

**MATHEMATICAL MODELING AND ANALYSIS OF
MULTI-MUTATION AND DRUG RESISTANCE: A
CASE OF IMMUNE-SUPPRESSION**

HOUÉNAFA ALAIN TOGBENON

**MASTER OF SCIENCE IN MATHEMATICS
(Computational Option)**

**PAN AFRICAN UNIVERSITY
INSTITUTE FOR BASIC SCIENCES,
TECHNOLOGY AND INNOVATION**

2018

**Mathematical Modeling and Analysis of Multi-Mutation and
Drug Resistance: A Case of Immune-Suppression**

Houénafa Alain TOGBENON

MC300-0003/17

**A Research Thesis submitted to the Pan African University
Institute for Basic Sciences, Technology and Innovation in
partial fulfillment of the requirements for the award of the
Degree of Master of Science in Mathematics (Computational
Option) of the Pan African University**

2018

Declaration

This research thesis is my original work and has not been submitted to any other university for a degree award.

Signature: 

Date: 29/10/2018.

Houénafa Alain TOGBENON

This thesis has been submitted with my approval as University Supervisor.

Signature: 

Date: 31/10/2018.

Dr. Mark Eric KIMATHI

School of Pure and Applied Sciences

Machakos University (MKsU), P.O.Box 136-90100, Machakos-Kenya.

This thesis has been submitted with my approval as University Supervisor.

Signature: 

Date: 31/10/2018.

Prof. Guy Aymard DEGLA

Institut de Mathématiques et de Sciences Physiques (IMSP), 01 BP 613 Porto-Novo, Benin.

University of Abomey-Calavi (UAC), Benin.

Dedication

This thesis is dedicated to my parents Mr. and Mrs. TOGBENON, my brothers, my sisters, my loving wife Akouvi ADJANOHUN, my beloved sons TOGBENON S. Bruno and TOGBENON G. Curtis. You will always remain my reason(s) for living.

Acknowledgement

Great thanks to Almighty God for giving me the gift of life and making this study a success.

My thanks to the many authors of books, papers, and articles as well as the new generation of contributors to electronic media (the World Wide Web) who have provided me with additional insight and ideas.

I am highly indebted to the African Union Commission (AUC) for offering me a scholarship to study M.Sc. Mathematics at the Pan African University, Institute for Basic Sciences, Technology and Innovation without which my dream would not have been realized. Merci beaucoup!

My thanks to Japan International Cooperation Agency (JICA) for the financial support during this study.

I acknowledge the very important role of my supervisors **Dr. Mark Eric KIMATHI** and **Prof. Guy Aymard DEGLA** for their guidance and motivation in the struggle of researching in this field. I also extend my sincere gratitude to the administrative and teaching staff of PAUISTI and JKUAT for their commitment and support offered to me during the whole study period.

Table of Contents

Declaration	ii
Dedication	iii
Acknowledgement	iv
List of Tables	viii
List of Figures	xi
Abstract	xi
Abstract (French version)	xii
1 Introduction	1
1.1 Problem statement	3
1.2 Justification of the study	3
1.3 Objectives of the study	4
1.3.1 General objective	4
1.3.2 Specific objectives	4
1.4 Significance of the Study	4
1.5 Scope of the study	5
1.6 Organization of the study	5
1.7 Published material	6
2 Literature Review	7
3 Model formulation.	13
3.1 Overview	13
3.2 Model of Kirschner and Panetta	13

3.3	Model of Feizabadi and Witten	15
3.4	Feizabadi's Model for multi-mutation and drug resistance	17
3.5	The proposed ODE Model	19
4	Analysis of the tumor-immunotherapy model	25
4.1	Introduction and preliminaries on differential systems	25
4.1.1	The Existence and uniqueness theorem	25
4.1.2	Local Stability	26
4.1.3	Nonstandard Finite difference Schemes	27
4.2	Mathematical analysis of tumor-immunotherapy model	29
4.2.1	Existence and uniqueness of solutions	30
4.2.2	Positivity and boundedness of solutions	31
4.3	Stability analysis of non-tumor states	34
4.3.1	No immunotherapy case ($\beta = 0$)	34
4.3.2	Immunotherapy case ($\beta > 0$)	35
5	Numerical simulations of the tumor-immunotherapy model	43
5.1	When the system expresses both intrinsic and drug-induced resistance .	44
5.2	When the system expresses only intrinsic resistance	50
5.3	When the system expresses only drug-induced resistance	54
5.4	When the system expresses neither intrinsic nor drug-induced resistance	59
6	Conclusion and Recommendations	63
	References	68
A	MATLAB Code for simulations	69
A.1	When the dynamical system expresses both intrinsic and drug-induced resistance	69
A.1.1	Absence of immunotherapy	69
A.1.2	Immunotherapy introduced at $t \geq 500days$	71

A.2	When the dynamical system expresses only intrinsic resistance	74
A.2.1	Absence of immunotherapy	74
A.2.2	Immunotherapy introduced at $t \geq 500days$	76
A.3	When the dynamical system expresses only drug-induced resistance	78
A.3.1	Absence of immunotherapy	78
A.3.2	Immunotherapy introduced at $t \geq 0days$	80
A.4	When the dynamical system expresses neither intrinsic nor drug-induced resistance	82
A.4.1	Absence of immunotherapy	82
A.4.2	Immunotherapy introduced at $t \geq 0days$	84

List of Tables

5.1	Description of simulation parameters of the model (4.2.1)	43
-----	---	----

List of Figures

3.1	The schematic view of the system interactions.	18
3.2	The schematic view of the new (Proposed) system interactions.	21
5.1	The behavior of tumor cells and immune system cells in the absence of immunotherapy.	44
5.2	A zoom of (5.1)for $0 \leq t \leq 375$	44
5.3	The behavior of immune system cells and resistant tumor cells in the absence of immunotherapy.	45
5.4	The behavior of Mutated tumor cells and of effector cells in the absence of immunotherapy.	45
5.5	The behavior of tumor cells and immune system cells in the presence of immunotherapy.	46
5.6	The behavior of immune system cells and resistant tumor cells in the presence of immunotherapy.	47
5.7	The behavior of tumor cells T and T_M in the presence of immunotherapy.	47
5.8	The behavior of tumor cells and immune system cells in the presence of immunotherapy (introduced at $t = 200days$).	48
5.9	The behavior of tumor cells T in the presence of immunotherapy (introduced at $t = 200days$).	48
5.10	The behavior of tumor cells T_M in the presence of immunotherapy (introduced at $t = 200days$).	49
5.11	The behavior of tumor cells and immune system cells in the absence of immunotherapy.	50
5.12	A zoom of (5.11)for $0 \leq t \leq 375$	50
5.13	The behavior of immune system cells and resistant tumor cells in the absence of immunotherapy.	51

5.14	The behavior of tumor cells and immune system cells in the presence of immunotherapy.	52
5.15	The behavior of tumor cells T in the presence of immunotherapy.	52
5.16	The behavior of tumor cells and immune system cells in the presence of immunotherapy (introduced at $t = 200$ days).	53
5.17	The behavior of tumor cells T in the presence of immunotherapy (introduced at $t = 200$ days).	53
5.18	The behavior of tumor cells and immune system cells in the absence of immunotherapy.	54
5.19	A zoom of (5.18) into the behavior of tumor cells T and T_M in the absence of immunotherapy.	55
5.20	The Phase diagram relating T and E in the absence of immunotherapy.	55
5.21	Phase diagram relating T_M and E in the absence of immunotherapy.	56
5.22	Zoom into the behavior of tumor cells T after the simulation time in the absence of immunotherapy,.	56
5.23	Zoom into the behavior of tumor cells T_M after the simulation time in the absence of immunotherapy.	57
5.24	The behavior of tumor cells and immune system cells in the presence of immunotherapy.	58
5.25	The behavior of tumor cells T and T_M in the presence of immunotherapy.	58
5.26	The behavior of tumor cells and immune system cells in the absence of immunotherapy.	59
5.27	The behavior of tumor cells T in the absence of immunotherapy.	60
5.28	Phase diagramm relating T and E in the absence of immunotherapy.	60
5.29	Zoom into the behavior of tumor cells T after the simulation time in the absence of immunotherapy.	61
5.30	The behavior of tumor cells and immune system cells in the presence of immunotherapy.	61
5.31	The behavior of tumor cells T in the presence of immunotherapy.	62

Abstract

A model that takes into account multi-mutation and drug resistance in a case of simple immune system and immune-suppression caused by drug resistant tumor cells is proposed. Since the methods for revising therapeutic approaches (immunotherapy and chemotherapy) during cancer treatment are still being explored, we have analyzed mathematically the corresponding tumor-immunotherapy model and its non tumor states using nonstandard finite difference method to identify under which conditions tumor can be eliminated. Numerical simulations of the tumor-immunotherapy model is done with the aid of MATLAB software using *ode45* function, in order to determine the effectiveness of the immunotherapy. Through the mathematical analysis, the existence, the uniqueness and the boundedness of solutions are shown. This study indicates that tumor can be eliminated under certain conditions in the presence of the immunotherapy drug and in the absence of the drug resistant tumor cells. Moreover, it provides an understanding of the evolution of tumor cells and immune system cells for all types of mutations, in the absence and in the presence of the immunotherapy drug. Effective treatment strategies are proposed when the drug resistant tumor cells are absent and when they are present.

Abstract (French version)

Un modèle prenant en compte la multi-mutation et la résistance aux médicaments dans un cas de système immunitaire simple et de suppression immunitaire provoquée par des cellules tumorales résistantes aux médicaments est proposé. Comme les méthodes de révision des approches thérapeutiques (immunothérapie et chimiothérapie) pendant le traitement du cancer sont encore à l'étude, nous avons analysé mathématiquement le modèle d'immunothérapie tumorale correspondant et ses états non-tumoraux en utilisant une méthode des différences finies non-standard. Des simulations numériques du modèle d'immunothérapie tumorale sont réalisées à l'aide du logiciel MATLAB en utilisant la fonction *ode45*, afin de déterminer l'efficacité de l'immunothérapie. L'analyse mathématique montre l'existence, l'unicité et la borne des solutions. Cette étude indique que la tumeur ne peut être éliminée que sous certaines conditions en présence du médicament d'immunothérapie et en absence des cellules tumorales résistantes aux médicaments. De plus, il permet de comprendre l'évolution des cellules tumorales et des cellules du système immunitaire pour tous les types de mutations, en absence et en présence du médicaments d'immunothérapie. Des stratégies de traitement efficaces sont proposées lorsque les cellules tumorales résistantes aux médicaments sont absentes et présentes.

Chapter 1

Introduction

Cancer is a disease characterized by the uncontrolled proliferation of cells, linked to an escape from the regulation mechanisms that ensure the harmonious development of our organism. By multiplying anarchically, they cause increasing tumors that develop by invading and destroying the surrounding areas (organs). By destroying its environment, cancer can become a real danger to the survival of the living being. It is a multi-scale disease and its overwhelming complexity depends upon the multiple interwind events occurring at both molecular and cellular levels, making it very difficult for therapeutic advancements in cancer research. The resistance to cancer drugs is a significant challenge faced by scientists nowadays. The roots of the problem reside not only at the molecular level due to multiple type of mutations in a single tumor but also at the cellular level of drug interactions with the tumor. The tumor heterogeneity is the term used by the oncologists for the involvement of multiple mutations in the development of a tumor at subcellular level. The mechanisms for tumor heterogeneity are rigorously being explored as a reason for drug resistance in cancer patients. It is important to observe cell interactions not only at intra-tumoral level but it is also essential to study the drug and tumor cell interactions at cellular level to have a complete picture of the underlying issue for the drug resistance ([Sameen et al., 2014](#)).

There are several types of cancer treatments: surgery, chemotherapy, targeted therapies, radiotherapy and hormone-therapy. Surgery and radiotherapy are local treatments while chemotherapy and hormone-therapy act throughout the body. Over the decades, the most common therapeutic approach to reduce the population of cancer

cells and control their progression is some combination of chemotherapy and of immunotherapy. However, on several occasions, the success of this treatment has failed due to the lack of knowledge of the type of tumor cells that occur and the effects that these tumors can have on the immune system ([Holohan et al., 2013](#)).

The proliferation of cancer cells depends on many factors including, but not limited to, cell growth rate, mutual interaction of cancer cells with surrounding normal cells and immune system response to cancer treatment strategies. This also depends on the mutations that may occur during cell divisions, which result in the inapplicability of chemotherapeutic treatments. Drug induced resistance is one of the main obstacles that can lead to therapeutic failure during cancer treatment. Different genetic alterations occur when the tumor cells divide. Among the new generations of tumor cells, some can express an intrinsic resistance to a specific chemotherapeutic agent ([Feizabadi & Witten, 2015](#)). In addition, some tumor cells may carry a gene that can develop resistance induced by the chemotherapeutic drug ([Feizabadi, 2017](#)). The methods by which therapeutic approaches need to be revised in the occurrence of drug induced resistance are still being explored. Because of that, many researchers and mathematicians such as [Kirschner & Panetta \(1998\)](#), [Kirschner & Tsygvintsev \(2009\)](#), [Feizabadi & Witten \(2010\)](#), [Feizabadi & Witten \(2011\)](#), [Feizabadi & Witten \(2015\)](#), [Feizabadi \(2017\)](#), introduced mathematical models to analyze the evolution of cells. [Feizabadi \(2017\)](#) modeled multi-mutation and drug resistance and assessed the response of cell populations as a function of time under different treatment strategies. The effects of a simple immune system and of the immune-suppression caused by drug resistant tumor cells are not yet considered in the model of [Feizabadi \(2017\)](#). Therefore the model which will take into account these multi-mutation and their effects is required together with an efficient treatment strategy that can overcome the mutation of tumor cells.

1.1 Problem statement

The effects of a simple immune system and immunodeficiency studied by [Feizabadi & Witten \(2011\)](#) on the dynamics of conjointly growing tumor and normal cells showed that the interdependency of tumor-normal cells, together with choice of drug and the nature of the immunodeficiency, leads to a variety of interesting patterns in the evolution of both the tumor and the normal cell populations. So to decide with regard to impactful therapy, the state of the patients immune system plays an important role. Different genetic alterations occur when tumor cells divide. Among new generations of tumor cells, some may express intrinsic resistance to a specific chemotherapeutic agent, see ([Feizabadi & Witten, 2015](#)). Also, some tumor cells may carry a gene that can develop resistance induced by the therapeutic drug, see ([Feizabadi, 2017](#)). Currently, to our best knowledge, the research done on this topic have not considered the effects of a simple immune system and of an immune-suppression when the system expresses both intrinsic and drug-induced resistance. Therefore, in this work we model and analyze multi-mutation and drug resistance in occurrence of a simple immune system and of an immune-suppression caused by drug resistant tumor cells.

1.2 Justification of the study

This study is worthy because methods for revising therapeutic approaches (immunotherapy and chemotherapy) during cancer treatment are still being explored. In ([Feizabadi, 2017](#)), multi-mutation and drug resistance have been modeled and analyzed for some case studies. The proposed study introduces the effects of a simple immune system and of an immune-suppression in Feizabadi's model. This is due to the fact that the state of the patients immune system plays an important role in making decisions with regard to impactful therapy. So building a model and analyzing the evolution of the cells will give more information about how tumor, normal and immune cells evolve and how therapies need to be revised in this case.

1.3 Objectives of the study

The following are the objectives of our study:

1.3.1 General objective

To model and analyze multi-mutation and drug resistance of tumor cells in a case of a simple immune system and of an immune-suppression.

1.3.2 Specific objectives

1. To construct a mathematical model which describes multi-mutation and drug resistance in a case of a simple immune system and of an immune-suppression caused by drug resistant tumor cells.
2. To analyze mathematically the corresponding tumor-immunotherapy model and its non tumor states using a nonstandard finite difference method, in order to identify under which conditions tumor can be eliminated.
3. To simulate numerically with the aid of MATLAB software using *ode45*, the corresponding tumor-immunotherapy model in order to determine the effectiveness of the immunotherapy and propose treatment strategies

1.4 Significance of the Study

The findings of this study will be of benefit to the society as cancer modeling plays an important role in the prediction of percussive therapy in the treatment of cancer. Repeated failure of the treatment, when the system expresses both intrinsic and drug-induced resistance, motivates the need for more information on the behavior of the tumor cells, the immune system cells and normal cells. This also motivates the need for more information on how therapeutic approaches need to be revised. Thus, the application of the approach that will be recommended from the results of this study will give a better treatment strategy against cancer. The scientific world will be guided on what needs to be underlined in order to improve the therapeutic approaches. For researchers, the study will help them discover the areas of possible improvements in

the cancer treatment process. Thus, a new theory on therapeutic approaches can be reached.

1.5 Scope of the study

This study is limited to the construction, analysis of non-tumor states and numerical simulations of a model that takes into account multi-mutation and drug resistance with immune-suppression caused by drug resistant tumor cells. Two variables are considered to be the main immune system components: the activated immune-system cells (effector cells), denoted by E and the concentration of IL-2 (Interleukine-2), denoted by I . The study assumes that all types of tumor cells grow under the logistic growth law and the immune-suppression factors are the resistant tumor cells.

1.6 Organization of the study

The rest of this work is organized as follows:

Chapter 2 provides a quick review of the necessary literature related to our study.

Chapter 3 deals with the construction of a mathematical Model which describes multi-mutation and drug resistance in a case of a simple immune system and of an immune-suppression caused by drug resistant tumor cells.

In Chapter 4, a mathematical analysis of the corresponding tumor-immunotherapy model and of its non-tumor states is done to identify under which conditions tumor can be eliminated. We proved the global stability of non-tumor states using nonstandard finite difference method.

In Chapter 5, numerical simulations of the tumor-immunotherapy model are performed with the aid of MATLAB software using *ode45* function, in order to determine the effectiveness of the immunotherapy and to propose some treatment strategies.

Finally in Chapter 6, we draw a Conclusion and give possible ideas for the extension of the study as future work and perspectives.

1.7 Published material

The part of thesis related to tumor-immunotherapy model and to numerical simulations has been published in ([Togbenon et al., 2018](#)), namely

Togbenon, H. A., Kimathi, M. E., & Degla, G. A. (2018). Modeling Multi-Mutation And Drug Resistance: A Case of Immune-Suppression. *Global Journal of Pure and Applied Mathematics*, 14(5), 689-709.

The complete study of the mathematical model for multi-mutation and drug resistance with immune-suppression and both immunotherapy and chemotherapy was accepted after per-review as a research article in the *Journal of Mathematical theory and Modeling*. It will be published very soon.

In the next chapter, we are going to provide a quick review of the necessary literature related to our study.

Chapter 2

Literature Review

In this chapter, we present some recent studies related to our study. Thus this chapter is primarily devoted to a brief literature review of the earlier investigations made on cancer modeling.

The behavior of normal and tumor cells during the cancer disease plays a major role in the choice of the therapy. In a conjoint setting, normal and tumor cells interact with one another during their growth. This mutual interaction between normal and tumor cells has been biologically detected and was initially modeled by [Witten \(1986\)](#) who assumed that tumor and normal cells grow under the logistic growth law.

The state of the patient's immune system plays an important roles in making decisions with regard to impactful therapy. A number of lines of evidence suggest that immunotherapy with the cytokine interleukin-2 (IL-2) may boost the immune system to fight tumors. Thus [Kirschner & Panetta \(1998\)](#) modeled the immunotherapy of the tumor-immune interaction and explored the effects of adoptive cellular immunotherapy (ACI) on the model and then described under what circumstances the tumor can be eliminated. They defined three populations: $E(t)$, the activated Immune-system cells (commonly called effector cells) such as cytotoxic T-cells, macrophages, and natural killer cells that are cytotoxic to the tumor cells; $T(t)$, the tumor cells; and $I_L(t)$, the concentration of IL-2 in the single tumor-site compartment they were modeling. Effector cells are stimulated to grow based on the direct presence of the tumor and IL-2 that

is produced by effector cells in both an autocrine and paracrine manner. However no global analytical results were originally presented. So, [Kirschner & Tsygvintsev \(2009\)](#) explored the global dynamics of the model in space by quasi-Lyapunov function techniques and found that under specific conditions, we can define exactly what conditions allow for tumor clearance.

[d’Onofrio \(2006\)](#) studied the influence of the proliferation response of effectors to tumor burden, and of cooperation and/or competition between immune system effectors, by means of three inter-related bi-dimensional meta-models. After studying their null-clines, he obtained the location and the local stability of the equilibria. Then, he investigated the existence and, in some cases, the uniqueness of stable limit cycles. The condition for the global asymptotically stable eradication under constant or slightly variable periodic immunotherapy was given. Finally, he discussed the implications of strong saturation in the effectors ability to kill tumor cells.

[Feizabadi & Witten \(2010\)](#) improved the model of [Witten \(1986\)](#) by finding that tumor cells can only be affected by the normal cells up to a certain point. After that, there is a constant effect. To represent this behavior, they chose a simple saturation function (Hill function of Hill coefficient 1). The tumor cell interaction with the normal cell is chosen as a logistic growth function. Then, they extended to address the medical scenario in which the conjoint cellular system interacts with a chemotherapeutic drug. They assumed that the drug kills both tumor cells and normal cells. These cells die due to drug toxicity. After that, they discussed the simulation of the evolution of both normal and tumor cells for various interactions (untreated system evolution, treated system by static drugs, treated system by dynamic drugs).

As suggested by [Gardner \(2000\)](#) and used in other studies ([De Pillis & Radunskaya, 2003](#); [de Pillis et al., 2006](#)), the drug interaction may be structured as $a_\phi(1 - e^{-MC})\phi$ where ϕ is the cell population number. The parameter C is the concentration of the drug at the tumor site at a specific time with the unit ($mg.m^{-2}$). M is associated to

the drug pharmacokinetics and known as the drug efficiency coefficient with the unit of $(m^2.mg^{-1})$. M is considered to be 1. The coefficient a_ϕ with the unit of $(time^{-1})$ expresses the rate of chemotherapy-induced death. The function $F(C) = a_\phi(1 - e^{-MC})$ is the fraction cell killed for a given concentration of drug " C ".

Furthermore, [Feizabadi & Witten \(2011\)](#) modeled the effects of a simple immune system and immunodeficiency on the dynamics of conjointly growing tumor and normal cells. They first considered their core model for the interaction of tumor cells with surrounding normal cells, made in 2010. They then added the effects of a simple immune system, and both immune-suppression factors and immuno-chemotherapeutic agents as well. Through a series of numerical simulations, they illustrated that the interdependency of tumor-normal cells, together with choice of drug and the nature of the immunodeficiency, leads to a variety of interesting patterns in the evolution of both the tumor and the normal cell populations. They considered that the viruses are the basis of the immunodeficiency. As explained in [Kirschner & Panetta \(1998\)](#) model, they considered two variables to be the main immune system components: the first is the activated immune-system cells (effector cells) including T-cells and the others are the immune cells that are cytotoxic to tumor cells. The second immune system component is the concentration of IL-2, which is the main cytokine responsible for T-cells activation, growth and differentiation at the tumor site.

The viruses can infect the activated immune cells. As a result of this infection, the population of activated cells decreases and this leads to a weakened immune system. In such a case, the treatment can consist of immune boosting drugs such as Interleukin-2 (IL-2) ([Kovacs et al., 1996](#)). [Kirschner & Webb \(1998\)](#) mathematically characterized the general interaction of the Human Immunodeficiency Virus and activated immune cells. The presence of immune-suppression factors reduces the efficiency of the immune system in battling tumor cells. Thus, [Feizabadi & Witten \(2011\)](#) added these same mathematical terms to their model to explain a simple possible immune deficiency. To control cancer progression, many approaches can be implemented, among them

chemotherapy, immunotherapy or some combination of the two. The enhancement of the immune system by immunotherapeutic agents that directly boost the number of T-cells has a key role in the reduction of both the number of tumor cells and viruses. Chemotherapeutic agents can kill the tumor population in a dose-dependent manner (De Pillis & Radunskaya, 2003; Pazdur, 2004).

Chemotherapeutic agents are cytotoxic not only to tumor cells, but also to normal and activated cells as well. Clinical evidence also indicates that some of the anticancer agents can control the replication of viruses in a dose-dependent manner. Some data supports and some discourage the use of anticancer agents for immunodeficient virus treatment. On the one hand, some drugs have strong anti-activity virus effects, but not the ability to kill rapidly proliferating tumor cells. On the other hand, some of the anti-proliferating drugs may not have a positive effect on controlling viruses (Sadaie et al., 2004). Consequently, it is obvious that therapeutic potential depends upon the impact and the cross-toxicity of the drug on different components of the system. Knowledge of these pharmacokinetic interactions are not considered in (Feizabadi & Witten, 2011).

Feizabadi & Witten (2015) modified their core model of 2010 to include the resistance that tumor cells may express against chemotherapeutic agents. To set this modification, they first considered that the control of normal cells over the growth of tumor cells is negligible as it is large tumor cells that mainly express resistance to the treatment. But the population of the normal cells is controlled by the tumor cell population. They then included a second group of tumor cells in the core model. They assumed that this new group of tumor cells would be created during cell division (mutation) and would carry a mutated gene that causes intrinsic resistance against a specific type of chemotherapeutic agent. Also, they assumed that this group of tumor cells would also grow under the logistic growth law. Finally, they analyzed this model in the presence of a specific anti-cancer agent, where the population of drug-responsive tumor cells is reduced as a result of the interaction with the drug.

([Songolo & Ramadhani, 2017](#)) constructed two nonstandard finite difference schemes and used them to study a mathematical model of cancer therapy. Several recent studies show various aspects of the immune response against the cancer. Their discrete models emphasize the role of antibodies in any form of therapy by taking into account the development of anticancer therapies (chemotherapy, immunotherapy, radiation therapy). Nonstandard finite difference models have been implemented by using Matlab. Their numerical simulations have shown the existence of a separation line between the basins of attraction of cancerous cell-free and the highest equilibrium cancerous cell.

Multi-mutation and drug resistance have been modeled and analyzed for some case studies. For instance, [Feizabadi \(2017\)](#) expanded the model of [Feizabadi & Witten \(2015\)](#). The drug-sensitive tumor cells create a new generation of tumor cells as they divide. [Feizabadi \(2017\)](#) assumed that the newly born tumor cells can be placed in one of the following three groups. The first group includes those that are still responsive to the administered drug, and are known as wild tumor cells, T . The second group is those tumor cells that are still responsive to the drug, but carry a mutated gene that causes drug resistance as they interact with the introduced drug. These tumor cells are placed in the category of mutated tumor cells, T_M . The tumor cells in the third group are those that are not responsive to the drug and intrinsically resist the administered drug. This group is identified by T_R . He assumed that all of these tumor cells grow under the logistic growth law. Then, he assessed the response of the cell population as a function of time under different treatment strategies by simulating the model using Mathematica V7.0. The outcome of his simulations clearly demonstrated that while some therapeutic strategies can overcome or control the intrinsic drug resistance, they may not be effective, and are even to some extent damaging, if the administered drug creates resistance by itself.

Currently, to the best of our knowledge, the research done on this topic have not yet considered the effects of a simple immune system and of an immune-suppression on

the dynamic, when the system expresses both intrinsic and drug-induced resistance (ie multi-mutation and drug resistance). Therefore, in this research thesis we model and analyze multi-mutation and drug resistance in occurrence of a simple immune system and of an immune-suppression caused by drug resistant tumor cells.

The next chapter focuses on the construction of a mathematical model which describes multi-mutation and drug resistance in a case of a simple immune system and of an immune-suppression caused by drug resistant tumor cells.

Chapter 3

Model formulation.

3.1 Overview

In this chapter, we shall construct a mathematical model which describes multi-mutation and drug resistance in a case of a simple immune system and of an immune-suppression caused by drug resistant tumor cells. This construction is more based on the three main last works on this topic namely: [Kirschner & Panetta \(1998\)](#); [Feizabadi & Witten \(2011\)](#); [Feizabadi \(2017\)](#). Therefore, We first introduce the model of [Kirschner & Panetta \(1998\)](#) that describes the dynamics between tumor cells, immune-effector cells and the concentration of IL-2, the model of [Feizabadi & Witten \(2011\)](#) that takes into account the effects of a simple immune system and immunodeficiency on the dynamics of conjointly growing tumor and normal cells and the model of [Feizabadi \(2017\)](#) that take into account multi-mutation and drug resistance.

3.2 Model of Kirschner and Panetta

Through a mathematical modeling, the dynamics between tumor cells, immune-effector cells and the concentration of IL-2 have been illustrated by [Kirschner & Panetta \(1998\)](#). They defined three populations: E, the activated immune-system cells (commonly called effector cells) such as cytotoxic T-cells, macrophages, and natural killer cells that are cytotoxic to the tumor cells; T, the tumor cells and I_L , the concentration of IL-2 in the single tumor-site compartment. Their model describing the interaction between the effector cells, tumor cells, and the concentration of IL-2 is as follows:

$$\left\{ \begin{array}{l} \frac{dT(t)}{dt} = r_2(1 - bT)T - \frac{aET}{g_2+T}; \quad T(0) = T_0 \\ \frac{dE(t)}{dt} = cT - \mu_2 E + \frac{p_1 EI_L}{g_1+I_L} + s_1; \quad E(0) = E_0 \\ \frac{dI_L(t)}{dt} = \frac{p_2 ET}{g_3+T} - \mu_3 I_L + s_2; \quad I_L(0) = I_{L_0} \end{array} \right. \quad (3.2.1)$$

The first equation describes the rate of change of the tumor cells. This can be described by the logistic growth function. The loss of tumor cells is represented by an immune-effector cell interaction at rate a . This rate constant, a represents the strength of the immune response and is modeled by Michaelis-Menten kinetics to indicate the limited immune response to the tumor. The second equation describes the rate of change for the effector-cell population. Effector cells are stimulated to grow based on two terms. One is a recruitment term (term 1) due to the direct presence of the tumor, where the parameter c models the antigenicity of the tumor. Antigenicity can be thought of as a measure of how different the tumor is from 'self'. The other growth/source term (term 3) is a proliferation term whereby effector cells are stimulated by IL-2 that is produced by effector cells in both an autocrine and paracrine manner. This term is of Michaelis-Menten form to indicate the saturated effects of the immune response. Effector cells have a natural lifespan of an average $\frac{1}{\mu_2}$ days. Lastly, s_1 is a treatment term that represents an external source of effector cells. The third equation gives the rate of change for the concentration of IL-2. Its source is the effector cells that are stimulated by interaction with the tumor and also has Michaelis-Menten kinetics to account for the self-limiting production of IL-2. In the next term $\mu_3 I_L$, μ_3 represents loss/degraded rate of IL-2. Finally, s_2 is a treatment term that represents an external input of IL-2 into the system.

3.3 Model of Feizabadi and Witten

During their growth, normal and tumor cells interact with one another. This interaction has been biologically detected and was initially modeled by [Witten \(1986\)](#). [Feizabadi & Witten \(2011\)](#) added in this model the concept of the interaction of the immune system established by [Kirschner & Panetta \(1998\)](#) and both immune-suppression factors and immuno-chemotherapeutic agents as well. They considered that the viruses are the basis of the immunodeficiency. Therefore, their model is as given below:

$$\left\{ \begin{array}{l} \frac{dT(t)}{dt} = r_T T \left(1 - \frac{T}{K_T}\right) - \beta \left(\frac{\rho_0 N}{\rho_1 + N}\right) - \frac{aET}{g_2 + T} - a_T (1 - e^{-\xi MC}) T; \\ \frac{dN(t)}{dt} = r_N N \left(1 - \frac{N}{K_N}\right) + kT \left(1 - \frac{T}{T^*}\right) - a_N (1 - e^{-\xi MC}) N; \\ \frac{dE(t)}{dt} = cT - \mu_2 E + \frac{p_1 EI}{g_1 + I} - \alpha V E - a_E (1 - e^{-\xi MC}) E + a_{EE} (1 - e^{-\xi M_i}) E; \\ \frac{dI(t)}{dt} = \frac{p_2 ET}{g_3 + T} - \mu_3 I; \\ \frac{dV(t)}{dt} = \frac{\eta V}{b + V} - \gamma V E - \mu_1 V; \end{array} \right. \quad \begin{array}{l} T(0) = T_0 \\ N(0) = N_0 \\ E(0) = E_0 \\ I(0) = I_0 \\ V(0) = V_0 \end{array} \quad (3.3.1)$$

In the two first equation, the second term represent the interaction between tumor cells $T(t)$ and normal cells $N(t)$. Also tumor and normal cells growth under logistic law. $E(t)$ represents the effector cells. $I(t)$ is the concentration of IL-2, which is the main cytokine responsible for T-cells activation, growth and differentiation at the tumor site. The loss of tumor cells, due to the immune-effector cells can be characterized with a Michaelis-Menten interaction term, $\frac{aET}{g_2 + T}$. Here, a is the rate of clearance of tumor cells as a result of these two populations and g_2 is the half-saturation for cancer clearance. Also, the activation happens because of the presence of IL-2 hormones and is given by the term $\frac{p_1 EI}{g_1 + I}$. This is also a Michaelis-Menten term. Here p_1 is the proliferation rate of immune cells and g_1 is the half-saturation for the proliferation term. To express the natural death of effector cells, the term $-\mu_2 E$ is added. In this term μ_2 is the death rate of the immune cells. The change in concentration of IL-2 is

expressed as: $\frac{p_2 ET}{g_3 + T}$ which is the activation due to the presence of the tumor. In this term, p_2 is the production rate of the effector molecules and g_3 is the half-saturation of production. Finally, $-\mu_3 I$, is the natural loss of IL-2 by the rate of μ_3 . The viruses can infect the activated immune cells. As a result of this infection, the population of activated cells decreases and this leads to a weakened immune system. In such a case, the treatment can consist of immune boosting drugs such as Interleukin-2 (IL-2) (Kovacs et al., 1996). Kirschner & Webb (1998) mathematically characterized the general interaction of the Human Immunodeficiency Virus and activated immune cells. The presence of immune suppression factors reduces the efficiency of the immune system in battling tumor cells. These same mathematical terms are, thus, added to the model to explain a simple possible immune deficiency. Similar to the approach of Kirschner & Webb (1998), the production source of virus, $V(t)$, is expressed as $\frac{\eta V}{b+V}$ where η is the production rate and b is the saturated term. $-\mu_1 V$ expresses the natural death of viruses at rate of μ_1 . The interaction between effector cells and viruses can reduce the size of both populations with different rates. This is expressed as: $-\alpha VE$ and $-\gamma VE$ to illustrate the interaction between virus and effector cells. As a result of this interaction, the immune effector cells decrease the population of viruses at rate α . Additionally, viruses infect some of the effector cells and, therefore, the population of uninfected effector cells decreases at the rate γ . As suggested by Gardner (2000) and used in other studies (De Pillis & Radunskaya, 2003; de Pillis et al., 2006), the drug interaction may be structured as $a_\phi(1 - e^{-\xi MC})\phi$ where ϕ is the cell population number. The parameter C is the concentration or amount of the drug at the tumor site at a specific time with the unit ($mg.m^{-2}$). ξM is associated to the drug pharmacokinetics and known as the drug efficiency coefficient with the unit of ($m^2.mg^{-1}$). ξM is considered to be 1. The coefficient a_ϕ when $\phi = E, N, T$ with the unit of ($time^{-1}$) expresses the rate of chemotherapy-induced death. The function $F(C) = a_\phi(1 - e^{-\xi MC})$ is the fraction cell killed for a given amount (concentration) of drug " C ". Additionally, the immunotherapeutic agent is described by the term $a_{EE}(1 - e^{-\xi M_i})$ and it acts as an immune-boosting agent. a_{EE} is the boosting rate and

i is the concentration of immunotherapy drug.

3.4 Feizabadi's Model for multi-mutation and drug resistance

Different genetic alterations occur when the tumor cells divide. Feizabadi (2017) assumed that the newly born tumor cells can be placed in one of the following three groups. The first group includes those that are still responsive to the administered drug, and are known as wild tumor cells, T . The second group is those tumor cells that are still responsive to the drug, but carry a mutated gene that causes drug resistance as they interact with the introduced drug. These tumor cells are placed in the category of mutated tumor cells, T_M . The third group of tumor cells is those that are not responsive to the drug and intrinsically resist the administered drug. This group is identified by T_R . He assumed that all of these tumor cells grow under the logistic law and the control of normal cells over the growth of tumor cells is negligible as it is large tumor cells that mainly express resistance to the treatment. But the population of the normal cells is controlled by the tumor cell population. The schematic view and model taking into account these multi-mutation and drug resistance are:

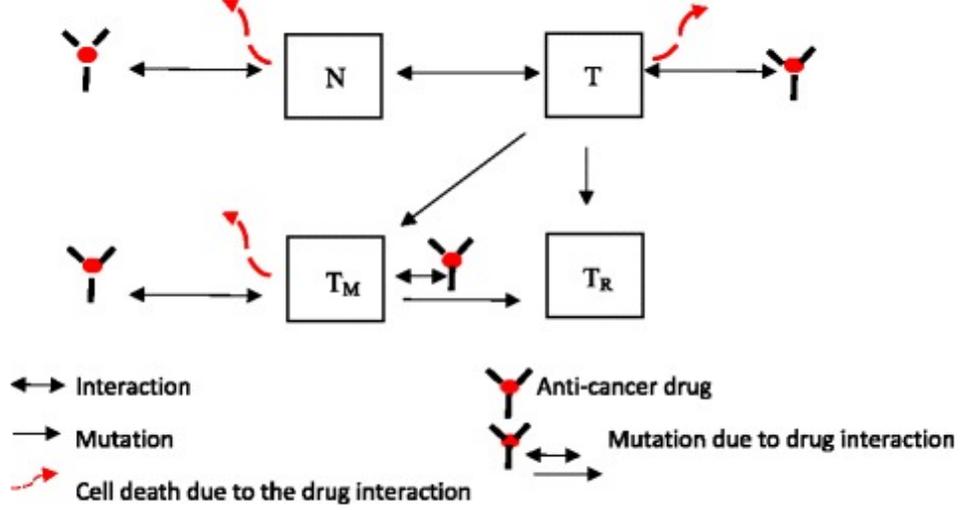


Fig. 3.1: The schematic view of the system interactions.

The system includes 4 types of cells: normal cells (N), wild tumor cells (T), mutated tumor cells (T_M), and drug resistant tumor cells (T_R). The population of normal, wild tumor and mutated tumor cells decreases as they interact with the drug. As the wild tumor cells divide, they can create mutated tumor cells or resistant tumor cells. As the mutated tumor cells interact with the drug, they can partially die and partially be transformed to resistant cells induced by the utilized anti-cancer drug.

$$\begin{cases}
 \frac{dT(t)}{dt} = r_T T \left(1 - \frac{T+T_R+T_M}{K_T}\right) - \tau_1 T(t) - \tau_2 T(t) - a_T (1 - e^{-MC}) T; \\
 \frac{dT_R(t)}{dt} = r_R T_R \left(1 - \frac{T+T_R+T_M}{K_R}\right) + \tau_1 T(t) + \tau_{M \rightarrow R} (1 - e^{-MC}) T_M; \\
 \frac{dT_M(t)}{dt} = r_M T_M \left(1 - \frac{T+T_R+T_M}{K_M}\right) + \tau_2 T(t) - a_{T_M} (1 - e^{-MC}) T_M - \tau_{M \rightarrow R} (1 - e^{-MC}) T_M; \\
 \frac{dN(t)}{dt} = r_N N \left(1 - \frac{N}{K_N}\right) + k(T + T_R + T_M) \left(1 - \frac{T+T_R+T_M}{T^*}\right) - a_N (1 - e^{-MC}) N; \\
 T(0) = T_0; T_R(0) = T_{R_0}; T_M(0) = T_{M_0}; N(0) = N_0;
 \end{cases}
 \tag{3.4.1}$$

where $N(t)$, $T(t)$, $T_M(t)$ and $T_R(t)$ are respectively the total number of normal cells, drug responsive tumor cells, mutated tumor cells and drug-resistant tumor cells with the unit of cells. K_N , K_T , K_M and K_R are the carrying capacity of normal cells and three types of tumor cells with the unit of cells. The per capita growth rate for the drug-responsive tumor cells, mutated tumor cells, drug-resistant tumor cells, and normal cells

are expressed by r_T, r_M, r_R, r_N with the unit of $(time^{-1})$. The T^* is the critical size of the collection of tumor cells with the unit of cells. The second term in the last equation represents the interaction between tumor and normal cells. In this term k with the units of $(time^{-1})$ represents the tumor-normal cell interaction rate. The term $\tau_1 T(t)$ in the two first equations expresses the transition from wild tumor cells (responsive tumor cells) to intrinsically resistant tumor cells with a mutation rate of $\tau_1 (time^{-1})$. The term $\tau_2 T(t)$ in the first and the third equations represents the transition from wild tumor cells to mutated tumor cells with a mutation rate of $\tau_2 (time^{-1})$. Also, the toxic effect of the administered drug, which leads to the reduction in populations of cells, has been expressed by $a_T(1 - e^{-MC})T$ on wild tumor cells where a_T is the death rate induced by the administered chemotherapeutic drug. The interaction of the drug with the mutated tumor cells partially kills them and partially turns them into drug-resistant tumor cells. The toxic effect of the drug which leads to the reduction of the population of mutated tumor cells has been expressed as $a_{T_M}(1 - e^{-MC})T_M$, where a_{T_M} is the killing rate of mutated tumor cells induced by the drug. The term that expresses the conversion from mutated tumor cells to drug-resistant tumor cells in the second and the third equations has been expressed by $\tau_{M \rightarrow R}(1 - e^{-MC})T_M$. In this term $\tau_{M \rightarrow R}$ with the unit of $(time^{-1})$ expresses the conversion rate from mutated tumor cells to resistant tumor cells due to the interaction with the drug.

3.5 The proposed ODE Model

Assumptions

- Two variables are considered to be the main immune system components: the activated immune-system cells (effector cells), denoted by E and the concentration of IL-2, denoted by I .
- The immune system can not distinguish between the responsive and the resistance tumor cells, so it acts on all the tumor cells.
- The resistant tumor cells are not affected by the action of the effector cells. That is the effector cells affect only the drug-sensitive tumor cells and the mutated tumor

cells, but not the resistant tumor cells.

- The immune-suppression factors are the resistant tumor cells.
- All type of tumor cells grow under the logistic growth law.

In this section, we add the concept of the interaction of the immune system established by [Kirschner & Panetta \(1998\)](#) and of the immune-suppression established by [Feizabadi & Witten \(2011\)](#) to the model of [Feizabadi \(2017\)](#). As considered in [Kirschner & Panetta \(1998\)](#) model, two variables are considered to be the main immune system components: the activated immune-system cells (effector cells) including T-cells and the immune cells that are cytotoxic to tumor cells, denoted by E ; and the concentration of IL-2, which is the main cytokine responsible for T-cells activation, growth and differentiation at the tumor site. This variable is denoted by I . While in [Feizabadi & Witten \(2011\)](#) the immune-suppression factors was the viruses, in this study we assume that the immune system cannot distinguish between the responsive and the resistance tumor cells, so it acts on all the tumor cells. However the resistant tumor cells are not affected by the action of the effector cells. That is the effector cells affect only the wild tumor cells and the mutated tumor cells, but not the resistant tumor cells. So the immune-suppression factors are assumed to be the resistant tumor cells. These resistant tumor cells infect the activated immune cells. As a result of this infection, the population of activated immune cells decrease and this leads to a weakened immune system. In such a case, the treatment will consist of immune boosting drugs (immunotherapy). Indeed, many approaches can be implemented to control cancer progression, among them chemotherapy, immunotherapy or some combination of both. The enhancement of the immune system by immunotherapeutic agents that directly boost the number of effector cells has a key role in the reduction of the number of tumor cells. Chemotherapeutic agents can kill the tumor population in a dose-dependent manner ([De Pillis & Radunskaya, 2003](#); [Pazdur, 2004](#)). Chemotherapeutic agents are cytotoxic not only to responsive tumor cells, but also to normal and activated-effector cells as well ([Feizabadi & Witten, 2011](#)). All of the tumor cells are assumed to grow

under the logistic law. The schematic view of the system describing the interactions between the immune system cells (E) and (I), wild tumor cells (T), mutated tumor cells (T_M), drug resistant tumor cells (T_R) and normal cells (N) is expressed in Fig. 3.2.

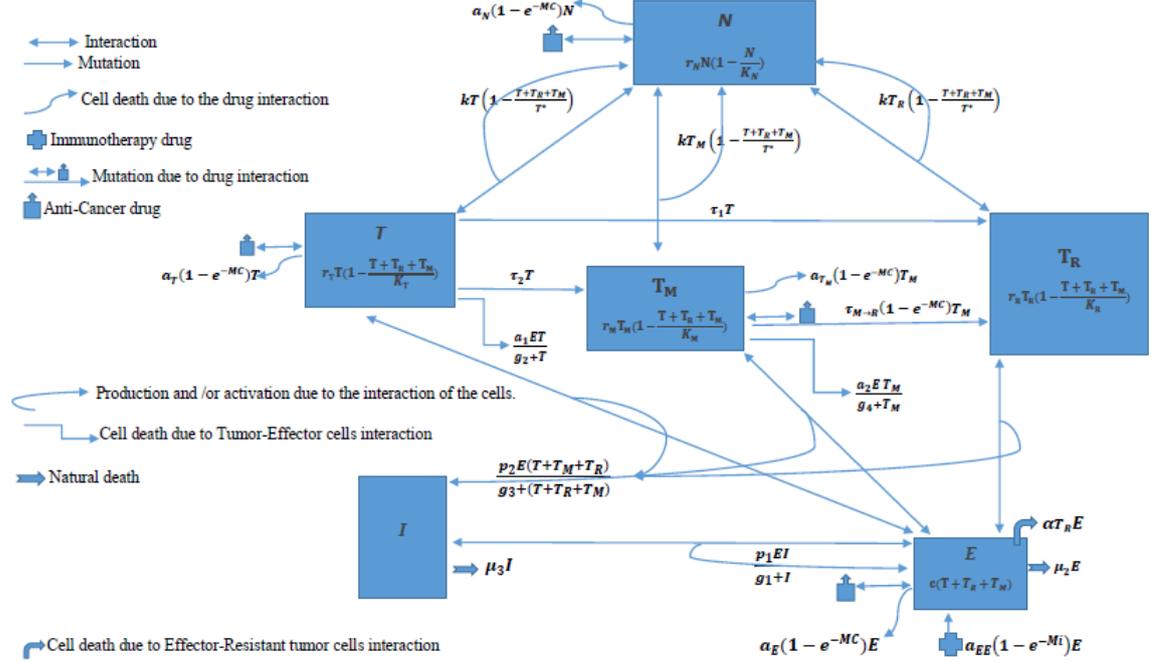


Fig. 3.2: The schematic view of the new (Proposed) system interactions. The system includes 5 types of cells: normal cells (N), wild tumor cells (T), mutated tumor cells (T_M), drug resistant tumor cells (T_R), and effector cells (E). (I) represents the concentration of IL-2. The population of normal, wild tumor, mutated tumor and effector cells decreases as they interact with the chemotherapy drug. As the wild tumor cells divide, they can create mutated tumor cells and/or resistant tumor cells. As the mutated tumor cells interact with the chemotherapy drug, they can partially die and partially be transformed to resistant cells induced by the utilized anti-cancer drug. The population of effector cells decreases as they interact with the Resistant tumor cells. This leads to a weakened immune system and in such a case, the treatment consists of immune boosting drugs (immunotherapy). The population of wild tumor, mutated tumor cells decreases as they interact with the effector cells. The effector cells are activated as they interact with the IL-2. Also IL-2 are activated as the effector cells interact with the tumor cells. Naturally, some of immune system cells die.

The dynamic of the system (proposed ODE model) can be expressed as follow:

$$\left\{ \begin{array}{l}
\frac{dT(t)}{dt} = r_T T \left(1 - \frac{T+T_R+T_M}{K_T}\right) - (\tau_1 + \tau_2)T - \frac{a_1 ET}{g_2+T} - a_T(1 - e^{-MC})T; \\
\frac{dT_R(t)}{dt} = r_R T_R \left(1 - \frac{T+T_R+T_M}{K_R}\right) + \tau_1 T + \tau_{M \rightarrow R}(1 - e^{-MC})T_M; \\
\frac{dT_M(t)}{dt} = r_M T_M \left(1 - \frac{T+T_R+T_M}{K_M}\right) + \tau_2 T - \frac{a_2 ET_M}{g_4+T_M} - a_{T_M}(1 - e^{-MC})T_M - \tau_{M \rightarrow R}(1 - e^{-MC})T_M; \\
\frac{dN(t)}{dt} = r_N N \left(1 - \frac{N}{K_N}\right) + k(T + T_R + T_M) \left(1 - \frac{T+T_R+T_M}{T^*}\right) - a_N(1 - e^{-MC})N; \\
\frac{dE(t)}{dt} = c(T + T_R + T_M) - \mu_2 E + \frac{p_1 EI}{g_1+I} - \alpha ET_R - a_E(1 - e^{-MC})E + a_{EE}(1 - e^{-Mi})E; \\
\frac{dI(t)}{dt} = \frac{p_2 E(T+T_R+T_M)}{g_3+(T+T_R+T_M)} - \mu_3 I; \\
T(0) = T_0, T_R(0) = T_{R_0}, T_M(0) = T_{M_0}, N(0) = N_0, E(0) = E_0, I(0) = I_0.
\end{array} \right. \tag{3.5.1}$$

where $N(t), T(t), T_M(t)$ and $T_R(t)$ are respectively at a time t the total number of normal cells, wild tumor cells, mutated tumor cells and drug-resistant tumor cells with the unit of cells. All of these tumor cells are assumed to grow under the logistic law. Also, K_N, K_T, K_M and K_R are the carrying capacity of normal cells and the three types of tumor cells with the unit of cells. The per capita growth rate for the drug-responsive tumor cells, mutated tumor cells, drug-resistant tumor cells, and normal cells are expressed by r_T, r_M, r_R, r_N with the unit of ($time^{-1}$). The T^* is the critical size of the collection of tumor cells with the unit of cells. The second term in the fourth equation represents the interaction between tumor and normal cells. This interaction is chosen as a logistic growth function (Feizabadi & Witten, 2010). In this term k with the units

of ($time^{-1}$) represent the tumor-normal cell interaction rate. The term $\tau_1 T$ in the first two equations expresses the transition from wild tumor cells (responsive tumor cells) to intrinsically resistant tumor cells with a mutation rate of $\tau_1 (time^{-1})$. The term $\tau_2 T$ in the first and the third equations represents the transition from wild tumor cells to mutated tumor cells with a mutation rate of $\tau_2 (time^{-1})$. The effector cells are stimulated to grow based on two terms: One is a recruitment term $c(T + T_R + T_M)$ due to the direct presence of the tumor, where the parameter c models the antigenicity of the tumor. Antigenicity can be thought of as a measure of how different the tumor is from 'self'. The second is due to the presence of IL-2 hormones and is given by the term $\frac{p_1 EI}{g_1 + I}$ (Kirschner & Panetta, 1998). This is of Michaelis-Menten form to indicate the saturated effects of immune response. p_1 is the proliferation rate of immune cells and g_1 is the half-saturation for the proliferation term. To express the natural death of effector cells, the term $-\mu_2 E$ is added. In this term μ_2 is the death rate of the immune cells. The change in concentration of IL-2 is expressed as: $\frac{p_2 E(T + T_R + T_M)}{g_3 + (T + T_R + T_M)}$, which is the activation due to the presence of the tumor. In this term, p_2 is the production rate of the effector molecules and g_3 is the half-saturation of production. $-\mu_3 I$, is the natural loss of IL-2 by the rate of μ_3 . The infection of the effector cells by the resistant tumor cells reduce the size of the populations of the effector cells. This is expressed as: $-\alpha ET_R$ with α the infection rate. The loss of tumor cells, due to the immune-effector cells can be characterized with the Michaelis-Menten interaction terms: $\frac{a_1 ET}{g_2 + T}$ on wild tumor cells (Feizabadi & Witten, 2011) and $\frac{a_2 ET_M}{g_4 + T_M}$ on mutated tumor cells. Here, ' a_1 ' is the rate of clearance of wild tumor cells as a result of these two populations and g_2 is the half-saturation for wild tumor cells clearance. ' a_2 ' is the rate of clearance of mutated tumor cells as a result of these two populations and g_4 is the half-saturation for mutated tumor cells clearance. The drug interaction may be structured as $a_\phi(1 - e^{-MC})\phi$ (Gardner, 2000) where ϕ is the cell population number. The parameter C is the concentration or amount of the drug at the tumor site at a specific time with the unit ($mg.m^{-2}$). M is associated to the drug pharmacokinetics and known as the drug efficiency coefficient with the unit of ($m^2.mg^{-1}$). The coefficient a_ϕ when $\phi = N, T, T_M$ and E with the unit

of ($time^{-1}$) expresses the death rate induced by the administered chemotherapeutic drug. The function $F(C) = a_\phi(1 - e^{-MC})$ is the fraction cell killed for a given amount (concentration) of drug "C". Thus the toxic effect of the administered drug, which leads to the reduction in populations of cells, has been expressed by $a_T(1 - e^{-MC})T$ on wild tumor cells, by $a_N(1 - e^{-MC})N$ on normal cells and by $a_E(1 - e^{-MC})E$ on effector cells. The interaction of the drug with the mutated tumor cells partially kills them and partially turns them into drug-resistant tumor cells. The toxic effect of the drug on the mutated tumor cells has been expressed as $a_{T_M}(1 - e^{-MC})T_M$. The term that expresses the conversion of mutated tumor cells to drug-resistant tumor cells has been expressed by $\tau_{M \rightarrow R}(1 - e^{-MC})T_M$. In this term $\tau_{M \rightarrow R}$ with the unit of ($time^{-1}$) expresses the conversion rate from mutated tumor cells to resistant tumor cells due to interaction with the drug. Additionally, the immunotherapeutic agent is described by the term $a_{EE}(1 - e^{-Mi})E$ and it acts as an immune-boosting agent.

Chapter 4

Analysis of the tumor-immunotherapy model

4.1 Introduction and preliminaries on differential systems

In this chapter, a mathematical analysis of the tumor-immunotherapy model is done to identify under which conditions tumor can be eliminated. First, the existence, the uniqueness and the boundedness of solutions are shown. Then, we study the local stability of non-tumor states. There are no generally applicable method for finding suitable Lyapunov functions. However, the failure of identifying a suitable Lyapunov function candidate to satisfy the conditions for global stability does not mean that the equilibrium is not globally stable. Thus, we prove the global stability of non tumor states by constructing a nonstandard finite difference scheme of the tumor immunotherapy ODE model.

4.1.1 The Existence and uniqueness theorem

Definition 4.1: ([Hirsch et al., 2012](#))

A function $F : \mathbb{R}^n \mapsto \mathbb{R}^n$ is said to be continuously differentiable at $a \in \mathbb{R}^n$, if all the partial derivatives of F exist and are continuous on a neighborhood of a . If F is continuously differentiable at each point of its domain, then we say simply that ' F is continuously differentiable' (or is of class ' C^1 ' for short).

- All the polynomial functions are of class C^1 in their domain.

- If f_1 and f_2 are of class C^1 in U and $\forall a \in U; f_2(a) \neq 0$, then $\frac{f_1}{f_2}$ is of class C^1 in U

Theorem 4.1: (Hirsch et al., 2012)

Consider the initial value problem $\frac{dX}{dt} = F(X); X(t_0) = X_0$ where $X_0 \in \mathbb{R}^n$. Suppose that $F : \mathbb{R}^n \mapsto \mathbb{R}^n$ is of class C^1 . Then, first of all, there exists a solution of this initial value problem and, secondly, this is the only such solution. More precisely, there exists an $\eta > 0$ and an unique solution $X : (t_0 - \eta; t_0 + \eta) \mapsto \mathbb{R}^n$ of this differential equation satisfying the initial condition $X(t_0) = X_0$.

4.1.2 Local Stability

A system may contain many equilibrium points or states and each of these equilibrium points or states could be locally stable. By local stability we mean that if we perturb the initial condition slightly, the system stays in the neighborhood of that equilibrium point.

To determine the local stability of the equilibrium point, we find the eigenvalues of the associated system (Campbell & Haberman, 2011).

The equilibrium point is

- **Hyperbolic** if none of the eigenvalues have zero real part.
- **Stable** if all eigenvalues have negative real part.
- **Unstable** if at least one eigenvalue has a positive real part.
- **Saddle(unstable)** if at least one eigenvalue has negative real part and one positive real part.

The stability of the equilibrium points of a system can be analyzed by

1. Nature of eigenvalues:

For a linear system, we find the eigenvalues of the system and establish stability based on the nature of the eigenvalues as explained above.

For nonlinear system, we first have to linearize the system by a process called

linearization. This process use the Jacobian of the system. Then by the nature of the eigenvalues of the linearized system we establish the stability of each equilibrium point as explained above. The anticipation is that the behavior of the resulting linearized system is a good approximation and representation of the behavior of the original nonlinear system.

2. **Phase portrait/Phase diagram:** A phase portrait is a two dimensional representation of the solution of a system of differential equations. The solution to the differential equation is called its trajectories. The trajectories shows the behavior of the solution near equilibrium points.

4.1.3 Nonstandard Finite difference Schemes

Introduced by Mickens around 1980, the nonstandard finite difference schemes are powerful numerical methods that preserve significant properties of differential equations (Dimitrov & Kojouharov, 2007). At the beginning, the general rules for such schemes are not precisely known (Mickens, 2000). However, Mickens proposed some rules for constructing nonstandard finite difference schemes for differential equations (Mickens, 2002). Used by many mathematicians such as Anguelov et al. (2011); Dimitrov & Kojouharov (2007); Gabbriellini (2012); Garba et al. (2011) and Songolo & Ramadhani (2017), nonstandard finite difference (NSFD) schemes have also a potential to preserve qualitative properties of the original system they approximate and to avoid ghost solutions (Mickens, 1994, 2005, 2007a,b; Mickens & Washington, 2012; Songolo & Ramadhani, 2017). These qualitative properties are not always preserved by the ordinary standard finite difference schemes (Yaghoubi & Najafi, 2015). This is why nonstandard finite difference schemes are appropriate and used for the stability of the differential systems they approximate.

A numerical scheme with a step size Δt , that approximates the solution $X(t_k)$ of an autonomous system $\frac{dX}{dt} = F(X)$; $X(t_0) = X_0$ where F is of class C^1 can be written in the form:

$$D_{\Delta t}(X_k) = F_{\Delta t}(X_k) \quad (4.1.1)$$

where $D_{\Delta t}(X_k) \simeq \frac{dX(t_k)}{dt}$; $X_k \simeq X(t_k)$; $F_{\Delta t}(X_k) \simeq F(X_k)$ and $t_k \simeq t_0 + k\Delta t$ (see, (Dimitrov & Kojouharov, 2007)).

Definition 4.2(Dimitrov & Kojouharov, 2007): The scheme (4.1.1) is called a non-standard finite difference scheme if at least one of the following conditions is satisfied:

1. $D_{\Delta t}(X_k) = \frac{X_{k+1} - \psi X_k}{\varphi(\Delta t)}$ where ψ and φ are non negative functions depending on the step-size Δt and other parameters occurring in the differential equation, and, in addition, satisfies the conditions: $\psi(\Delta t) = 1 + O(\Delta t)$ and $\varphi(\Delta t) = \Delta t + O(\Delta t^2)$.
2. $F_{\Delta t}(X_k) = g(X_k, X_{k+1}, \Delta t)$ where g is a nonlocal approximation of the right-hand side of the system of the differential equation.

Definition 4.3(Dimitrov & Kojouharov, 2007): The nonstandard finite difference scheme is called elementary stable, if, for any value of the step size, its only fixed points are those of the original differential system, the linear stability properties of each fixed points being the same for both the differential system and the discrete scheme.

Remark 4.1 (Mickens, 2002): The functions ψ and φ vary from one equation to another and no clear a priori set of guidelines exist for determining them. However,

In most applications, ψ is usually selected to be 1; and φ (called the “denominator function”) is determined in our case as follows: $\varphi(\Delta t) = \frac{1 - e^{-R^* \Delta t}}{R^*}$ where $R^* = \max\{|R_i|_{i=1;2;\dots}\}$ with $R_i = \left. \frac{\partial f}{\partial x_i} \right|_{X=0}$ and $0 < \varphi(\Delta t) < \frac{1}{R^*}$

Note also that nonstandard finite difference (NSFD) scheme are topologically equivalent to their original system that they approximate (for more details, see: (Anguelov et al., 2011)).

Now, we present the rules for the construction of NSFD schemes as proposed by Mickens (2002).

Rule 1: The order of the discrete derivatives must be equal to the order of the corresponding derivatives of the differential equations.

Rule 2: Denominator functions for the discrete derivatives must, in general, be expressed in terms of more complicated functions of the step-sizes than those conventionally used.

Rule 3: Nonlinear terms should, in general, be modeled nonlocally. However, sometimes more general forms may be required, such as: $u^2 = 2u^2 - u^2 \rightarrow 2u_k^2 - u_{k+1}u_k$ **Rule 4:** Special conditions that hold for the solutions of the differential equations should also hold for the solutions of the finite difference scheme.

Rule 5: The finite difference equations should not have solutions that don't correspond exactly to solutions of the differential equations.

Definition 4.4(Mickens, 2002): A nonstandard finite difference scheme is any discrete representation of a system of differential equations that is constructed according to the above rules.

4.2 Mathematical analysis of tumor-immunotherapy model

Taking the ODE model (3.5.1) without its fourth equation and without all the chemotherapy terms as well as the third term of its second equation, we obtain the corresponding tumor-immunotherapy model of as follows:

$$\left\{ \begin{array}{l} \frac{dT(t)}{dt} = r_T T \left(1 - \frac{T+T_R+T_M}{K_T} \right) - (\tau_1 + \tau_2)T - \frac{a_1 ET}{g_2+T}; \\ \frac{dT_R(t)}{dt} = r_R T_R \left(1 - \frac{T+T_R+T_M}{K_R} \right) + \tau_1 T; \\ \frac{dT_M(t)}{dt} = r_M T_M \left(1 - \frac{T+T_R+T_M}{K_M} \right) + \tau_2 T - \frac{a_2 ET_M}{g_4+T_M}; \\ \frac{dE(t)}{dt} = c(T + T_R + T_M) - \mu_2 E + \frac{p_1 EI}{g_1+I} - \alpha ET_R + a_{EE}(1 - e^{-Mi})E; \\ \frac{dI(t)}{dt} = \frac{p_2 E(T+T_R+T_M)}{g_3+(T+T_R+T_M)} - \mu_3 I; \end{array} \right. \quad \begin{array}{l} T(0) = T_0 \\ T_R(0) = T_{R_0} \\ T_M(0) = T_{M_0} \\ E(0) = E_0 \\ I(0) = I_0 \end{array}$$

(4.2.1)

4.2.1 Existence and uniqueness of solutions

A solution of (4.2.1) is a function $X : t \in J \subset \mathbb{R} \mapsto X(t) = \begin{pmatrix} T(t) \\ T_R(t) \\ T_M(t) \\ E(t) \\ I(t) \end{pmatrix} \in \mathbb{R}^5$

Let $F : X \in \mathbb{R}^5 \mapsto F(X) \in \mathbb{R}^5$ with

$$F(X) = \begin{cases} r_T T \left(1 - \frac{T+T_R+T_M}{K_T} \right) - (\tau_1 + \tau_2)T - \frac{a_1 ET}{g_2+T} \\ r_R T_R \left(1 - \frac{T+T_R+T_M}{K_R} \right) + \tau_1 T \\ r_M T_M \left(1 - \frac{T+T_R+T_M}{K_M} \right) + \tau_2 T - \frac{a_2 ET_M}{g_4+T_M} \\ c(T + T_R + T_M) - \mu_2 E + \frac{p_1 EI}{g_1+I} - \alpha ET_R + a_{EE}(1 - e^{-Mi})E \\ \frac{p_2 E(T+T_R+T_M)}{g_3+(T+T_R+T_M)} - \mu_3 I \end{cases}$$

The system (4.2.1) becomes $\frac{dX}{dt} = F(X); X(0) = X_0 = \left(T_0; T_{R_0}; T_{M_0}; E_0; I_0 \right)^T$.

From the definition 4.1 and the theorem 4.1, F is of class C^1 in its domain. Then, first of all, there exists a solution of this initial value problem and ,secondly, this is the only such solution. More precisely, there exists a unique solution of this differential equation satisfying the initial condition $X(0) = X_0$.

4.2.2 Positivity and boundedness of solutions

Let $T_0; T_{R_0}; T_{M_0}; E_0$ and I_0 be non negative. Since $T(t); T_R(t); T_M(t); E(t)$ and $I(t)$ are respectively the number of cells and the concentration of IL-2 at time t , then, $T(t); T_R(t);$

$T_M(t); E(t)$ and $I(t)$ must be non negative for all $t > 0$.

Lemma 4.1: If $T_0; T_{R_0}; T_{M_0}; E_0$ and I_0 are non negative, then, $T(t); T_R(t); T_M(t); E(t)$ and $I(t)$ are non negative for all $t > 0$.

Proof of Lemma 4.1: Suppose that $T_0; T_{R_0}; T_{M_0}; E_0$ and I_0 are non negative.

Let us consider the first equation of the system (4.2.1). We have:

$$\begin{aligned} \frac{dT(t)}{dt} &= r_T T \left(1 - \frac{T + T_R + T_M}{K_T} \right) - (\tau_1 + \tau_2) T - \frac{a_1 E T}{g_2 + T} \\ &\geq - \left(\tau_1 + \tau_2 + \frac{a_1 E}{g_2 + T} \right) T \\ &\geq \lambda_1 T \quad \text{where} \quad \lambda_1 = - \left(\tau_1 + \tau_2 + \frac{a_1 E}{g_2 + T} \right) \end{aligned}$$

Up on integrating the inequality we obtain analytic solution as $T(t) \geq T_0 e^{\int \lambda_1 dt}$ for any $t > 0$. Since $T_0 \geq 0$, and the exponential function always positive, it is clear that $T(t) \geq 0$ for any $t > 0$.

Considering the second equation of the system (4.2.1),

$$\begin{aligned}
\frac{dT_R(t)}{dt} &= r_R T_R \left(1 - \frac{T + T_R + T_M}{K_R}\right) + \tau_1 T \\
&\geq r_R T_R \left(1 - \frac{T + T_R + T_M}{K_R}\right) \\
&\geq \lambda_2 T_R \quad \text{where} \quad \lambda_2 = r_R \left(1 - \frac{T + T_R + T_M}{K_R}\right)
\end{aligned}$$

It follows that: $\forall t > 0, T_R(t) \geq T_{R_0} e^{\int \lambda_2 dt}$. Then, $T_R(t) \geq 0$ for any $t > 0$

Similarly, we obtain from the last three equations of the system (4.2.1) the following:

$$\begin{aligned}
\forall t > 0, T_M(t) &\geq T_{M_0} e^{\int \lambda_3 dt} \quad \text{where} \quad \lambda_3 = \frac{-a_2 E}{g_4 + T_M} \\
\forall t > 0, E(t) &\geq E_0 e^{\int \lambda_4 dt} \quad \text{where} \quad \lambda_4 = -(\mu_2 + \alpha T_R) \\
\forall t > 0, I(t) &\geq I_0 e^{-\mu_3 t}
\end{aligned}$$

Therefore, the solutions of the system (4.2.1) with non negative initial conditions remain non negative for all $t > 0$.

Lemma 4.2: Let $K = \max\{K_T; K_R; K_M\}$ and $r = \max\{r_T; r_R; r_M\}$. All feasible solutions of the system (4.2.1) are bounded and enter the region:

$$\Omega = \left\{ (T; T_R; T_M; E; I) \in \mathbb{R}_+^5 : E \leq 3K; T + T_R + T_M + E + I \leq \frac{3K(r+c+2\mu_3+p_1+p_2+a_{EE}-\mu_2)}{\mu_3} \right\}$$

Proof of Lemma 4.2: Let $P(t) = T(t) + T_R(t) + T_M(t) + E(t) + I(t)$, $K = \max\{K_T; K_R; K_M\}$, $r = \max\{r_T; r_R; r_M\}$ and $(T(t); T_R(t); T_M(t); E(t); I(t)) \in \mathbb{R}_+^5$ be any solution with positive initial condition.

- Taking the fourth equation of the model (4.2.1), we have:

$$\begin{aligned}
\frac{dE(t)}{dt} &= c(T + T_R + T_M) - \mu_2 E + \frac{p_1 EI}{g_1 + I} - \alpha ET_R \\
&\quad + a_{EE}(1 - e^{-Mi})E \\
&\leq c(K_T + K_R + K_M) + p_1 E + a_{EE}E \\
&\leq 3cK + (p_1 + a_{EE})E \\
&\leq 3K + (p_1 + a_{EE})E, \text{ since } (0 < c < 1)
\end{aligned}$$

Integrating and applying the initial condition $E(0) = E_0$, $E(t) \leq 3K - (3K - E_0)e^{(p_1 + a_{EE})t}$.

Since $3K - E_0 > 0$, $E(t) \leq 3K$.

- Adding the five equations of the model (4.2.1), we have:

$$\begin{aligned}
\frac{dP(t)}{dt} &= r_T T \left(1 - \frac{T + T_R + T_M}{K_T}\right) + r_R T_R \left(1 - \frac{T + T_R + T_M}{K_R}\right) \\
&\quad + r_M T_M \left(1 - \frac{T + T_R + T_M}{K_M}\right) + c(T + T_R + T_M) + \frac{p_1 EI}{g_1 + I} + \frac{p_2 E(T + T_R + T_M)}{g_3 + (T + T_R + T_M)} \\
&\quad + a_{EE}(1 - e^{-Mi})E - \left(\frac{a_1 ET}{g_2 + T} + \frac{a_2 ET_M}{g_4 + T_M} + \mu_2 E + \alpha ET_R + \mu_3 I\right) \\
&\leq r_T T + r_R T_R + r_M T_M + c(T + T_R + T_M) + p_1 E + p_2 E + a_{EE}E - (\mu_2 E + \mu_3 I) \\
&= (r + c + \mu_3)(T + T_R + T_M) + (p_1 + p_2 + a_{EE} - \mu_2 + \mu_3)E - \mu_3 P \\
&\leq 3K(r + c + 2\mu_3 + p_1 + p_2 + a_{EE} - \mu_2) - \mu_3 P(t)
\end{aligned}$$

It follows that

$$0 < P(t) \leq \frac{3K(r+c+2\mu_3+p_1+p_2+a_{EE}-\mu_2)}{\mu_3} + \left(P(0) - \frac{3K(r+c+2\mu_3+p_1+p_2+a_{EE}-\mu_2)}{\mu_3}\right)e^{-\mu_3 t}, \text{ where}$$

$P(0)$ represents initial value of the total population.

$$\text{Thus } 0 < P(t) \leq \frac{3K(r+c+2\mu_3+p_1+p_2+a_{EE}-\mu_2)}{\mu_3} \text{ as } t \rightarrow \infty.$$

Therefore all feasible solutions of system (4.2.1) enter the region

$$\Omega = \left\{ \left(T; T_R; T_M; E; I \right) \in \mathbb{R}_+^5 : E \leq 2K; T + T_R + T_M + E + I \leq \frac{3K(r+c+2\mu_3+p_1+p_2+a_{EE}-\mu_2)}{\mu_3} \right\}.$$

ie any trajectory of the system (4.2.1) starting from an initial state in Ω remains in Ω . Also, existence, uniqueness and continuation results for system (4.2.1) hold in this region.

□

4.3 Stability analysis of non-tumor states

$a_{EE}(1 - e^{-Mi})E$ is a treatment term (immunotherapy) that represents an external source of effector cells. For the stability analysis, assuming that the immunotherapy drug is constant, we set $a_{EE}(1 - e^{-Mi})E = \beta$ with β a parameter. We present the stability analysis of non-tumor states for two cases: no immunotherapy case ($\beta = 0$) and immunotherapy case ($\beta > 0$). The non-tumor state is the state where all the populations of tumor cells are zero. Our aim here is to determine under which conditions tumor can be eliminated for each type of mutation.

4.3.1 No immunotherapy case ($\beta = 0$)

- For this case, we have the trivial non-tumor states where all the populations are zero. Evaluating the Jacobian matrix of (4.2.1) at the trivial non-tumor state defined by $S_0 = (T_0^*; T_{R_0}^*; T_{M_0}^*; E_0^*; I_0^*) = (0; 0; 0; 0; 0)$ when the system expresses both intrinsic resistance and drug induced resistance, we have:

$$J_{S_0} = \begin{pmatrix} r_T - \tau_1 - \tau_2 & 0 & 0 & 0 & 0 \\ \tau_1 & r_R & 0 & 0 & 0 \\ \tau_2 & 0 & r_M & 0 & 0 \\ c & c & c & -\mu_2 & 0 \\ 0 & 0 & 0 & 0 & -\mu_3 \end{pmatrix}$$

J_{S_0} is a triangular matrix. So its eigenvalues are: $r_T - \tau_1 - \tau_2$; r_R ; r_M ; $-\mu_2$; $-\mu_3$. At least one eigenvalue has negative real part and one positive real part. Therefore, S_0 is always a unstable saddle point.

- We have the same result when the system expresses only intrinsic resistance (ie presence of wild tumor cells (T) and drug resistant tumor cells (T_R)); when

the system expresses only drug induced resistance (i.e. presence of wild tumor cells (T) and mutated tumor cells (T_M)) and when the system expresses neither intrinsic nor drug induced resistance (ie presence of wild tumor cells (T) only).

4.3.2 Immunotherapy case ($\beta > 0$)

For the immunotherapy case ($\beta > 0$), we have the non-tumor states, where $E^\# = \frac{\beta}{\mu_2}$ and $I^\# = 0$. This implies that the tumor can be eliminated by effector cells if these equilibrium points are stable.

The system expresses both intrinsic and drug-induced resistance

The Jacobian matrix of (4.2.1) evaluated at the state denoted by $S_{E_{R;M}^\#} = (0; 0; 0; E^\#; 0)$ when the system expresses both intrinsic and drug induced resistance is:

$$J_{S_{E_{R;M}^\#}} = \begin{pmatrix} r_T - \tau_1 - \tau_2 - \frac{\beta a_1}{\mu_2 g_2} & 0 & 0 & 0 & 0 \\ \tau_1 & r_R & 0 & 0 & 0 \\ \tau_2 & 0 & r_M - \frac{\beta a_2}{\mu_2 g_4} & 0 & 0 \\ c & \frac{c\mu_2 - \alpha\beta}{\mu_2 g_3} & c & -\mu_2 & \frac{\beta p_1}{\mu_2 g_1} \\ \frac{\beta p_2}{\mu_2 g_3} & \frac{\mu_2}{\beta p_2} & \frac{\beta p_2}{\mu_2 g_3} & 0 & -\mu_3 \end{pmatrix}$$

The eigenvalues of $J_{S_{E_{R;M}^\#}}$ are: $r_T - \tau_1 - \tau_2 - \frac{\beta a_1}{\mu_2 g_2}$; r_R ; $r_M - \frac{\beta a_2}{\mu_2 g_4}$; $-\mu_2$; $-\mu_3$. From analyzing the eigenvalues, at least one has negative real part and one positive real part. Thus the state $S_{E_{R;M}^\#}$ is unstable saddle. This implies that the immunotherapy drug can not eliminate all the tumor cells when the system expresses both intrinsic and drug-induced resistance (i.e. presence of wild tumor cells (T), drug resistant tumor cells (T_R), and mutated tumor cells (T_M)).

The system expresses only intrinsic resistance

The immunotherapy drug can not also eliminate all the tumor cells in the case where the system expresses only intrinsic resistance (i.e. Presence of wild tumor cells (T) and drug resistant tumor cells (T_R)).

Indeed, the eigenvalues of the Jacobian matrix evaluated at the non-tumor state denoted by $S_{E_R^\#} = (0; 0; E^\#; 0)$ when the system expresses only intrinsic resistance are:

$r_T - \tau_1 - \frac{\beta a_1}{\mu_2 g_2}; r_R; -\mu_2; -\mu_3$. Thus the state $S_{E_R^\#}$ is unstable saddle

The system expresses only drug-induced resistance

When the system expresses only drug-induced resistance (ie Presence of wild tumor cells (T) and mutated tumor cells (T_M)), the eigenvalues of the Jacobian matrix evaluated at the non-tumor state denoted by $S_{E_M^\#} = (0; 0; E^\#; 0)$ are: $r_T - \tau_2 - \frac{\beta a_1}{\mu_2 g_2}; r_M - \frac{\beta a_2}{\mu_2 g_4}; -\mu_2; -\mu_3$. From analyzing, this state is locally asymptotically stable (that is the immunotherapy drug can eliminate all tumor cells) if $\beta > \frac{\mu_2 g_2 (r_T - \tau_2)}{a_1}$ and $\beta > \frac{r_M \mu_2 g_4}{a_2}$. If one of those conditions is not satisfied, $S_{E_M^\#}$ is unstable.

Theorem 4.2: When the system expresses only drug-induced resistance, the non-tumor state $S_{E_M^\#}$ is globally asymptotically stable if $\beta > \frac{\mu_2 g_2 (r_T - \tau_2)}{a_1}$ and $\beta > \frac{r_M \mu_2 g_4}{a_2}$.

Proof of Theorem 4.2:

The proof is done by induction by constructing a Nonstandard Finite Difference (NSFD) scheme of the tumor-immunotherapy model.

When the system expresses only drug-induced resistance, we have the following model:

$$\left\{ \begin{array}{l} \frac{dT(t)}{dt} = r_T T \left(1 - \frac{T+T_M}{K_T} \right) - \tau_2 T - \frac{a_1 E T}{g_2 + T}; \\ \frac{dT_M(t)}{dt} = r_M T_M \left(1 - \frac{T+T_M}{K_M} \right) + \tau_2 T - \frac{a_2 E T_M}{g_4 + T_M}; \\ \frac{dE(t)}{dt} = c(T + T_M) - \mu_2 E + \frac{p_1 E I}{g_1 + I} + \beta; \\ \frac{dI(t)}{dt} = \frac{p_2 E (T+T_M)}{g_3 + (T+T_M)} - \mu_3 I; \\ T(0) = T_0, T_M(0) = T_{M_0}, E(0) = E_0, I(0) = I_0. \end{array} \right. \quad (4.3.1)$$

Based on the definition of NSFD scheme and rules for its construction, the NSFD scheme of (4.3.1) is given by:

$$\left\{ \begin{array}{l}
 \frac{T^{n+1}-T^n}{\varphi_1(\Delta t)} = r_T T^{n+1} \left(1 - \frac{T^n+T_M^n}{K_T}\right) - \tau_2 T^{n+1} - \frac{a_1 E^n T^{n+1}}{g_2+T^n}; \quad \varphi_1(\Delta t) = \frac{1 - e^{-(r_T-\tau_2)\Delta t}}{r_T - \tau_2} \\
 \\
 \frac{T_M^{n+1}-T_M^n}{\varphi_2(\Delta t)} = r_M T_M^{n+1} \left(1 - \frac{T^n+T_M^n}{K_M}\right) + \tau_2 T^{n+1} - \frac{a_2 E^n T_M^{n+1}}{g_4+T_M^n}; \quad \varphi_2(\Delta t) = \frac{1 - e^{-r_M \Delta t}}{r_M} \\
 \\
 \frac{E^{n+1}-E^n}{\varphi_3(\Delta t)} = c(T^n + T_M^n) - \mu_2 E^{n+1} + \frac{p_1 E^n I^n}{g_1+I^n} + \beta; \quad \varphi_3(\Delta t) = \frac{1 - e^{-c\Delta t}}{c} \\
 \\
 \frac{I^{n+1}-I^n}{\varphi_4(\Delta t)} = \frac{p_2 E^n (T^n+T_M^n)}{g_3+(T^n+T_M^n)} - \mu_3 I^{n+1}; \quad \varphi_4(\Delta t) = \frac{1 - e^{-\mu_3 \Delta t}}{\mu_3}
 \end{array} \right. \quad (4.3.2)$$

In explicit form, we have:

$$\left\{ \begin{array}{l}
T^{n+1} = \frac{T^n}{1 + (\tau_2 - r_T)\varphi_1(\Delta t) + r_T \left(\frac{T^n + T_M^n}{K_T} \right) \varphi_1(\Delta t) + \frac{a_1 E^n \varphi_1(\Delta t)}{g_2 + T^n}}; \quad \varphi_1(\Delta t) = \frac{1 - e^{-(r_T - \tau_2)\Delta t}}{r_T - \tau_2} \\
T_M^{n+1} = \frac{T_M^n + \tau_2 T^{n+1} \varphi_2(\Delta t)}{1 + r_M \left(\frac{T^n + T_M^n}{K_M} \right) \varphi_2(\Delta t) + \frac{a_2 E^n \varphi_2(\Delta t)}{g_4 + T^n} - r_M \varphi_2(\Delta t)}; \quad \varphi_2(\Delta t) = \frac{1 - e^{-r_M \Delta t}}{r_M} \\
E^{n+1} = \frac{c(T^n + T_M^n)\varphi_3(\Delta t) + \frac{p_1 E^n I^n \varphi_3(\Delta t)}{g_1 + I^n} + \beta \varphi_3(\Delta t) + E^n}{1 + \mu_2 \varphi_3(\Delta t)}; \quad \varphi_3(\Delta t) = \frac{1 - e^{-c\Delta t}}{c} \\
I^{n+1} = \frac{\frac{p_2 E^n (T^n + T_M^n)}{g_3 + (T^n + T_M^n)} \varphi_4(\Delta t) + I^n}{1 + \mu_3 \varphi_4(\Delta t)}; \quad \varphi_4(\Delta t) = \frac{1 - e^{-\mu_3 \Delta t}}{\mu_3}
\end{array} \right. \tag{4.3.3}$$

With given initial conditions $T(0) = T_0$, $T_M(0) = T_{M_0}$, $E(0) = E_0$, $I(0) = I_0$.

It is clear that the non tumor state of the system of the differential equations (4.3.1) is exactly the non tumor state of its corresponding NSFD scheme (4.3.3).

We must show that the sequence (T^n, T_M^n, E^n, I^n) converge to $S_{E_M^\#} = (0, 0, E^\#, 0)$ for any positive initial conditions when $\beta > \frac{\mu_2 g_2 (r_T - \tau_2)}{a_1}$ and $\beta > \frac{r_M \mu_2 g_4}{a_2}$ for every value of Δt .

The state $S_{E_M^\#} = (0, 0, E^\#, 0)$ is locally stable when $\beta > \frac{\mu_2 g_2 (r_T - \tau_2)}{a_1}$ and $\beta > \frac{r_M \mu_2 g_4}{a_2}$. Now suppose that for a certain $k > 0$, (T^k, T_M^k, E^k, I^k) converge to $S_{E_M^\#} = (0, 0, E^\#, 0)$ and show that $(T^{k+1}, T_M^{k+1}, E^{k+1}, I^{k+1})$ converge also to $S_{E_M^\#} = (0, 0, E^\#, 0)$.

(i) For T^{k+1} ,

$$T^{k+1} = \frac{T^k}{1 + (\tau_2 - r_T)\varphi_1(\Delta t) + r_T \left(\frac{T^k + T_M^k}{K_T} \right) \varphi_1(\Delta t) + \frac{a_1 E^k \varphi_1(\Delta t)}{g_2 + T^k}}$$

Then $T^{k+1} \rightarrow 0$ when $k \rightarrow \infty$.

(ii) For T_M^{k+1} ,

$$T_M^{k+1} = \frac{T_M^k + \tau_2 T^{k+1} \varphi_2(\Delta t)}{1 + r_M \left(\frac{T^k + T_M^k}{K_M} \right) \varphi_2(\Delta t) + \frac{a_2 E^k \varphi_2(\Delta t)}{g_4 + T^k} - r_M \varphi_2(\Delta t)}$$

Then $T_M^{k+1} \rightarrow 0$ when $k \rightarrow \infty$.

(iii) For E^{k+1} ,

$$E^{k+1} = \frac{c(T^k + T_M^k)\varphi_3(\Delta t) + \frac{p_1 E^k I^k \varphi_3(\Delta t)}{g_1 + I^k} + \beta \varphi_3(\Delta t) + E^k}{1 + \mu_2 \varphi_3(\Delta t)}$$

Then $E^{k+1} \rightarrow E^\# = \frac{\beta}{\mu_2}$ when $k \rightarrow \infty$.

(iv) For I^{k+1}

$$I^{k+1} = \frac{\frac{p_2 E^k (T^k + T_M^k)}{g_3 + (T^k + T_M^k)} \varphi_4(\Delta t) + I^k}{1 + \mu_3 \varphi_4(\Delta t)}$$

Then $I^{k+1} \rightarrow 0$ when $k \rightarrow \infty$.

Hence, the non-tumor state $S_{E_M^\#} = (0, 0, E^\#, 0)$ is globally stable when $\beta > \frac{\mu_2 g_2 (r_T - \tau_2)}{a_1}$ and $\beta > \frac{r_M \mu_2 g_4}{a_2}$ for every value of Δt .

□

The system expresses neither intrinsic nor drug-induced resistance

When the system expresses neither intrinsic nor drug-induced resistance (ie Presence of wild tumor cells (T) only), the eigenvalues of the Jacobian matrix evaluated at the non-tumor state denoted by $S_{E^\#} = (0; E^\#; 0)$ are: $r_T - \frac{\beta a_1}{\mu_2 g_2}$; $-\mu_2$; $-\mu_3$. From

analyzing these eigenvalues, it is clear that this state is locally asymptotically stable (that is the immunotherapy drug can eliminate the tumor) if $\beta > \frac{r_T \mu_2 g_2}{a_1}$ and unstable if $\beta < \frac{r_T \mu_2 g_2}{a_1}$

Theorem 4.3: When the system expresses neither intrinsic nor drug-induced resistance, the non-tumor state $S_{E^\#}$ is globally stable if $\beta > \frac{r_T \mu_2 g_2}{a_1}$.

Proof of Theorem 4.3: When the system expresses neither intrinsic nor drug-induced resistance, we have the following model:

$$\left\{ \begin{array}{l} \frac{dT(t)}{dt} = r_T T \left(1 - \frac{T+T_M}{K_T} \right) - \frac{a_1 ET}{g_2+T}; \\ \frac{dE(t)}{dt} = cT - \mu_2 E + \frac{p_1 EI}{g_1+I} + \beta; \\ \frac{dI(t)}{dt} = \frac{p_2 ET}{g_3+T} - \mu_3 I; \\ T(0) = T_0, T_M(0) = T_{M_0}, E(0) = E_0, I(0) = I_0. \end{array} \right. \quad (4.3.4)$$

The explicit form of NSFD scheme of (4.3.4) is:

$$\left\{ \begin{array}{l}
T^{n+1} = \frac{T^n}{1 + r_T \frac{T^n}{K_T} \varphi_1(\Delta t) + \frac{a_1 E^n \varphi_1(\Delta t)}{g_2 + T^n} - r_T \varphi_1(\Delta t)}; \quad \varphi_1(\Delta t) = \frac{1 - e^{-r_T \Delta t}}{r_T} \\
E^{n+1} = \frac{c T^n \varphi_2(\Delta t) + \frac{p_1 E^n I^n \varphi_2(\Delta t)}{g_1 + I^n} + \beta \varphi_2(\Delta t) + E^n}{1 + \mu_2 \varphi_2(\Delta t)}; \quad \varphi_2(\Delta t) = \frac{1 - e^{-c \Delta t}}{c} \\
I^{n+1} = \frac{\frac{p_2 E^n T^n}{g_3 + T^n} \varphi_3(\Delta t) + I^n}{1 + \mu_3 \varphi_3(\Delta t)}; \quad \varphi_3(\Delta t) = \frac{1 - e^{-\mu_3 \Delta t}}{\mu_3}
\end{array} \right. \tag{4.3.5}$$

With given initial conditions $T(0) = T_0$, $E(0) = E_0$, $I(0) = I_0$.

We must show that the sequence (T^n, E^n, I^n) converge to $S_{E^\#} = (0, E^\#, 0)$ for any positive initial conditions when $\beta > \frac{r_T \mu_2 g_2}{a_1}$ for every value of Δt .

The state $S_{E^\#} = (0, E^\#, 0)$ is locally stable when $\beta > \frac{r_T \mu_2 g_2}{a_1}$. Now suppose that for a certain $k > 0$, (T^k, E^k, I^k) converge to $S_{E^\#} = (0, E^\#, 0)$ and show that $(T^{k+1}, E^{k+1}, I^{k+1})$ converge also to $S_{E^\#} = (0, E^\#, 0)$.

(i) For T^{k+1} ,

$$T^{k+1} = \frac{T^k}{1 + r_T \frac{T^k}{K_T} \varphi_1(\Delta t) + \frac{a_1 E^k \varphi_1(\Delta t)}{g_2 + T^k} - r_T \varphi_1(\Delta t)}$$

Then $T^{k+1} \rightarrow 0$ when $k \rightarrow \infty$.

(ii) For E^{k+1} ,

$$E^{k+1} = \frac{c T^k \varphi_2(\Delta t) + \frac{p_1 E^k I^k \varphi_2(\Delta t)}{g_1 + I^k} + \beta \varphi_2(\Delta t) + E^k}{1 + \mu_2 \varphi_2(\Delta t)}$$

Then $E^{k+1} \rightarrow E^\# = \frac{\beta}{\mu_2}$ when $k \rightarrow \infty$.

(iii) For I^{k+1} ,

$$I^{k+1} = \frac{\frac{p_2 E^k T^k}{g_3 + T^k} \varphi_3(\Delta t) + I^k}{1 + \mu_3 \varphi_3(\Delta t)}$$

Then $I^{k+1} \rightarrow 0$ when $k \rightarrow \infty$.

Hence, the non tumor state $S_{E^\#} = (0, E^\#, 0)$ is globally stable when $\beta > \frac{r_T \mu_2 g_2}{a_1}$ for every value of Δt .

□

Chapter 5

Numerical simulations of the tumor-immunotherapy model

Since our aim here is to see whether the immunotherapy drug is effective, we present the numerical simulations results of the model (4.2.1) in the absence of immunotherapy to show how resistant tumor cells are weakening the immune system. Then we present the numerical simulations results of tumor-immunotherapy model (ie model (4.2.1) in the presence of immunotherapy). These Numerical Simulations are performed for each type of mutation and are done in MATLAB using ode45 function. Data supporting this model come from recently published articles and has been duly cited in table 5.1. Parameter values extracted from published articles are cited at appropriate places in table 5.1 as references.

Table 5.1: Description of simulation parameters of the model (4.2.1)

Parameters	Units	Description	Estimated value	Reference Source
r_T	Day^{-1}	Growth rate for wild tumor cells	0.15	Assumed
r_R	Day^{-1}	Growth rate for resistant tumor cells	0.015	Assumed
r_M	Day^{-1}	Growth rate for mutated tumor cells	0.1515	Assumed
$K_T; K_R; K_M$	Cells	Carrying capacity of cells	10^6	Feizabadi (2017)
τ_1	Day^{-1}	Mutation rate	10^{-4}	Feizabadi (2017)
τ_2	Day^{-1}	Mutation rate	10^{-5}	Assumed
a_1	Day^{-1}	rate of clearance of wild tumor cells	1.5	Assumed
g_2	Cells	Half-saturation for wild tumor cells clearance	10^5	Feizabadi & Witten (2011)
a_2	Day^{-1}	rate of clearance of mutated tumor cells	1.5	Assumed
g_4	Cells	Half-saturation for mutated tumor cells clearance	10^5	Assumed
c	Day^{-1}	Antigenicity	0.5	Assumed
μ_2	Day^{-1}	Death rate of immune cells	0.003	Assumed
μ_3	Day^{-1}	Death rate of IL-2	10	Feizabadi & Witten (2011)
p_1	Day^{-1}	Proliferation rate of immune cells	0.1245	Feizabadi & Witten (2011)
g_1	Cells	Half-saturation for the proliferation	2×10^7	Feizabadi & Witten (2011)
p_2	Day^{-1}	Production rate of IL-2	5	Feizabadi & Witten (2011)
g_3	Cells	Half-saturation of production	30	Feizabadi & Witten (2011)
α	Day^{-1}	Effector-Resistant tumor cells interation rate	3×10^{-4}	Assumed

5.1 When the system expresses both intrinsic and drug-induced resistance

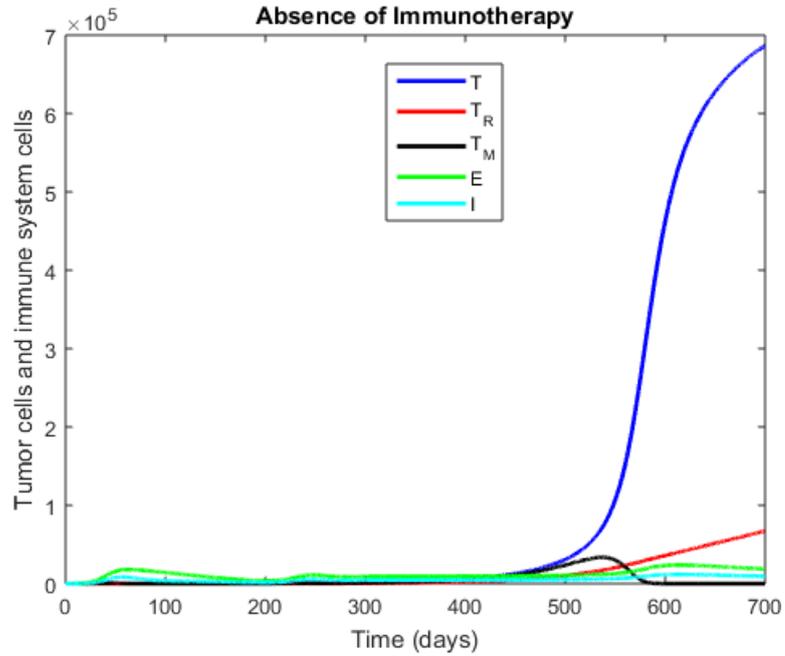


Fig. 5.1: The behavior of tumor cells and immune system cells in the absence of immunotherapy.

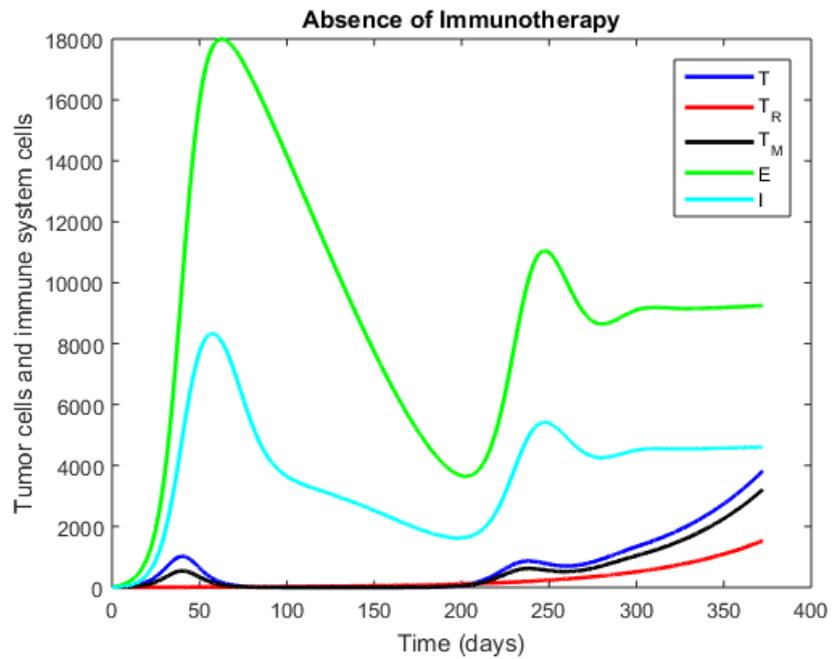


Fig. 5.2: A zoom of (5.1) for $0 \leq t \leq 375$.

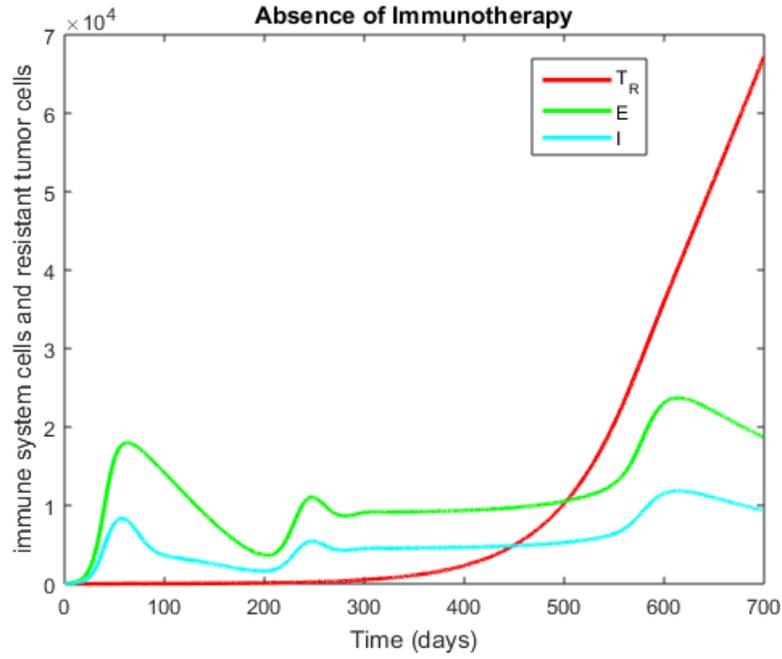


Fig. 5.3: The behavior of immune system cells and resistant tumor cells in the absence of immunotherapy.

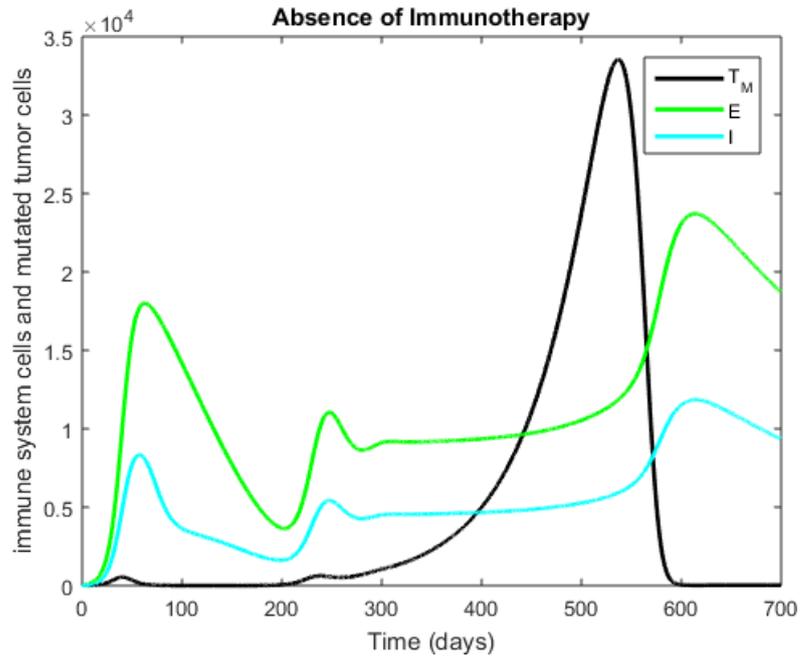


Fig. 5.4: The behavior of Mutated tumor cells and of effector cells in the absence of immunotherapy.

The outcome of the simulation expressed in (5.1) and (5.4) shows that the population of mutated tumor cells (T_M) have been successfully controlled by the immune system in the time frame of simulation ($t = 700days$). The wild tumor cells (T) and the drug

resistant tumor cells (T_R) have started to grow as well. Around ($t = 580days$) the wild tumor cells can be detectable. It can be seen through the figure (5.3) that when the drug resistant tumor cells have started to grow, the immune system cells have started to decrease from 600th day. This is due to the effects of the drug resistance tumor cells on the effector cells to make the immune system weak. The figure (5.2) shows that as the tumor cells started to grow, the immune system cells started to grow as well and this happened from the beginning of simulation time up to 350th day. It can be seen that between 50 days and 200 days the wild tumor cells and the mutated tumor cells have been controlled by the immune system. Note that the drug resistant tumor cells have started to grow well from 250th day.

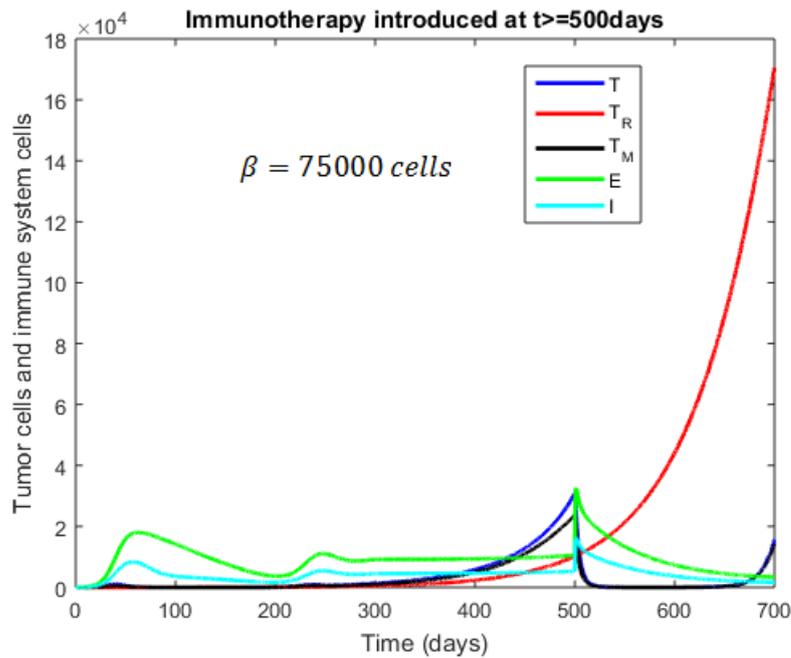


Fig. 5.5: The behavior of tumor cells and immune system cells in the presence of immunotherapy.

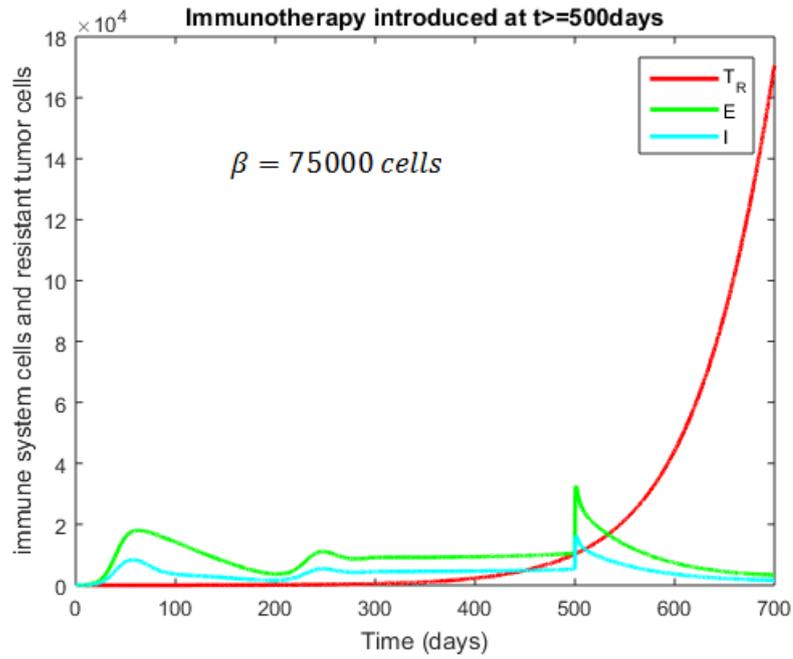


Fig. 5.6: The behavior of immune system cells and resistant tumor cells in the presence of immunotherapy.

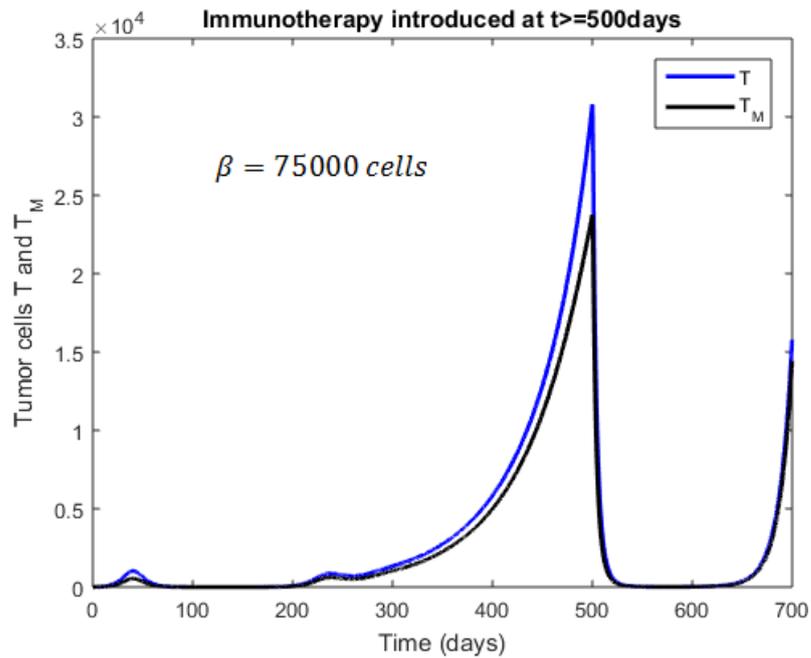


Fig. 5.7: The behavior of tumor cells T and T_M in the presence of immunotherapy.

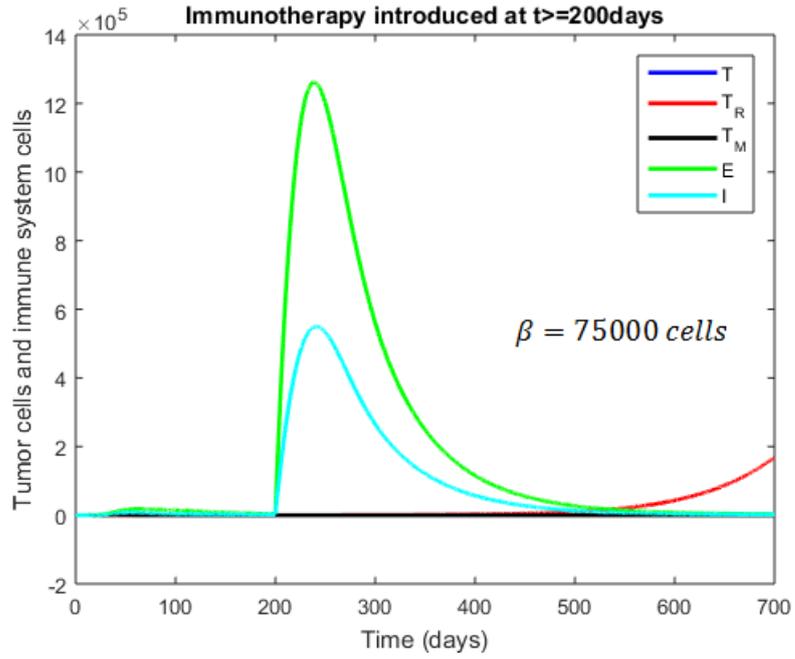


Fig. 5.8: The behavior of tumor cells and immune system cells in the presence of immunotherapy (introduced at $t = 200$ days).

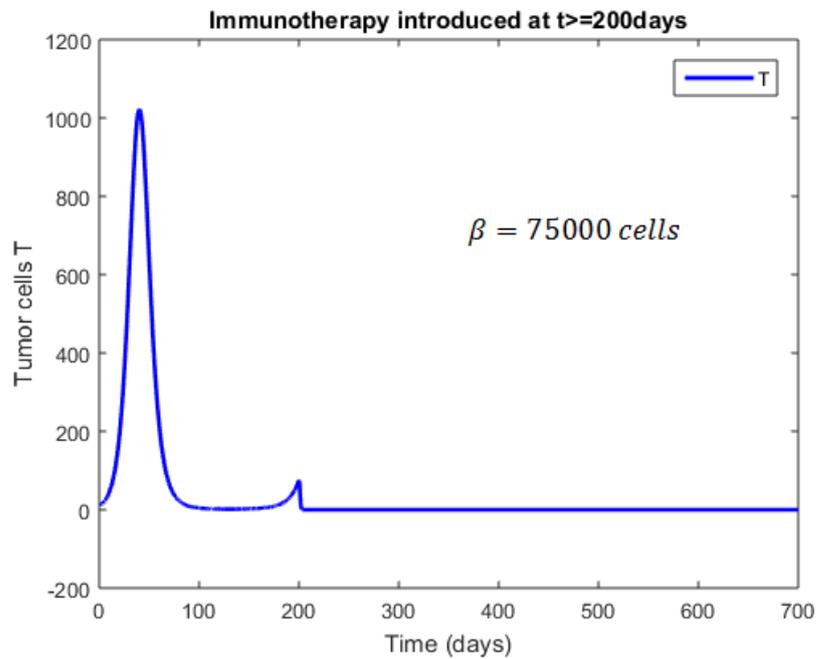


Fig. 5.9: The behavior of tumor cells T in the presence of immunotherapy (introduced at $t = 200$ days).

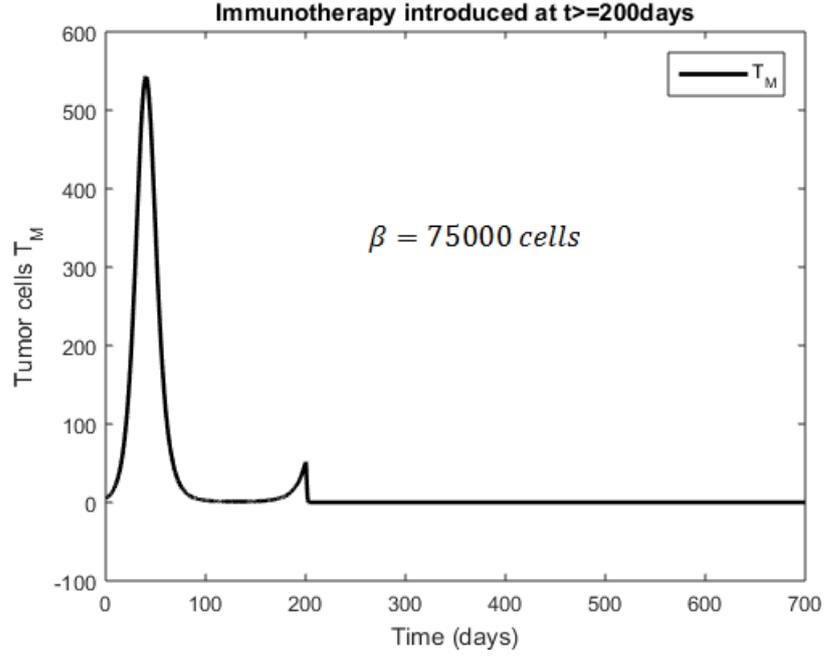


Fig. 5.10: The behavior of tumor cells T_M in the presence of immunotherapy (introduced at $t = 200$ days).

The effectiveness of the immunotherapy can be seen through the figures (5.5) and (5.7). Unlike the figures (5.1) and (5.3), here the wild tumor cells and the mutated tumor cells started to die out from the date that the immunotherapy drug is introduced. But it can be seen that in the end of the simulation time, those two populations started to grow again. Thus a periodic immunotherapy can eliminate the responsive tumor cells. Of course, through the figure (5.6) the immune system cells started to decrease when the resistant tumor cells started to grow. We can conclude that a periodic immunotherapy and a specific chemotherapy drug on the resistant tumor cells can clear the tumor. So far, it can be seen that the state $(0, T_{R_1}^\#, 0, E_1^\#, I_1^\#)$ is stable when the immunotherapy drug is introduced at the early stage ($t = 200$ days) (see figures (5.8), (5.9), (5.10)).

Two treatment strategies can be proposed in this case: Periodic and constant immunotherapy drug starting around $t = 500$ days and a specific chemotherapy drug on the resistant tumor cells, or constant immunotherapy drug at the early stage (around $t = 200$ days) and a specific chemotherapy drug on the resistant tumor cells.

5.2 When the system expresses only intrinsic resistance

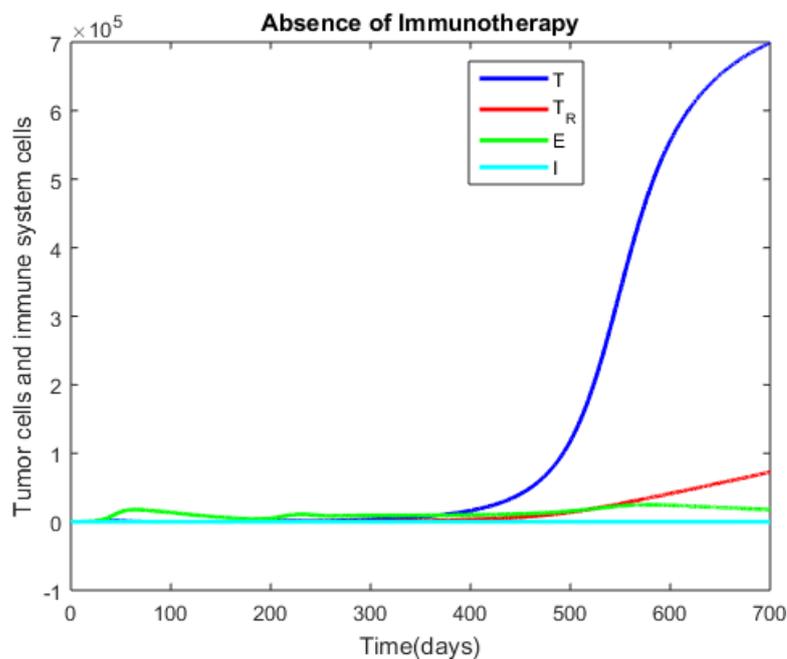


Fig. 5.11: The behavior of tumor cells and immune system cells in the absence of immunotherapy.

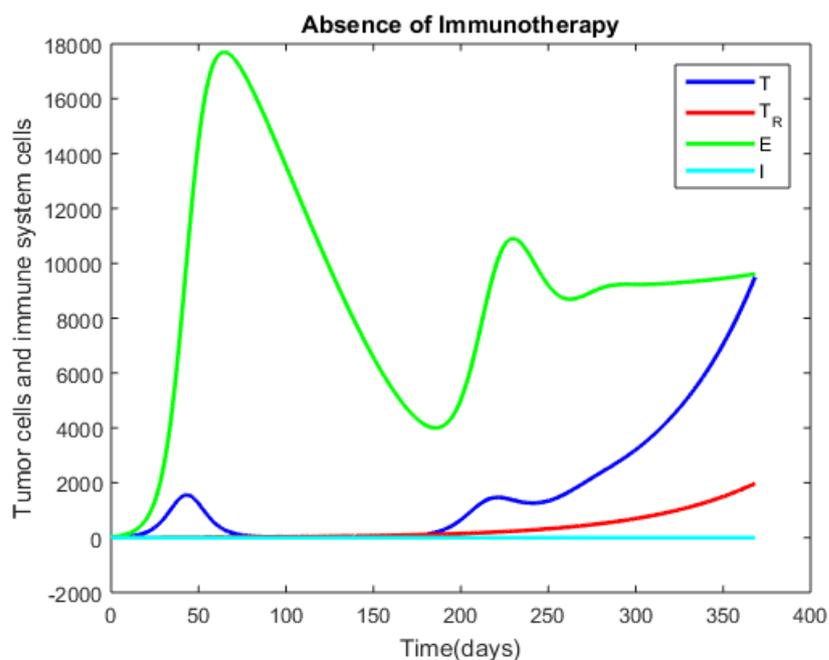


Fig. 5.12: A zoom of (5.11) for $0 \leq t \leq 375$.

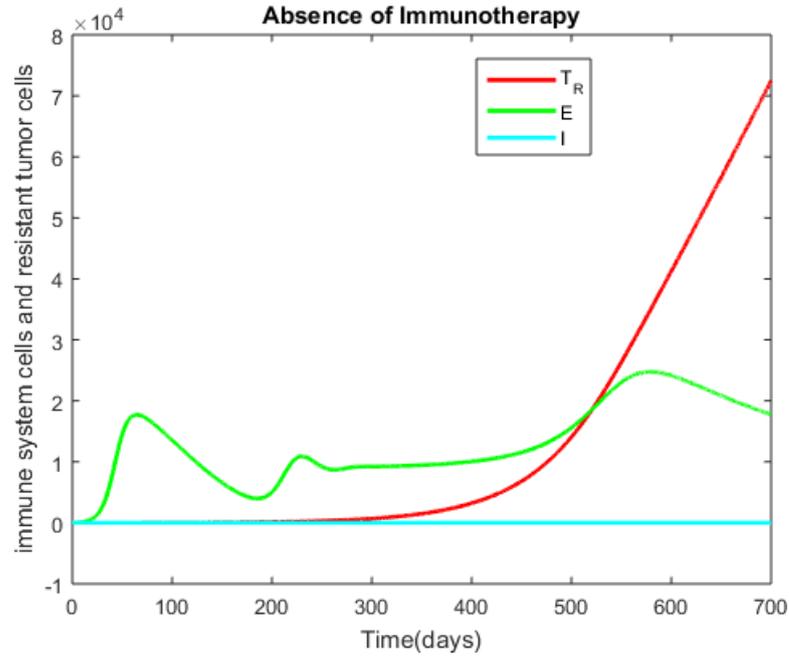


Fig. 5.13: The behavior of immune system cells and resistant tumor cells in the absence of immunotherapy.

The figures (5.11) and (5.12) show that as the wild tumor cells started to grow, the effector cells started to grow also and this happened up to 285th day. It can be seen that the wild tumor cells are controlled by the effector cells between 75th day and 185th day. From 150th day the drug resistant tumor cells started to grow (see figure (5.13)). This has started to reduce the population of the effector cells. This reduction of effector cells allowed the wild tumor cells to grow logistically from 285th day up to the end of the simulation time ($t = 700$ days). They become detectable around $t = 543$ days. Due to the high mortality rate of IL-2, the concentration of IL-2 is negligible.

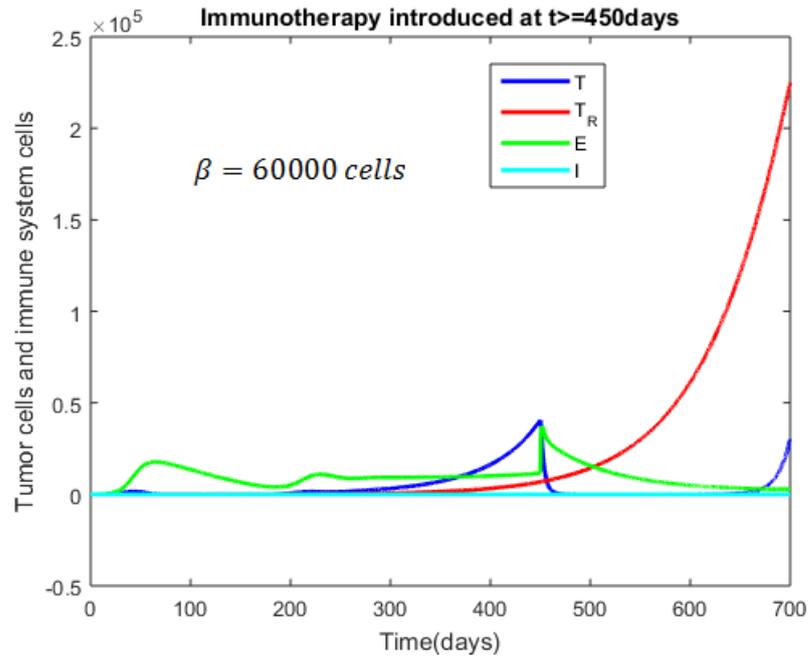


Fig. 5.14: The behavior of tumor cells and immune system cells in the presence of immunotherapy.

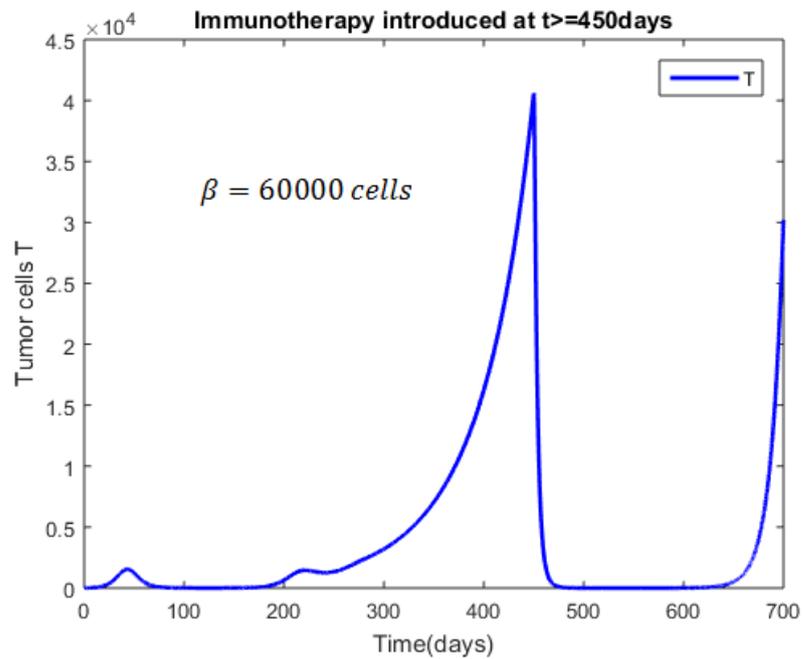


Fig. 5.15: The behavior of tumor cells T in the presence of immunotherapy.

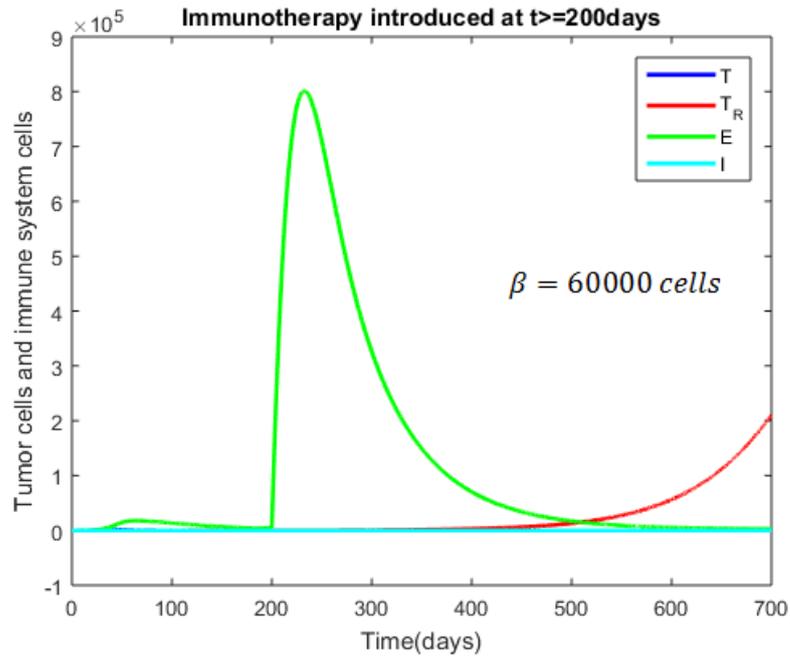


Fig. 5.16: The behavior of tumor cells and immune system cells in the presence of immunotherapy (introduced at $t = 200$ days).

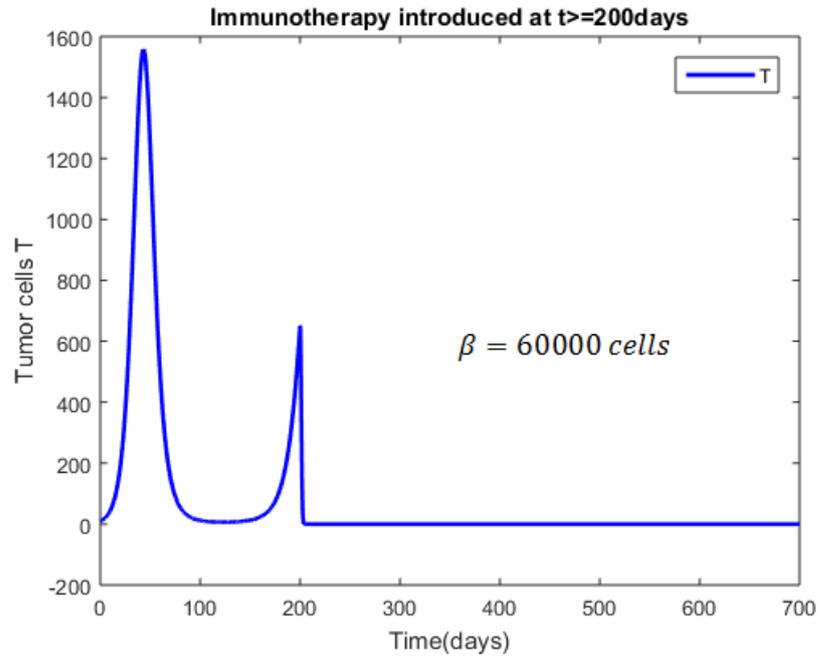


Fig. 5.17: The behavior of tumor cells T in the presence of immunotherapy (introduced at $t = 200$ days).

The effectiveness of the immunotherapy can be seen through the figures (5.14) and (5.15). The wild tumor cells started to die out from the date that the immunotherapy drug is introduced and started to grow again in the end of the simulation time. Thus,

here also a periodic immunotherapy can eliminate the responsive tumor cells. Of course, through the figure (5.14) the immune system cells started to decrease when the resistant tumor cells started to grow. We can conclude here also that a periodic immunotherapy and a specific chemotherapy drug on the resistant tumor cells can clear all the tumor. So far, the figures (5.16) and (5.17) show that the state $(0; T_{R_2}^\#, E_2^\#, I_2^\#)$ is stable when the immunotherapy drug is introduced at the early stage ($t = 200$ days). So the two treatment strategies proposed in the case where the system expresses both intrinsic and drug-induced resistance are also proposed here.

5.3 When the system expresses only drug-induced resistance

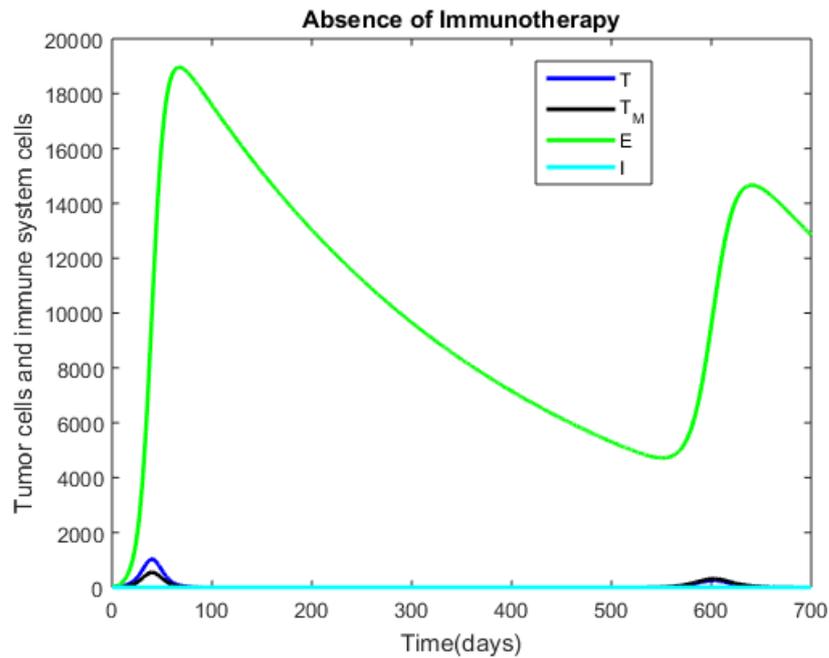


Fig. 5.18: The behavior of tumor cells and immune system cells in the absence of immunotherapy.

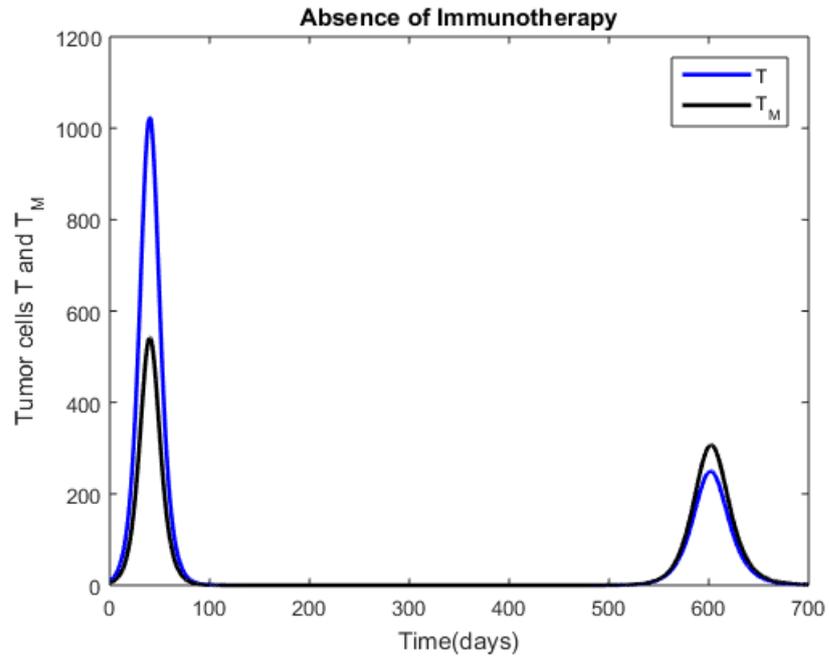


Fig. 5.19: A zoom of (5.18) into the behavior of tumor cells T and T_M in the absence of immunotherapy.

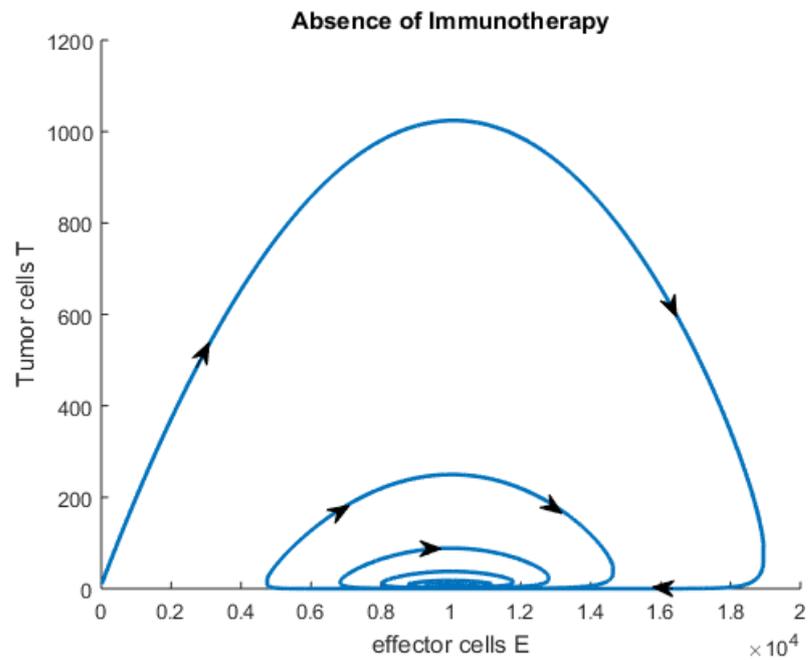


Fig. 5.20: The Phase diagram relating T and E in the absence of immunotherapy.

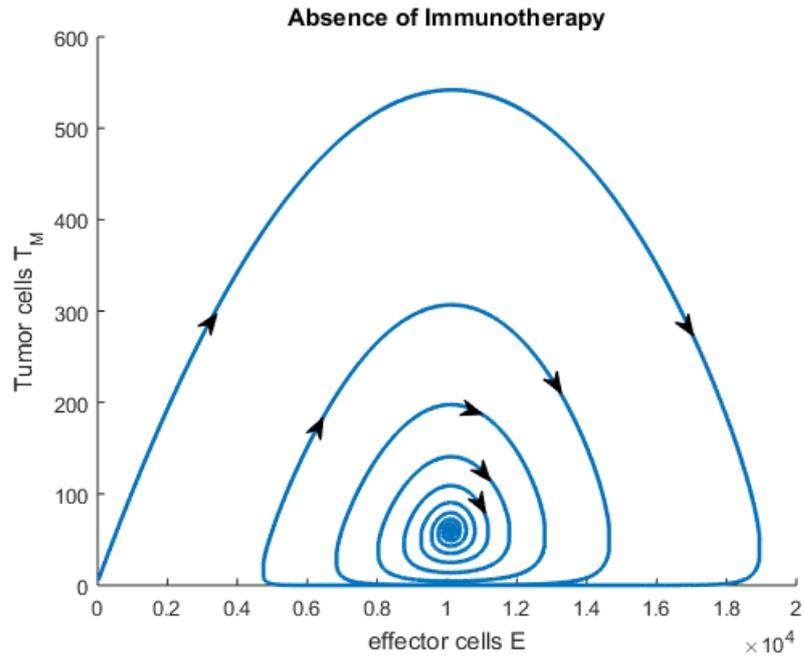


Fig. 5.21: Phase diagram relating T_M and E in the absence of immunotherapy.

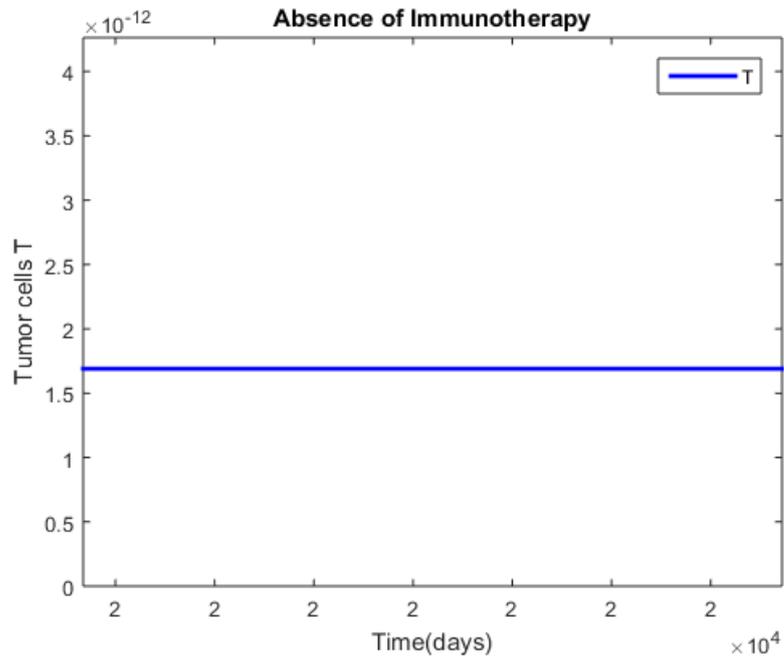


Fig. 5.22: Zoom into the behavior of tumor cells T after the simulation time in the absence of immunotherapy,.

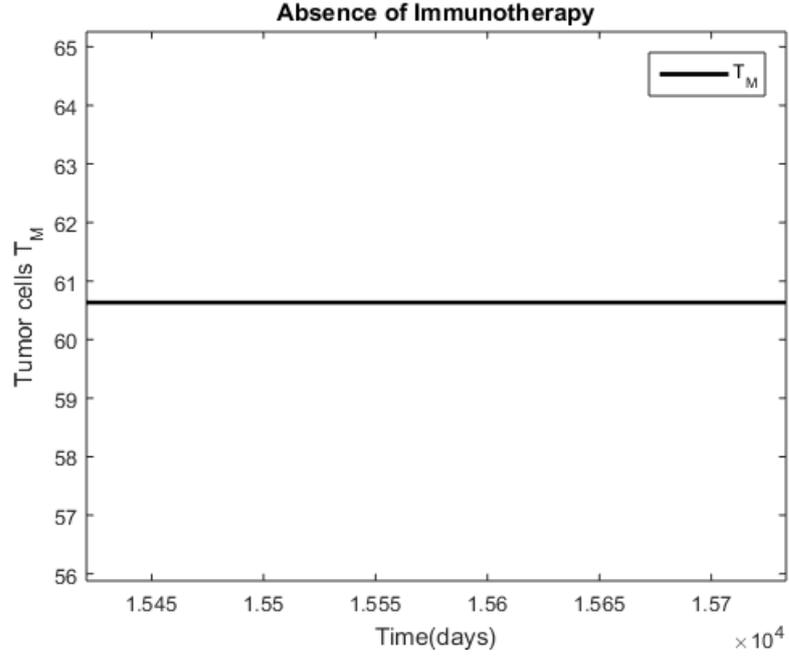


Fig. 5.23: Zoom into the behavior of tumor cells T_M after the simulation time in the absence of immunotherapy.

In the figure (5.18) and (5.19) it can be seen that the wild tumor cells and the mutated tumor cells have been controlled by the immune system. This happened because of the absence of resistant tumor cells which suppress the immune system. Through the figures (5.20), (5.21), (5.22),(5.23) the state $(T_1^*, T_{M_1}^*, E_1^*, I_1^*)$ for coexistence is stable with

$$1.5 \times 10^{-12} \leq T_1^* \leq 2 \times 10^{-12}, 60 \leq T_{M_1}^* \leq 61, 10^4 \leq E_1^* \leq 1.2 \times 10^4.$$

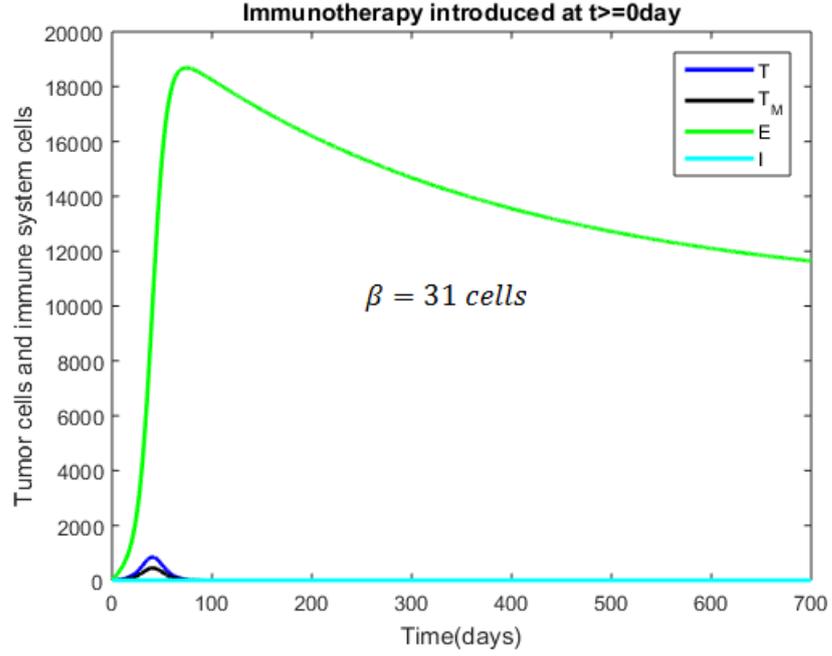


Fig. 5.24: The behavior of tumor cells and immune system cells in the presence of immunotherapy.

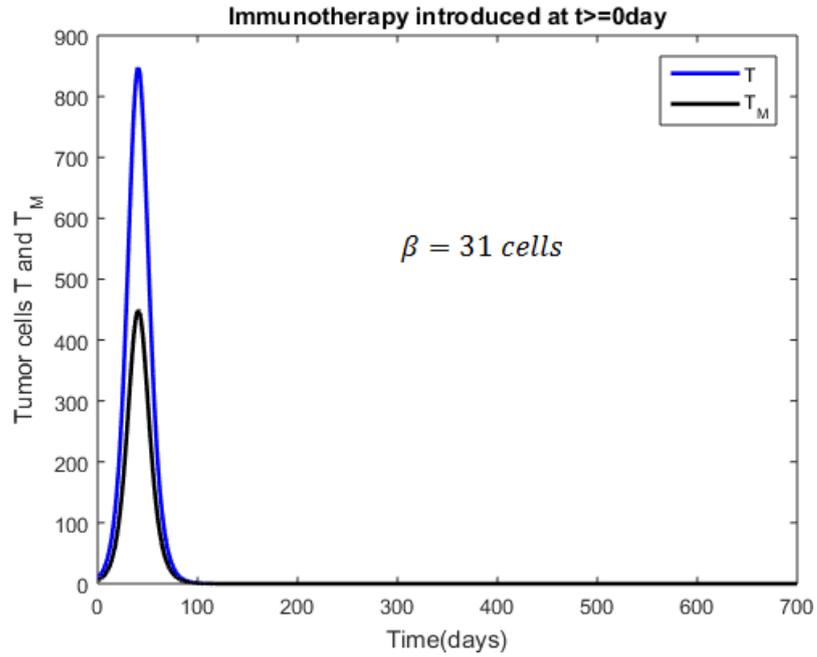


Fig. 5.25: The behavior of tumor cells T and T_M in the presence of immunotherapy.

The figures (5.24) and (5.25) show and support the stability of the state $S_{E_M^\#} = (0; 0; E^\#; 0)$ for $\beta > \frac{\mu_2 g_2 (r_T - \tau_2)}{a_1}$ and $\beta > \frac{r_M \mu_2 g_4}{a_2}$, since all the tumor cells are eliminated by the immunotherapy drug from 100th day. We can conclude that the

introduction of the immunotherapy drug at the beginning of the disease can save the patients when the system expresses only drug induced resistance.

5.4 When the system expresses neither intrinsic nor drug-induced resistance

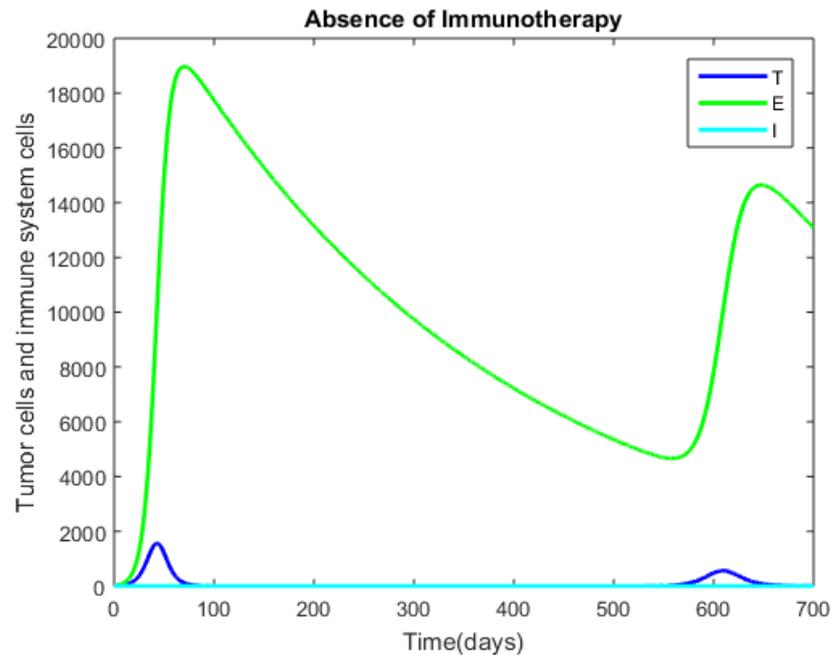


Fig. 5.26: The behavior of tumor cells and immune system cells in the absence of immunotherapy.

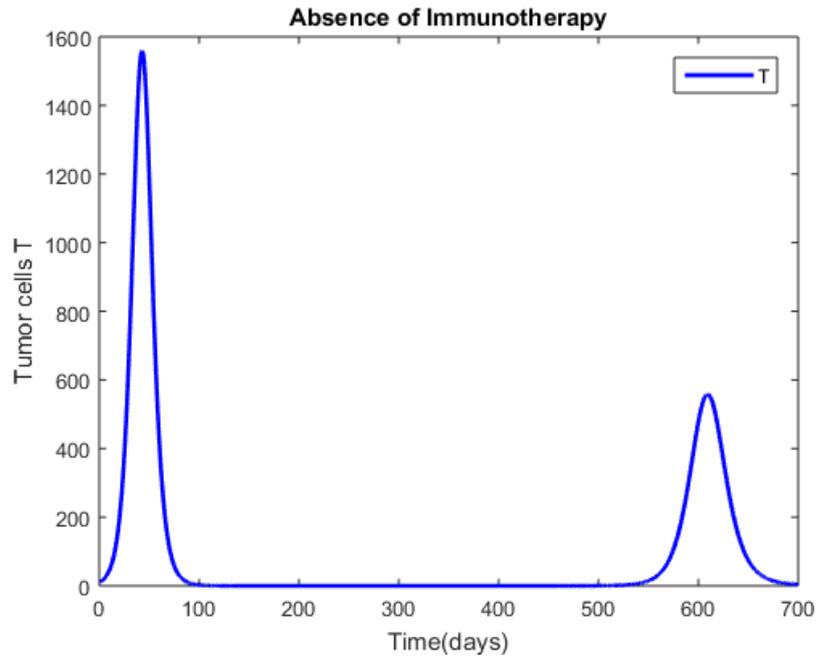


Fig. 5.27: The behavior of tumor cells T in the absence of immunotherapy.

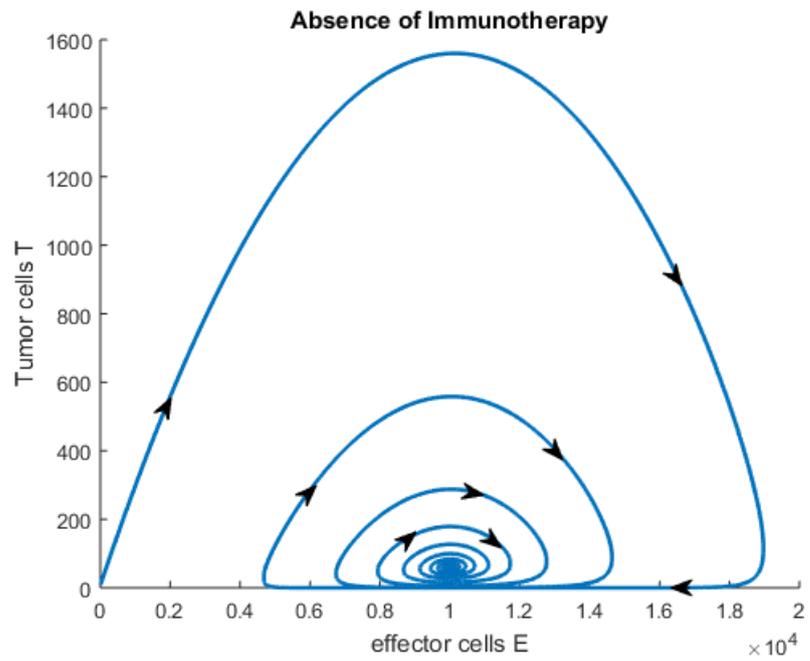


Fig. 5.28: Phase diagram relating T and E in the absence of immunotherapy.

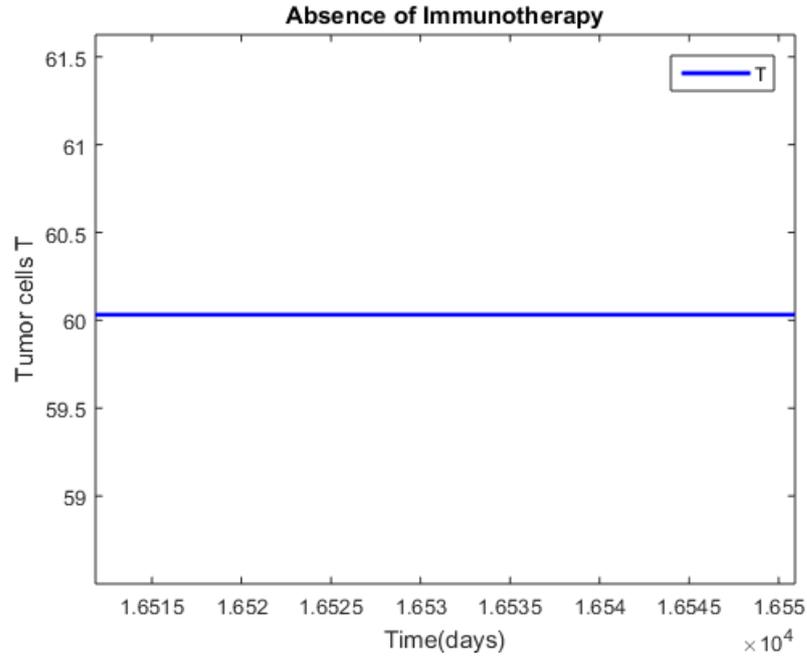


Fig. 5.29: Zoom into the behavior of tumor cells T after the simulation time in the absence of immunotherapy.

The wild tumor cells have been controlled by the immune system through the figures (5.26) and (5.27). Moreover the state (T_2^*, E_2^*, I_2^*) for coexistence is stable with $60 < T_2^* < 61$, $10^4 < E_2^* < 1.2 \times 10^4$ (see figures (5.28) and (5.29)).

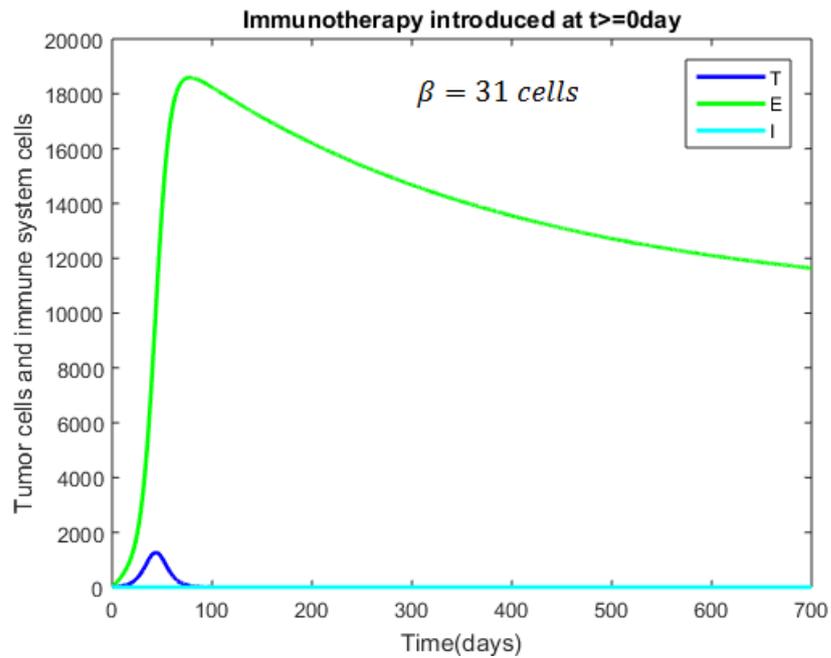


Fig. 5.30: The behavior of tumor cells and immune system cells in the presence of immunotherapy.

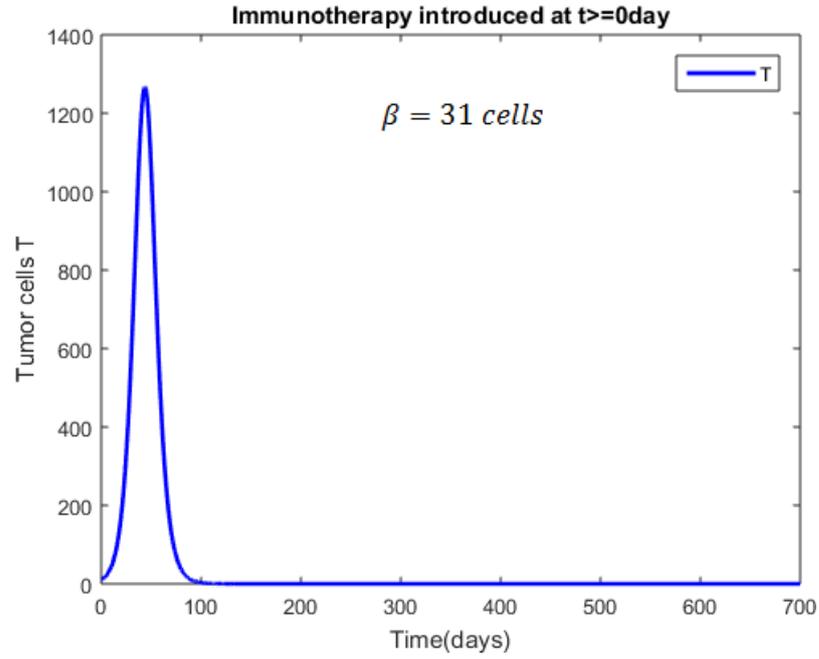


Fig. 5.31: The behavior of tumor cells T in the presence of immunotherapy.

Here also, all the tumor cells are eliminated by the immunotherapy drug from 100th day (see the figures (5.30) and (5.31)). So these figures show and support the global stability of the state $S_{E^\#} = (0; E^\#; 0)$ for $\beta > \frac{r_T \mu_2 g_2}{a_1}$. This implies that the introduction of the immunotherapy drug at the beginning of the disease can save the patients when the system expresses neither intrinsic nor drug-induced resistance.

Chapter 6

Conclusion and Recommendations

In this study, a model that take into account multi-mutation and drug resistance in a case of simple immune system and immuno-suppression caused by drug resistant tumor cells was proposed to understand the dynamic of wild tumor cells (T), drug resistant tumor cells (T_R), mutated tumor cells (T_M), normal cells (N) and immune system cells (E) and (I). A mathematical analysis of the corresponding tumor-immunotherapy model was carried out to show the existence, the uniqueness, and the boundedness of solutions. Also the stability of the non-tumor states, when the dynamical system expresses both intrinsic and drug induced resistance, only intrinsic resistance, only drug induced resistance, and neither intrinsic nor drug induced resistance was discussed in the absence and in the presence of the immunotherapy drug. Global stabilities are shown using nonstandard finite difference method. Then a detailed numerical analysis of the corresponding tumor-immunotherapy model was done to identify an effective treatment strategies in each case.

The findings of this study indicates that tumor cells can be eliminated under certain conditions (see, theorem 4.2 and theorem 4.3) in the presence of the immunotherapy, when the dynamical system expresses only drug induced resistance, and when it expresses neither intrinsic nor drug induced resistance.

Two treatment strategies were proposed when the dynamical system expresses both intrinsic and drug induced resistance (presence of wild tumor cells (T), drug resistant tumor cells (T_R) and mutated tumor cells (T_M)), or only intrinsic resistance (presence of wild tumor cells (T) and drug resistant tumor cells (T_R)): Periodic and constant

immunotherapy drug starting around $t = 500days$ and a specific chemotherapy drug on the resistant tumor cells, or constant immunotherapy drug at the early stage (around $t = 200days$) and a specific chemotherapy drug on the resistant tumor cells.

In the case where the dynamical system expresses only drug induced resistance (presence of wild tumor cells (T) and mutated tumor cells (T_M)) or neither intrinsic nor drug induced resistance (presence of wild tumor cells (T) only), the introduction of the immunotherapy drug at the beginning of the disease was observed to be effective in treating the cancer. Due to the high mortality rate of IL-2, we observed in the simulation results that the concentration of IL-2 is negligible.

Some open concerns include whether mutations occur at a constant rate or whether the rate may be affected by the immunotherapy drug. Also, one can study the behavior of each population of the above model, in the presence of only chemotherapy and/or in the presence of both immunotherapy and chemotherapy.

We recommend our mathematical model to bio-mathematicians because it plays an important role in predicting effective therapies. The treatment strategies we proposed are of importance in fight against cancer because they take into account multiple mutations of cancer cells, drug resistance and the state of the immune system. Finally, we recommend the nonstandard finite difference schemes we have constructed to analyze the stability of the endemic state of the model because there is no way and it is almost impossible to find the appropriate Lyapunov function for the global stability of the model.

References

- Anguelov, R., Lubuma, J.-S., & Shillor, M. (2011). Topological dynamic consistency of non-standard finite difference schemes for dynamical systems. *Journal of Difference Equations and Applications*, 17(12), 1769–1791.
- Campbell, S. L. & Haberman, R. (2011). *Introduction to differential equations with dynamical systems*. Princeton university press.
- de Pillis, L. G., Gu, W., & Radunskaya, A. E. (2006). Mixed immunotherapy and chemotherapy of tumors: modeling, applications and biological interpretations. *Journal of theoretical biology*, 238(4), 841–862.
- De Pillis, L. G. & Radunskaya, A. (2003). The dynamics of an optimally controlled tumor model: A case study. *Mathematical and Computer Modelling*, 37(11), 1221–1244.
- Dimitrov, D. T. & Kojouharov, H. V. (2007). Nonstandard numerical methods for a class of predator-prey models with predator interference. In *Proceedings of the 6th Mississippi State-UBA Conference on Differential Equations and Computational Simulations*, in: *Electronic Journal of Differential Equations Conference*, volume 15, (pp. 67–75).
- d’Onofrio, A. (2006). Tumor-immune system interaction: modeling the tumor-stimulated proliferation of effectors and immunotherapy. *Mathematical Models and Methods in Applied Sciences*, 16(08), 1375–1401.
- Feizabadi, M. S. (2017). Modeling multi-mutation and drug resistance: analysis of some case studies. *Theoretical Biology and Medical Modelling*, 14(1), 6.
- Feizabadi, M. S. & Witten, T. M. (2010). Chemotherapy in conjoint aging-tumor sys-

- tems: some simple models for addressing coupled aging-cancer dynamics. *Theoretical Biology and Medical Modelling*, 7(1), 21.
- Feizabadi, M. S. & Witten, T. M. (2011). Modeling the effects of a simple immune system and immunodeficiency on the dynamics of conjointly growing tumor and normal cells. *International journal of biological sciences*, 7(6), 700.
- Feizabadi, M. S. & Witten, T. M. (2015). Modeling drug resistance in a conjoint normal-tumor setting. *Theoretical Biology and Medical Modelling*, 12(1), 3.
- Gabriellini, G. (2012). Non standard finite difference scheme for mutualistic interaction description. *arXiv preprint arXiv:1201.0535*.
- Garba, S. M., Gumel, A. B., & Lubuma, J.-S. (2011). Dynamically-consistent non-standard finite difference method for an epidemic model. *Mathematical and Computer Modelling*, 53(1-2), 131–150.
- Gardner, S. N. (2000). A mechanistic, predictive model of dose-response curves for cell cycle phase-specific and-nonspecific drugs. *Cancer research*, 60(5), 1417–1425.
- Hirsch, M. W., Smale, s., & Devaney, R. L. (2012). *Differential equations, dynamical systems, and an introduction to chaos*. Academic press; Édition : 3 (26 avril 2012).
- Holohan, C., Van Schaeybroeck, S., Longley, D. B., & Johnston, P. G. (2013). Cancer drug resistance: an evolving paradigm. *Nature Reviews Cancer*, 13(10), 714.
- Kirschner, D. & Panetta, J. C. (1998). Modeling immunotherapy of the tumor-immune interaction. *Journal of mathematical biology*, 37(3), 235–252.
- Kirschner, D. & Tsygvintsev, A. (2009). On the global dynamics of a model for tumor immunotherapy. *Mathematical Biosciences and Engineering*, 6(3), 573–583.
- Kirschner, D. E. & Webb, G. (1998). Immunotherapy of hiv-1 infection. *Journal of Biological Systems*, 6(01), 71–83.

- Kovacs, J. A., Vogel, S., Albert, J. M., Falloon, J., Davey Jr, R. T., Walker, R. E., Polis, M. A., Spooner, K., Metcalf, J. A., Baseler, M., et al. (1996). Controlled trial of interleukin-2 infusions in patients infected with the human immunodeficiency virus. *New England Journal of Medicine*, *335*(18), 1350–1356.
- Mickens, R. E. (1994). *Nonstandard finite difference models of differential equations*. World Scientific Publishing Co. Pte. Ltd.
- Mickens, R. E. (2000). *Applications of nonstandard finite difference schemes*. World Scientific Publishing Co. Pte. Ltd.
- Mickens, R. E. (2002). Nonstandard finite difference schemes for differential equations. *The Journal of Difference Equations and Applications*, *8*(9), 823–847.
- Mickens, R. E. (2005). *Advances in the Applications of Nonstandard Finite Difference Schemes*. World Scientific Publishing Co. Pte. Ltd.
- Mickens, R. E. (2007a). Calculation of denominator functions for nonstandard finite difference schemes for differential equations satisfying a positivity condition. *Numerical Methods for Partial Differential Equations: An International Journal*, *23*(3), 672–691.
- Mickens, R. E. (2007b). Numerical integration of population models satisfying conservation laws: Nsfed methods. *Journal of Biological Dynamics*, *1*(4), 427–436.
- Mickens, R. E. & Washington, T. M. (2012). A note on an nsfd scheme for a mathematical model of respiratory virus transmission. *Journal of Difference Equations and Applications*, *18*(3), 525–529.
- Pazdur, R. (2004). *Cancer management: a multidisciplinary approach, medical, surgical & radiation oncology*. P R R Inc; 7th edition.
- Sadaie, M. R., Mayner, R., & Doniger, J. (2004). A novel approach to develop anti-hiv drugs: adapting non-nucleoside anticancer chemotherapeutics. *Antiviral research*, *61*(1), 1–18.

- Sameen, S., Barbuti, R., Milazzo, P., & Cerone, A. (2014). A mathematical model for assessing kras mutation effect on monoclonal antibody treatment of colorectal cancer. In *International Conference on Software Engineering and Formal Methods*, (pp. 243–258). Springer.
- Songolo, M. E. & Ramadhani, I. (2017). Analysis of a mathematical model for cancer treatment by the nonstandard finite difference methods. *Journal of Difference Equations and Applications*, *23*(7), 1222–1240.
- Togbenon, H. A., Kimathi, M. E., & Degla, G. A. (2018). Modeling multi-mutation and drug resistance: A case of immune-suppression. *Global Journal of Pure and Applied Mathematics*, *14*(5), 689–709.
- Witten, T. (1986). Modeling the dynamics of conjoint tumor-normal cell culture systems: Ii. further thoughts on the aging-cancer question. *Modeling of Biomedical Systems. North-Holland, Amsterdam: North Holland Publishing Co*, 65–70.
- Yaghoubi, A. & Najafi, H. S. (2015). Comparison between standard and non-standard finite difference methods for solving first and second order ordinary differential equations. *International Journal of Applied Mathematics Research*, *4*(2), 316.

Appendix

MATLAB Code for simulations

The system of ODE (4.2.1) is simulated in the following computer programme code developed using MATLAB software.

A.1 When the dynamical system expresses both intrinsic and drug-induced resistance

A.1.1 Absence of immunotherapy

```
function SEBID() clear all; clc;

global rT kT t2 a1 g2 rR kR t1 rM kM a2 g4 c u2 p1 g1 a b p2 g3 u3

rT=0.15; kT=1000000; t1=0.0001; t2=0.00001;a1=1.5; g2=100000; rR=0.015;kR=1000000;
rM=0.1515;kM=1000000;a2=1.5;g4=100000;c=0.5;u2=0.003;p1=0.1245;g1=20000000;a=0.0003;
p2=5;g3=30;u3=10;

options = odeset('RelTol',1e-4,'AbsTol',[1e-4 1e-4 1e-4 1e-4 1e-4]);
[T, X]= ode45(@odesys,[0 700],[10 4 5 10 5],options);

figure(1)

plot(T,X(:,1),'b',T,X(:,2),'r',T,X(:,3),'k',T,X(:,4),'g',T,X(:,5),'c','linewidth',2)

xlabel('Time (days)')

ylabel('Tumor cells and immune system cells')

title('Absence of Immunotherapy')

legend('T','T_R','T_M','E','I')

figure(2)

plot(T(1:floor(0.5*length(T))),X(1:floor(0.5*length(T)),1),'b',T(1:floor(0.5*length(T))),
X(1:floor(0.5*length(T)),2),'r',T(1:floor(0.5*length(T))),X(1:floor(0.5*length(T)),3),'k',
```

```

T(1:floor(0.5*length(T))),X(1:floor(0.5*length(T)),4),'g',T(1:floor(0.5*length(T))),
X(1:floor(0.5*length(T)),5),'c','linewidth',2)
xlabel('Time (days)')
ylabel('Tumor cells and immune system cells')
title('Absence of Immunotherapy')
legend('T','T_R','T_M','E','I')
figure(3)
plot(T,X(:,2),'r',T,X(:,4),'g',T,X(:,5),'c','linewidth',2)
xlabel('Time (days)')
ylabel('immune system cells and resistant tumor cells')
title('Absence of Immunotherapy')
legend('T_R','E','I')
figure(4)
plot(T,X(:,3),'k',T,X(:,4),'g',T,X(:,5),'c','linewidth',2)
xlabel('Time (days)')
ylabel('immune system cells and mutated tumor cells')
title('Absence of Immunotherapy')
legend('T_M','E','I')
figure(5)
plot(T,X(:,1),'b',T,X(:,3),'k','linewidth',2)
xlabel('Time (days)')
ylabel('Tumor cells T and T_M')
title('Absence of Immunotherapy')
legend('T','T_M')
figure(6)
plot3(X(:,4),X(:,1),T,'linewidth',2);view(2)
xlabel('effector cells E')
ylabel('Tumor cells T')
figure(7)

```

```

plot3(X(1:floor(0.5*length(T)),4),X(1:floor(0.5*length(T)),3),T(1:floor(0.5*length(T))),
'linewidth',2);view(2)
xlabel('effector cells E')
ylabel('Tumor cells T_M')
figure(8)
plot3(X(:,4),X(:,2),T,'linewidth',2);view(2)
xlabel('effector cells E')
ylabel('Tumor cells T_R')
function dx=odesys(t,x)
dx=zeros(5,1);
boost1=find(t>=200);b=zeros(length(t));b(boost1)=000;
dx(1)=rT*x(1)*(1-(x(1)+x(2)+x(3))/kT)-(t1+t2)*x(1)-a1*x(4)*x(1)/(g2+x(1));
dx(2)=rR*x(2)*(1-(x(1)+x(2)+x(3))/kR)+t1*x(1);
dx(3)=rM*x(3)*(1-(x(1)+x(2)+x(3))/kM)+t2*x(1)-a2*x(4)*x(3)/(g4+x(3));
dx(4)=c*(x(1)+x(2)+x(3))-u2*x(4)+p1*x(4)*x(5)/(g1+x(5))-a*x(2)*x(4)+b;
dx(5)=p2*x(4)*((x(1)+x(2)+x(3))/(g3+x(1)+x(2)+x(3)))-u3*x(5);
end
end

```

A.1.2 Immunotherapy introduced at $t \geq 500days$

```

function SEBID() clear all; clc;
global rT kT t2 a1 g2 rR kR t1 rM kM a2 g4 c u2 p1 g1 a b p2 g3 u3
rT=0.15; kT=1000000; t1=0.0001; t2=0.00001;a1=1.5; g2=100000; rR=0.015;kR=1000000;
rM=0.1515;kM=1000000;a2=1.5;g4=100000;c=0.5;u2=0.003;p1=0.1245;g1=20000000;a=0.0003;
p2=5;g3=30;u3=10;
options = odeset('RelTol',1e-4,'AbsTol',[1e-4 1e-4 1e-4 1e-4 1e-4]);
[T, X]= ode45(@odesys,[0 700],[10 4 5 10 5],options);
figure(1)

```

```

plot(T,X(:,1),'b',T,X(:,2),'r',T,X(:,3),'k',T,X(:,4),'g',T,X(:,5),'c','linewidth',2)
xlabel('Time (days)')
ylabel('Tumor cells and immune system cells')
title('Immunotherapy introduced at t>=500days')
legend('T','T_R','T_M','E','I')
figure(2)
plot(T(1:floor(0.5*length(T))),X(1:floor(0.5*length(T)),1),'b',T(1:floor(0.5*length(T))),
X(1:floor(0.5*length(T)),2),'r',T(1:floor(0.5*length(T))),X(1:floor(0.5*length(T)),3),'k',
T(1:floor(0.5*length(T))),X(1:floor(0.5*length(T)),4),'g',T(1:floor(0.5*length(T))),
X(1:floor(0.5*length(T)),5),'c','linewidth',2)
xlabel('Time (days)')
ylabel('Tumor cells and immune system cells')
title('Immunotherapy introduced at t>=500days') legend('T','T_R','T_M','E','I')
figure(3)
plot(T,X(:,2),'r',T,X(:,4),'g',T,X(:,5),'c','linewidth',2)
xlabel('Time (days)')
ylabel('immune system cells and resistant tumor cells')
title('Immunotherapy introduced at t>=500days') legend('T_R','E','I')
figure(4)
plot(T,X(:,3),'k',T,X(:,4),'g',T,X(:,5),'c','linewidth',2)
xlabel('Time (days)')
ylabel('immune system cells and mutated tumor cells')
title('Immunotherapy introduced at t>=500days') legend('T_M','E','I')
figure(5)
plot(T,X(:,1),'b',T,X(:,3),'k','linewidth',2)
xlabel('Time (days)')
ylabel('Tumor cells T and T_M')
title('Fig 1d:Immunotherapy introduced at t>=200days') legend('T','T_M')
figure(6)

```

```

plot3(X(:,4),X(:,1),T,'linewidth',2);view(2)
xlabel('effector cells E')
ylabel('Tumor cells T')
figure(7)
plot3(X(1:floor(0.5*length(T)),4),X(1:floor(0.5*length(T)),3),T(1:floor(0.5*length(T))),
'linewidth',2);view(2)
xlabel('effector cells E')
ylabel('Tumor cells T_M')
figure(8)
plot3(X(:,4),X(:,2),T,'linewidth',2);view(2)
xlabel('effector cells E')
ylabel('Tumor cells T_R')
function dx=odesys(t,x)
dx=zeros(5,1);
boost1=find(t>=500);b=zeros(length(t));b(boost1)=75000;
dx(1)=rT*x(1)*(1-(x(1)+x(2)+x(3))/kT)-(t1+t2)*x(1)-a1*x(4)*x(1)/(g2+x(1));
dx(2)=rR*x(2)*(1-(x(1)+x(2)+x(3))/kR)+t1*x(1);
dx(3)=rM*x(3)*(1-(x(1)+x(2)+x(3))/kM)+t2*x(1)-a2*x(4)*x(3)/(g4+x(3));
dx(4)=c*(x(1)+x(2)+x(3))-u2*x(4)+p1*x(4)*x(5)/(g1+x(5))-a*x(2)*x(4)+b;
dx(5)=p2*x(4)*((x(1)+x(2)+x(3))/(g3+x(1)+x(2)+x(3)))-u3*x(5);
end
end

```

A.2 When the dynamical system expresses only intrinsic resistance

A.2.1 Absence of immunotherapy

```
function SEOI()
clear all; clc;

global rT kT a1 g2 rR kR t1 c u2 p1 g1 a b p2 g3 u3
rT=0.15;kT=1000000;t1=0.0001;a1=1.5;g2=100000;rR=0.015;kR=1000000;c=0.5;
u2=0.003;p1=0.1245;g1=20000000;a=0.0003;p2=5;g3=30;u3=10;
options = odeset('RelTol',1e-4,'AbsTol',[1e-4 1e-4 1e-4 1e-4]);
[T, X]= ode45(@odesys,[0 10000],[10 5 10 5],options);
figure(1)
plot(T,X(:,1),'b',T,X(:,2),'r',T,X(:,3),'g',T,X(:,4),'c','linewidth',2)
xlabel('Time(days)')
ylabel('Tumor cells and immune system cells')
title('Absence of Immunotherapy')
legend('T','T_R','E','I')
figure(2)
plot(T(1:floor(0.4*length(T))),X(1:floor(0.4*length(T)),1),'b',T(1:floor(0.4*length(T))),
X(1:floor(0.4*length(T)),2),'r',T(1:floor(0.4*length(T))),X(1:floor(0.4*length(T)),3),
'g',T(1:floor(0.4*length(T))),X(1:floor(0.4*length(T)),4),'c','linewidth',2)
xlabel('Time(days)')
ylabel('Tumor cells and immune system cells')
title('Absence of Immunotherapy')
legend('T','T_R','E','I')
figure(3)
plot(T,X(:,2),'r',T,X(:,3),'g',T,X(:,4),'c','linewidth',2)
xlabel('Time(days)')
```

```
ylabel('immune system cells and resistant tumor cells')
```

```
title('Absence of Immunotherapy')
```

```
legend('T_R','E','I')
```

```
figure(4)
```

```
plot(T,X(:,1),'b','linewidth',2)
```

```
xlabel('Time(days)')
```

```
ylabel('Tumor cells T')
```

```
title('Absence of immunotherapy')
```

```
legend('T')
```

```
figure(5)
```

```
plot3(X(:,3),X(:,1),T,'linewidth',2);view(2)
```

```
xlabel('effector cells E')
```

```
title('Absence of immunotherapy')
```

```
ylabel('Tumor cells T')
```

```
figure(6)
```

```
plot3(X(:,3),X(:,2),T,'linewidth',2);view(2)
```

```
xlabel('effector cells E')
```

```
ylabel('Tumor cells T_R')
```

```
function dx=odesys(t,x)
dx=zeros(4,1);
boost1=find(t>=200);b=zeros(length(t));b(boost1)=0000;
dx(1)=rT*x(1)*(1-(x(1)+x(2))/kT)-t1*x(1)-a1*x(3)*x(1)/(g2+x(1));
dx(2)=rR*x(2)*(1-(x(1)+x(2))/kR)+t1*x(1);
dx(3)=c*(x(1)+x(2))-u2*x(3)+p1*x(3)*x(4)/(g1+x(4))-a*x(2)*x(3)+b;
dx(4)=p2*x(4)*(x(1)+x(2))/(g3+x(1)+x(2))-u3*x(4);
end
end
```

A.2.2 Immunotherapy introduced at $t \geq 500$ days

```
function SEOI()
clear all; clc;
global rT kT a1 g2 rR kR t1 c u2 p1 g1 a b p2 g3 u3
rT=0.15;kT=1000000;t1=0.0001;a1=1.5;g2=100000;rR=0.015;kR=1000000;c=0.5;
u2=0.003;p1=0.1245;g1=20000000;a=0.0003;p2=5;g3=30;u3=10;

options = odeset('RelTol',1e-4,'AbsTol',[1e-4 1e-4 1e-4 1e-4]);
[T, X]= ode45(@odesys,[0 10000],[10 5 10 5],options);
figure(1)
plot(T,X(:,1),'b',T,X(:,2),'r',T,X(:,3),'g',T,X(:,4),'c','linewidth',2)
xlabel('Time(days)')
ylabel('Tumor cells and immune system cells')
title('Immunotherapy introduced at t>=500days')
legend('T','T_R','E','I')
figure(2)
plot(T(1:floor(0.4*length(T))),X(1:floor(0.4*length(T)),1),'b',T(1:floor(0.4*length(T))),
X(1:floor(0.4*length(T)),2),'r',T(1:floor(0.4*length(T))),X(1:floor(0.4*length(T)),3),
'g',T(1:floor(0.4*length(T))),X(1:floor(0.4*length(T)),4),'c','linewidth',2)
xlabel('Time(days)')
ylabel('Tumor cells and immune system cells')
title('Immunotherapy introduced at t>=500days')
legend('T','T_R','E','I')
figure(3)
plot(T,X(:,2),'r',T,X(:,3),'g',T,X(:,4),'c','linewidth',2)
xlabel('Time(days)')
ylabel('immune system cells and resistant tumor cells')
title('Immunotherapy introduced at t>=500days')
```

```

legend('T_R','E','I')
figure(4)
plot(T,X(:,1),'b','linewidth',2)
xlabel('Time(days)')
ylabel('Tumor cells T')
title('Immunotherapy introduced at t>=200days')

```

```

legend('T')
figure(5)
plot3(X(:,3),X(:,1),T,'linewidth',2);view(2)
xlabel('effector cells E')
ylabel('Tumor cells T')

```

```

figure(6)
plot3(X(:,3),X(:,2),T,'linewidth',2);view(2)
xlabel('effector cells E')
ylabel('Tumor cells T-R')

```

```

function dx=odesys(t,x)
dx=zeros(4,1);
boost1=find(t>=500);b=zeros(length(t));b(boost1)=60000;
dx(1)=rT*x(1)*(1-(x(1)+x(2))/kT)-t1*x(1)-a1*x(3)*x(1)/(g2+x(1));
dx(2)=rR*x(2)*(1-(x(1)+x(2))/kR)+t1*x(1);
dx(3)=c*(x(1)+x(2))-u2*x(3)+p1*x(3)*x(4)/(g1+x(4))-a*x(2)*x(3)+b;
dx(4)=p2*x(4)*(x(1)+x(2))/(g3+x(1)+x(2))-u3*x(4);
end
end

```

A.3 When the dynamical system expresses only drug-induced resistance

A.3.1 Absence of immunotherapy

```
function SEOD()
clear all; clc;

global rT kT t2 a1 g2 rM kM a2 g4 c u2 p1 g1 b p2 g3 u3
rT=0.15;kT=1000000;t2=0.00001;a1=1.5;g2=100000;rM=0.1515;kM=1000000;
a2=1.5;g4=100000;c=0.5;u2=0.003;p1=0.1245;g1=20000000;p2=5;g3=30;u3=10;
options = odeset('RelTol',1e-4,'AbsTol',[1e-4 1e-4 1e-4 1e-4]);
[T, X]= ode45(@odesys,[0 10000],[10 5 10 5],options);
figure(1)
plot(T,X(:,1),'b',T,X(:,2),'k',T,X(:,3),'g',T,X(:,4),'c','linewidth',2)
xlabel('Time(days)')
ylabel('Tumor cells and immune system cells')
title('Absence of immunotherapy')
legend('T','T_M','E','I')
figure(2)
plot(T,X(:,3),'g',T,X(:,4),'c','linewidth',2)
xlabel('Time(days)')
ylabel('immune system cells')
title('Absence of immunotherapy')
legend('E','I')
figure(3)
plot(T,X(:,1),'b',T,X(:,2),'k','linewidth',2)
xlabel('Time(days)')
ylabel('Tumor cells T and T_M')
title('Absence of immunotherapy')
```

```

legend('T','T_M')
figure(4)
plot3(X(:,3),X(:,1),T,'linewidth',2);view(2)
xlabel('effector cells E')
title('Absence of Immunotherapy')
ylabel('Tumor cells T')
figure(5)
plot3(X(:,3),X(:,2),T,'linewidth',2);view(2)
xlabel('effector cells E')
title('Absence of Immunotherapy')
ylabel('Tumor cells T_M')
figure(6)
plot(T,X(:,1),'b','linewidth',2)
xlabel('Time(days)')
ylabel('Tumor cells T')
title('Absence of Immunotherapy')
legend('T')
figure(7)
plot(T,X(:,2),'k','linewidth',2)
xlabel('Time(days)')
ylabel('Tumor cells T_M')
title('Absence of Immunotherapy')
legend('T_M')
figure(8)
plot(T,X(:,4),'c','linewidth',2)
xlabel('Time(days)')
ylabel('concentration of IL-2')
legend('I')
figure(9)

```

```

plot3(X(:,3),X(:,4),T,'linewidth',2)
xlabel('effector cells E')
ylabel('IL-2')

function dx=odesys(t,x)
dx=zeros(4,1);
boost1=find(t>=0);b=zeros(length(t));b(boost1)=0;
dx(1)=rT*x(1)*(1-(x(1)+x(2))/kT)-t2*x(1)-a1*x(3)*x(1)/(g2+x(1));
dx(2)=rM*x(2)*(1-(x(1)+x(2))/kM)+t2*x(1)-a2*x(3)*x(2)/(g4+x(2));
dx(3)=c*(x(1)+x(2))-u2*x(3)+p1*x(3)*x(4)/(g1+x(4))+b;
dx(4)=p2*x(4)*(x(1)+x(2))/(g3+x(1)+x(2))-u3*x(4);
end
end

```

A.3.2 Immunotherapy introduced at $t \geq 0$ days

```

function SEOD()
clear all; clc;
global rT kT t2 a1 g2 rM kM a2 g4 c u2 p1 g1 b p2 g3 u3
rT=0.15;kT=1000000;t2=0.00001;a1=1.5;g2=100000;rM=0.1515;kM=1000000;
a2=1.5;g4=100000;c=0.5;u2=0.003;p1=0.1245;g1=20000000;p2=5;g3=30;u3=10;

options = odeset('RelTol',1e-4,'AbsTol',[1e-4 1e-4 1e-4 1e-4]);
[T, X]= ode45(@odesys,[0 10000],[10 5 10 5],options);
X(:,1)
figure(1)
plot(T,X(:,1),'b',T,X(:,2),'k',T,X(:,3),'g',T,X(:,4),'c','linewidth',2)
xlabel('Time(days)')
ylabel('Tumor cells and immune system cells')

```

```

title('Immunotherapy introduced at t>=0day')
legend('T','T_M','E','I')
figure(2)
plot(T,X(:,3),'g',T,X(:,4),'c','linewidth',2)
xlabel('Time(days)')
ylabel('immune system cells')
title('Immunotherapy introduced at t>=0day')
legend('E','I')
figure(3)
plot(T,X(:,1),'b',T,X(:,2),'k','linewidth',2)
xlabel('Time(days)')
ylabel('Tumor cells T and T_M')
title('Immunotherapy introduced at t>=0day')
legend('T','T_M')
figure(4)
plot3(X(:,3),X(:,1),T,'linewidth',2);view(2)
xlabel('effector cells E')
title('Immunotherapy introduced at t>=0day')
ylabel('Tumor cells T')
figure(5)
plot3(X(:,3),X(:,2),T,'linewidth',2);view(2)
xlabel('effector cells E')
title('Immunotherapy introduced at t>=0day')
ylabel('Tumor cells T_M')
figure(6)
plot(T,X(:,1),'b','linewidth',2)
xlabel('Time(days)')
ylabel('Tumor cells T')
title('Immunotherapy introduced at t>=0day')

```

```

legend('T')
figure(7)
plot(T,X(:,2),'k','linewidth',2)
xlabel('Time(days)')
ylabel('Tumor cells  $T_M$ ')
title('Immunotherapy introduced at  $t \geq 0$  day')
legend('T_M')

```

```

function dx=odesys(t,x)
dx=zeros(4,1);
boost1=find(t>=0);b=zeros(length(t));b(boost1)=31;
dx(1)=rT*x(1)*(1-(x(1)+x(2))/kT)-t2*x(1)-a1*x(3)*x(1)/(g2+x(1));
dx(2)=rM*x(2)*(1-(x(1)+x(2))/kM)+t2*x(1)-a2*x(3)*x(2)/(g4+x(2));
dx(3)=c*(x(1)+x(2))-u2*x(3)+p1*x(3)*x(4)/(g1+x(4))+b;
dx(4)=p2*x(4)*(x(1)+x(2))/(g3+x(1)+x(2))-u3*x(4);
end
end

```

A.4 When the dynamical system expresses neither intrinsic nor drug-induced resistance

A.4.1 Absence of immunotherapy

```

function Sno()
clear all; clc;
global rT kT a1 g2 c u2 p1 g1 b p2 g3 u3
rT=0.15;kT=1000000;a1=1.5;g2=100000;c=0.5;u2=0.003;p1=0.1245;g1=20000000;p2=5;g3=30;
u3=10;
options = odeset('RelTol',1e-4,'AbsTol',[1e-4 1e-4 1e-4]);
[T, X]= ode45(@odesys,[0 700],[10 10 4],options);

```

```

figure (1)
plot(T,X(:,1),'b',T,X(:,2),'g',T,X(:,3),'c','linewidth',2)
xlabel('Time(days)')
ylabel('Tumor cells and immune system cells')
title('Absence of Immunotherapy')
legend('T','E','I')

```

```

figure(2)
plot(T,X(:,2),'g',T,X(:,3),'c','linewidth',2)
xlabel('Time(days)')
ylabel('immune system cells')
title('Absence of Immunotherapy')
legend('E','I')

```

```

figure(3)
plot(T,X(:,1),'b','linewidth',2)
xlabel('Time(days)')
ylabel('Tumor cells T')
title('Absence of Immunotherapy')
legend('T')

```

```

figure(4)
plot3(X(:,2),X(:,1),T,'linewidth',2);view(2)
xlabel('effector cells E')
title('Absence of Immunotherapy')
ylabel('Tumor cells T')

```

```

function dx=odesys(t,x)
dx=zeros(3,1);
boost1=find(t>=0);b=zeros(length(t));b(boost1)=0;
dx(1)=rT*x(1)*(1-(x(1))/kT)-a1*x(2)*x(1)/(g2+x(1));
dx(2)=c*x(1)-u2*x(2)+p1*x(2)*x(3)/(g1+x(3))+b;

```

```

dx(3)=p2*x(3)*x(1)/(g3+x(1))-u3*x(3);
end
end

```

A.4.2 Immunotherapy introduced at $t \geq 0$ days

```

function Sno()
clear all; clc;
global rT kT a1 g2 c u2 p1 g1 b p2 g3 u3
rT=0.15;kT=1000000;a1=1.5;g2=100000;c=0.5;u2=0.003;p1=0.1245;g1=20000000;p2=5;g3=30;
u3=10;
options = odeset('RelTol',1e-4,'AbsTol',[1e-4 1e-4 1e-4]);
[T, X]= ode45(@odesys,[0 700],[10 10 4],options);
figure (1)
plot(T,X(:,1),'b',T,X(:,2),'g',T,X(:,3),'c','linewidth',2)
xlabel('Time(days)')
ylabel('Tumor cells and immune system cells')
title('Immunotherapy introduced at t>=0day')
legend('T','E','I')
figure(2)
plot(T,X(:,2),'g',T,X(:,3),'c','linewidth',2)
xlabel('Time(days)')
ylabel('immune system cells')
title('Immunotherapy introduced at t>=0day')
legend('E','I')
figure(3)
plot(T,X(:,1),'b','linewidth',2)
xlabel('Time(days)')
ylabel('Tumor cells T')
title('Immunotherapy introduced at t>=day')

```

```

legend('T')
figure(4)
plot3(X(:,2),X(:,1),T,'linewidth',2);view(2)
xlabel('effector cells E')
title('Immunotherapy introduced at t>=0day')
ylabel('Tumor cells T')

```

```

function dx=odesys(t,x)
dx=zeros(3,1);
boost1=find(t>=0);b=zeros(length(t));b(boost1)=31;
dx(1)=rT*x(1)*(1-(x(1))/kT)-a1*x(2)*x(1)/(g2+x(1));
dx(2)=c*x(1)-u2*x(2)+p1*x(2)*x(3)/(g1+x(3))+b;
dx(3)=p2*x(3)*x(1)/(g3+x(1))-u3*x(3);
end
end

```