F - \lambda & 0 \\ 0 & G & H & Z - \lambda \end{vmatrix} = 0$$

On solving we obtain the values of $\lambda_1, \lambda_2, \lambda_3$ and λ_4 as follows

$\lambda_1 = A$, $\lambda_2 = Z$

$$\lambda_3 = \frac{(C + F) + \sqrt{C^2 + F^2 - 2CF + 4DY}}{2}$$

and

$$\lambda_4 = \frac{(C + F) - \sqrt{C^2 + F^2 - 2CF + 4DY}}{2}$$

The Cancer Free Equilibrium point (ε_0) in the model equations is locally stable if $\lambda_1, \lambda_2, \lambda_3, \lambda_4 < 0$ and unstable if at least one of the $\lambda_1, \lambda_2, \lambda_3, \lambda_4$ is greater than zero for all $\mu_1, \mu_2, \mu_3, \mu_4, \sigma, \beta, \eta, \alpha, \Lambda$ and γ being positive. The first two eigenvalues $\lambda_1 = -\mu_1$ and $\lambda_2 = -\mu_4$, which are real negative values, a sufficient condition for local stability. It is also clear that λ_4 is less dominant to λ_3. λ_3 is therefore the most dormant eigen value. Hence

$$\frac{(C + F) + \sqrt{C^2 + F^2 - 2CF + 4DY}}{2} < 0 \tag{2.22}$$

for the stability of the Cancer Free Equilibrium point

$$\text{Equation (2.22) yields } DY < CF \tag{2.23}$$

which gives

$$\left(\frac{\gamma\Lambda e^{-\lambda\tau}}{\mu_1}\right)\left(\beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau}\right) < (\mu_2 + \sigma + \beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau})(\mu_3 + \alpha e^{-\lambda\tau} + \eta e^{-\lambda\tau})$$

$$\frac{\Lambda\gamma e^{-\lambda\tau}\left(\beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau}\right)}{\mu_1(\mu_2 + \sigma + \beta e^{-\lambda\tau} - \sigma\beta e^{-\lambda\tau})(\mu_3 + \alpha e^{-\lambda\tau} + \eta e^{-\lambda\tau})} < 1$$

$R_0 < 1$ hence the Cancer Free Equilibrium is stable

3 Main Results

The numerical simulations of the equations of the model were determined using the following parameters and their estimated values.

Table 1. Table of parameters and their values

| Parameter	Description	Value
S(0)	Initial Susceptible population	1000(estimated)
E(0)	Initial Exposed population	500(estimated)
I(0)	Initial Infected population	400(estimated)
R(0)	Initial Recovered population	300(estimated)
N(0)	Initial Total population	2200(estimated)
γ	Rate at which Susceptible cells become exposed by one infectious cell per contact time	0.500(estimated)
β	Rate at which the exposed cells become infectious	0.020(estimated)
σ	Recovery rate of exposed cells due to autoimmunity	0.030(estimated)
η	Recovery rate of symptomatic cells due to chemotherapy	0.010(estimated)
Λ	Constant influx rate of new susceptible cells	0.020(estimated)
μ_1	Coefficient of Natural mortality rate of Susceptible cells	0.005(estimated)
μ_2	Natural mortality rate of Exposed cells	0.020(estimated)
μ_3	Natural mortality rate of Infective cells	0.050(estimated)
μ_4	Rate of mortality of the recovered sick cells	0.010(estimated)
α	Natural recovery rate of symptomatic infected cells	0.020(estimated)
τ	Time Delay	To be determined
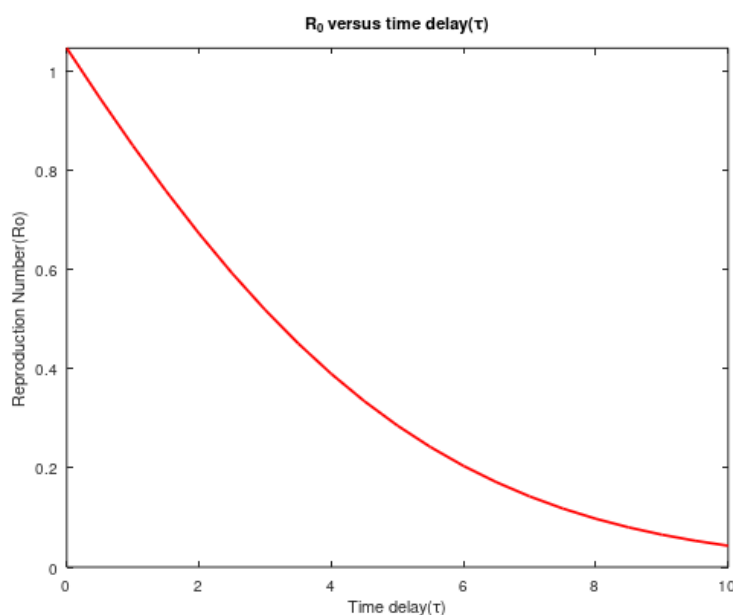
Fig. 1. A plot of Reproduction number (R_o) against Time Delay (years) (τ)

Fig. 1 shows a plot of the Reproduction number (R_0) against the Time delay (τ) in years. From the graph it's clear that as the Time delay increases the number of new tumor cells decreases. The graph presents the comparison of the delay factor and reproduction number. An increase in the delay time reduces the number of new tumor cells.
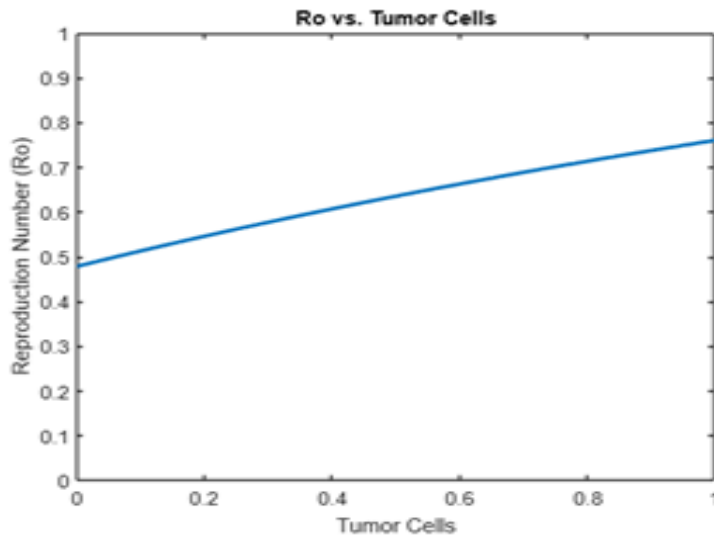

Fig. 2. A plot of Reproduction number (R_0) against the Number of Tumor Cells

Fig. 2 shows a plot of the Reproduction number (R_0) against the Number of Tumor Cells. From the graph it can be seen clearly that there is an increase in the amount of Tumor cells as the Reproduction Number increases. Also at low replication rate the Number of Tumor cells are lower.
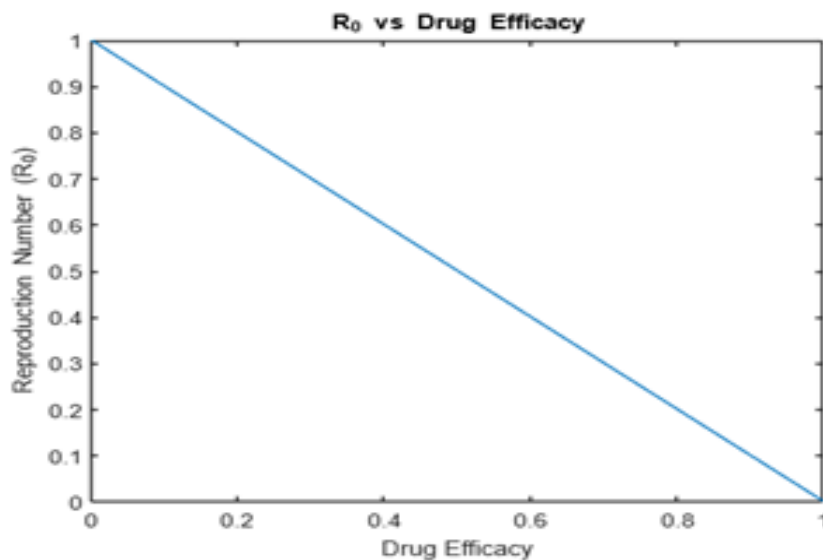

Fig. 3. A plot of Reproduction number (R_0) against the Drug Efficacy

Fig. 3 shows a plot of the Reproduction number (R_0) against the Drug Efficacy. It shows that as the drug efficacy increases, the reproduction number decreases. This therefore depicts that chemotherapy plays an important role in reducing the tumor replication for stability to be attained at $R_0 < 1$
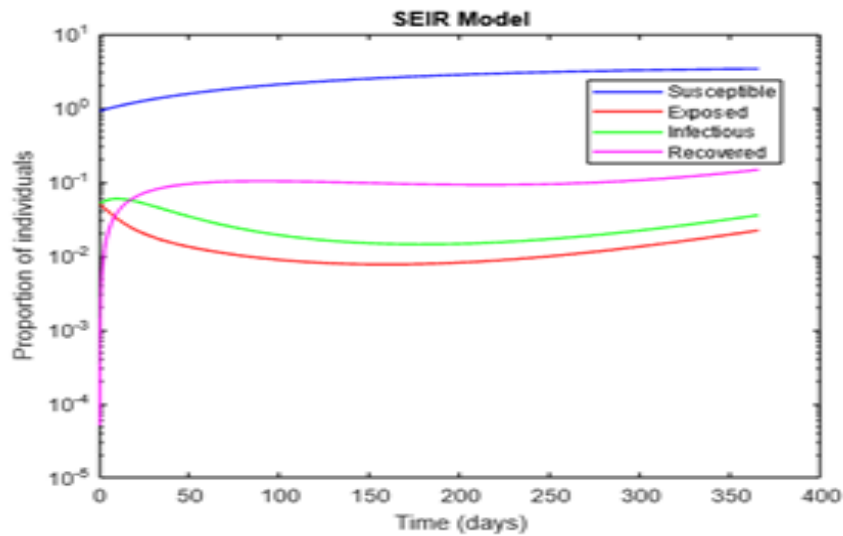
Fig. 4. A plot of Proportion of individuals against the Time (days)

Fig 4 shows a plot of the Proportion of individuals against the Time in days. It gives the dynamics of the various compartments of the SEIR model with time. From the graph it's clear that the number of the susceptible cells are more than the infected cells. The number of infectious cells reduces due to chemotherapy while at the same time the number of recovered cells increases. This dynamics reduces the number of exposed cells.

4 Summary, Conclusion and Recommendations

4.1 Introduction

The chapter outlines in summary the effects of incubation and chemotherapy on both the Cancer Free Equilibrium Point (CFEP).

4.2 Summary

The major aim of this research was to formulate a SEIR model for the Tumor dynamics using delay differential equations and then study the effects of time delay and the effects of chemotherapy or drug efficacy on the stability of both the Cancer Free Equilibrium Point (CFEP). These effects are analyzed analytically and numerically using MATLAB DDE23 solver and assumed parameter values. In Chapter One, an introduction of the thesis is given. Starting with background information of the research is discussed by highlighting cancer modeling, definition of cancer and types of Tumors are illustrated including a summary discussion on cancer statistics and its methods of treatment. The definition of Delay Differential Equations, types of Delay Differential Equations, simulations of delay differential equations and their analytic solutions are also discussed. Finally, the problem statement for the research, the objectives of the research and the significance of the research are also given attention in this chapter. Chapter Two outlines a brief literature cancer modeling, methods used, findings and limitations of such studies. Here the research gaps were identified which formed the basis of this study. Chapter three, outlines the methodology of the research. The SEIR model for the Tumor dynamics, its assumptions and the model equations. The model preliminary analysis, the determination of the basic reproductive number, computation of the Cancer Free Equilibrium Point and Cancer Endemic Equilibrium Point and the stability analysis of the equilibrium points both local and global were also discussed in this chapter. In Chapter Four, numerical simulations were obtained using MATLAB DDE23 and analytic results derived in Chapter Three were verified.

4.3 Conclusions

The research was a formulation of a Delay Differential Equation of SEIR Tumor growth dynamics model. The CFEP was attained when $R_0 < 1$. Numerical simulation of the model was carried out to validate the analytic results. The results show that the CFEP is stable when R_0 is 0.6667 otherwise unstable. The reproduction number is critical in minimizing the growth of Tumor. The increased educational awareness for early screening also helps in early detection for ease of management.

4.4 Recommendations

This research has not exhausted all the scientific studies on Tumor growth dynamics and treatment. The effects of immune response to Tumor growth dynamics were not considered. The model can be extended to include reaction-diffusion effects on the Tumor growth dynamics. Public knowledge through education on pre-disposing factors and early screening are also possible insights for further research work on Tumor growth dynamics. An advancement for a vaccine therapy against the Tumor development and growth should also be considered in future studies.

5 Suggestions for Further Research

The research recommends future work should consider inclusion of reaction –diffusion model and the effect of the immune response and chemotherapy. This is because of possible spread of Tumor to other parts of the body hence reaction-diffusion.

Competing Interests

Authors have declared that no competing interests exist.

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5.9   APPENDIX IV : NACOSTI Research permit

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