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Master's Thesis

Dynamics of Tumor-Immune Systems

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I hereby declare that this thesis is entirely the result of my own work except where otherwise indicated. I have only used the resources given in the list of references.

Garching, September 9, 2023 Yifan Chen

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Thank you!

Abstract

The use of mathematical models in the field of tumor-immune interactions offers an analytical framework, which allows the study of specific questions related to tumor-immune dynamics and potential approaches for tumor treatment. This thesis deals with various mathematical approaches to describe tumor-immune interactions using systems of ordinary and delay differential equations.

Zusammenfassung

Die Verwendung mathematischer Modelle bei der Untersuchung von Tumor-Immun Interaktionen bietet einen analytischen Rahmen, welcher die Untersuchung spezifischer Fragen im Zusammenhang mit der Tumor-Immun Dynamik und möglicher Ansätze für die Tumortherapie erlaubt. Die vorliegende Arbeit befasst sich mit verschiedenen mathematischen Ansätzen zur Beschreibung von Tumor-Immun Interaktionen mithilfe von Systemen von gewöhnlichen und retardierten Differentialgleichungen.

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1 Introduction

Cancer is a group of diseases which are characterized by the uncontrolled proliferation of abnormal cells. They have the ability to exceed their typical boundaries to infiltrate neighboring regions and propagate to other organs. According to the WHO, cancer stands as the world's second leading cause of death, which is responsible for approximately 9.6 millions of deaths, constituting one out of every six deaths in 2018. While lung, prostate, colorectal, stomach, and liver cancer are the most common cancer types among men, women most commonly experience breast, colorectal, lung, cervical, and thyroid cancer types [WHO].

There is biological evidence that supports the role of the immune system in tumorgenesis. In fact, the immune system reacts to a growing tumor in a cell-mediated fashion, which is primarily driven by cytotoxic T cells and natural killer cells. It is observed that these immune cells are able to actively attack and eliminate tumor cells. However, there are still many important questions which remain unanswered, such as which elements of the immune system hold significant importance in responding to immunotherapy and how the strength of an individual's immune response effects the outcome of tumor progression. The application of mathematical models to describe the tumor-immune systems provides an analytical framework to address and understand such questions. Over the past decades, many researchers have developed different mathematical models to understand various aspects of the tumor-immune system. For an overview, see for example [EKM14; BP00].

This thesis begins with a short description of the biological background of tumor progression as well as the role of the immune system, including the aspect of T cell exhaustion and different countermeasures developed by tumor cells in the interaction with immune cells. After that, the third chapter gives a sketch of the mathematical background consisting of formal definitions of dynamical systems, ordinary differential equations, and delay differential equations as well as relevant properties of such systems, which will be used in the later chapters. As all mathematical models discussed in this work are based on the model in [Kuz+94], chapter four summarizes their relevant results, which serve as a basis for the rest of the chapters. The subsequent two chapters five and six modify the model in [Kuz+94] by introducing other facets of the tumor-immune interactions, which establish similar phenomena as the original model, while enabling more flexibility in the dynamics. A detailed analysis of the model is also conducted in chapter five, where the model is further modified and extended into a delay model, presented in chapter seven.

In the last chapter, we conclude the work by discussing how to further extend the considered models.

2 Biological background

Most cancers manifest in tumors, which are not foreign bodies, but masses derived from normal tissues. Oncologists usually reserve the word cancer for malignant cells that have a substantial potential of threatening the life of the individual carrying them. However, in the scope of this thesis, we use cancer more loosely to include all types of abnormal growths of cells and particularly, it is used synonymously with tumor. The following chapter provides some background on the immune system and the development of tumors and builds on publications in [Wei14; SOS11; LS16; CM13; Jia+21]. Following a brief overview of tumor formation and the functionality of the immune system in presence of foreign substance, we briefly summarize the important aspects of cancer immunoediting, immune escape mechanisms and, lastly, T cell exhaustion in the tumor microenvironment.

The formation of a tumor is a complex process, which usually progresses over a long period of time and consists of multiple stages. The term *tumor progression* is used to describe the process through which normal cells evolve into cells with increasingly neoplastic phenotypes. This process is driven by a sequence of mutations and epigenetic modifications of the cancer cells' genome that affect so called proto-oncogenes and tumor suppressor genes. In the early stage of tumor progression, cancer cells multiply uncontrollably near the site where their ancestor cells first began to proliferate, resulting in a *primary tumor* mass. Keeping in mind that a cubic centimeter of tissue contains approximately 10^9 cells, tumors may often reach a size of 10^{10} or 10^{11} cells before they become detectable. Cancer cells that leave the primary tumor mass to seek out new sites throughout the body are able to form new colonies are referred to as *metastases*. In the scope of this work, we will focus on the development of a primary tumor mass and refer to the environment around it as the *tumor microenvironment* (TME).

Besides each cell's internal mechanisms to prevent it from transforming into a cancerous cell, the immune system acts as another line of defence. It consists of the innate and the adaptive immune system and aims to recognize and eliminate foreign agents from the body. It also detects and targets deregulated tissue cells while preventing damage to the body. Immunocytes, which express Fc receptors, such as macrophages and natural killer cells (NK cells), belong to the innate immunity. They have the innate ability to recognize cells that should be destroyed.

With few exceptions, human cells routinely present oligopeptide fragments of the proteins they produce on their cell surface using major histocompatibility complex

class I molecules (MHC class I molecules). Professional antigen-presenting cells, such as macrophages and dendritic cells, use MHC class II molecules to present fragments collected from tissue environments to T lymphocytes. These oligopeptide fragments represent the antigens, which are recognized by T cell receptors of helper and cytotoxic T cells. T lymphocytes are part of the adaptive immunity. They develop the ability to recognize antigenic targets through the display of T cell receptors. These T lymphocytes largely consist of cytotoxic T cells (cytotoxic T lymphocytes, CTLs, T_C's, or $CD8^+$ cells), helper T cells (T_H's), and regulatory T cells (T_{reg}'s). The helper T cells aid cytotoxic T cells to develop the ability to eliminate cells that need to be destroyed, while the regulatory T cells are responsible for the suppression of helper T cells and cytotoxic T cells to prevent the development of autoimmune attacks on the body's own tissue. A simplified illustration of this process is shown in Figure 2.1, which is created with [Bio] on the basis of [cf. Wei14, Figure 15.11].

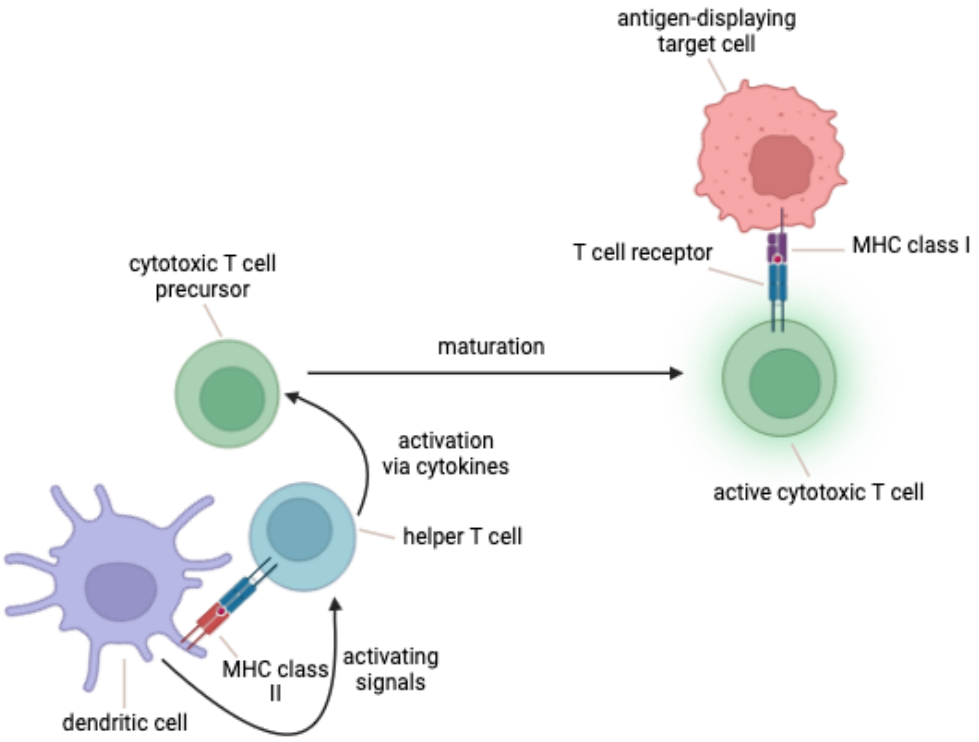


Figure 2.1: Activation of T cells by dendritic cells and killing of antigen-expressing target cells by cytotoxic T cells.

In general, we refer to immune cells with the ability to kill as *effector cells*. Elimination of tumor cells by effector cells can happen through direct damage of the tumor cell's membrane via the protein perforin (PRF1), or by the initiation of apoptosis through the Fas ligand (FasL) molecules. These proteins are produced

by effector cells in a limited amount leading to the decrease of their ability to kill after each interaction.

In order to initiate a priming and an activation of tumor-specific T cells, tumor cells must express immunogenic tumor antigens, which are essential to provoke an adaptive immune response. Cancer cells are derived from normal cells and are, in many respects, indistinguishable from the body's normally functioning cells. However, certain tumor-associated antigens (TAAs) may nevertheless induce an immune response, because they are expressed at aberrant level or because they are usually displayed only in certain specific circumstances, e.g. in embryos, which is why tolerance towards these cellular antigens has not developed. Killing of the cancer cells releases additional TAAs, which are able to recruit more T cells.

In 2001-2002 a hypothesis was proposed to describe the process, where the immune system not only protects against tumor formation, but also stimulates the development of cancer cells that are capable of escaping immune control. This phenomenon is called immunoediting and consists of three component phases – elimination, equilibrium, and escape. Experimental studies have demonstrated that the immune system is able to identify and destroy growing cancers (*elimination phase*), sustain tumor cells in a state of immune-induced growth dormancy (*equilibrium phase*), and shape or decrease the immunogenicity of tumor cells, resulting in "altered"/"edited" tumor cells that are capable of evading immune regulation (*escape phase*).

2.1 The three E's of cancer immunoediting

Elimination. The elimination phase is also known as cancer immunosurveillance. It involves both the innate and the adaptive immune system identifying and eradicating an evolving tumor prior to its clinical appearance. It has been observed that the activation of innate immunity can protect against tumor development, however, in most scenarios, it is generally the engagement of the adaptive immune system that yields effective cancer immunosurveillance responses. In case of a successful tumor cell destruction, the elimination phase signifies an endpoint of the cancer immunoediting process.

Equilibrium. When uncommon tumor cell variants survive the elimination phase, they may enter the so-called equilibrium phase, during which the adaptive immune system hinders the proliferation of tumor cells while shaping the immunogenicity of the tumor cells. In particular, the immune system is no longer capable of eliminating remaining tumor cells but still manages to maintain them in an equilibrium state called immune-mediated dormancy. Many researchers, including Schreiber, Old, and Smyth, regard this phase to be the longest phase of the cancer immunoediting process as it can extend throughout the lifetime of the host.

Escape. During this stage of the cancer immunoediting process, "altered" cancer cells begin to grow unhindered due to immune escape mechanisms including reduced immune recognition of the tumor cells and immune suppression by the tumor cells. In the next section, we will discuss different immune escape mechanisms leading to "altered" cancer cells.

2.2 Immune escape mechanisms

To avoid immune-mediated elimination, antigenic tumor cells can escape elimination by decreasing their immunogenicity using various mechanisms. This leads to the creation of localized microenvironments, in which immune function is compromised. As mentioned earlier, one of the methods used by cytotoxic lymphocytes to eliminate cancerous cells is to bind and activate the Fas death receptor displayed on the cells' surface using the FasL molecules. This leads to the activation of the extrinsic apoptotic pathway. However, many tumor cells are able to develop resistance to FasL-mediated killing or produce and release soluble forms of FasL themselves. These molecules do not affect the tumor cells, but they may activate the Fas death receptors displayed on the surface of lymphocytes resulting in their death. Another strategy is used by many types of human cancer cells, which have been found to release either TGF-β or interleukin-10 (IL-10). Both of these proteins are greatly immunosuppressive and can have strong inhibitory effects on T lymphocytes, prevent the matruation of dendritic cells, and suppress their expression of MHC type II molecules.

Another immunoevasive strategy involves the release of the chemotactic factor CCL22 to attract and activate regulatory T cells. These cells can directly inhibit and even kill cytotoxic and helper T cells, which recognize the same antigen as the one recognized by the regulatory T cells. Among the population of $CD4^+$ lymphocytes in normal individuals, 5 to 10% are regulatory T cells, while the remainder consists of helper T cells. However, in cancer patients, this number may increase to 30%. Furthermore, regulatory T cells have been found in large numbers among the tumor-infiltrating lymphocytes.

2.3 Exhausted cytotoxic T cells in the TME

The following section deals with the aspect of T cell exhaustion and is based on [Jia+21]. When naive $CD8^+$ T cells encounter antigens during an acute infection, they are activated and differentiate into cytotoxic effector T cells, which clear the pathogen. However, when encountering persistent antigen stimulation in chronic virus infections or tumors, T cell differentiation is found to be in a hyporesponsive state called *exhaustion*. T cell exhaustion is therefore defined as progressive loss of effector function and sustained expression of inhibitory receptors, such as PD-1. In

particular, the term exhaustion describes a functional but yet hyporesponsive state of cytotoxic T cells.

Tumorgenesis is a long-term process in which interactions between tumor and immune cells remodel the TME, which influences the differentiation of $CD8^+$ T cells. While the immune system eliminates tumor cells during immune surveillance, immunosuppressive cells may be recruited as a countermeasure. As we have seen in the previous section, these can secrete related inhibitory factors to generate the immunosuppressive tumor environment in order to persistently suppress T cell immune function with increasing tumor development. This may lead to a situation where cytotoxic T cells often go into an exhaustion state and fail to control tumor progression in the later stages.

3 Mathematical background

In the scope of this thesis, we will consider continuous-time approaches to describe the tumor-immune dynamics. The following chapter deals with a brief overview of mathematical concepts and ideas, including ordinary differential equations (ODEs) as well as delay differential equations (DDEs), which will serve as a foundation for the later work.

3.1 Differential equations and dynamical systems

First, we give a brief outline of the concepts related to the theory of dynamical systems and ordinary differential equations. Main results in this section are adapted from [BK20; Küh23; Kut20].

Dynamical systems

Following [Küh23], we consider the following definitions and properties of dynamical systems.

Definition 3.1 (Dynamical system)**.** A dynamical system is a triplet (T, X, ϕ_t), where T is the time set, X is the state space, and $\phi_t : X \to X$ is a family of evolution operators parametrized by $t \in T$ satisfying

(i) $\phi_0 = \mathrm{id}$,

(ii) $\phi_{t+s} = \phi_t \circ \phi_s \quad \forall\, t, s \in T$.

Definition 3.2 (Equilibrium)**.** A point $\bar{x} \in X$ is called an equilibrium (steady state), if $\phi_t(\bar{x}) = \bar{x}$ for all $t \in T$.

Definition 3.3 (Cycle)**.** A cycle is a non-equilibrium periodic orbit $\bar{L}$, such that there exists a fixed $\bar{T} > 0$ such that each point $\bar{x} \in \bar{L}$ satisfies $\phi_{t+\bar{T}}(\bar{x}) = \phi_t(\bar{x})$ for all $t \in T$.

Definition 3.4 (Stability)**.** Let (T, X, ϕ_t) be a dynamical system and $\bar{x}$ be an equilibrium. We say that $\bar{x}$ is stable if for any given neighbourhood U of $\bar{x}$, there exists another neighbourhood $V \subset U$ such that $\phi_t(V) \subset U$ holds for all $t \geq 0$. If

$\bar{x}$ is not stable, it is called unstable. Lastly, $\bar{x}$ is called asymptotically stable if it is stable and there exists a neighbourhood U such that $\lim_{t\to\infty} \phi_t(x_0) = \bar{x}$ for all $x_0 \in U$.

Further, we use the term *local asymptotic stability* to emphasize that U may have to be chosen small enough.

Ordinary differential equations

One way to define a continuous-time dynamical system is by a system of differential equations with $X = \mathbb{R}^n$, and $T \subset \mathbb{R}$. In the scope of this work, we consider dynamical systems generated by ODEs and DDEs. The latter will be discussed in the later part of this chapter. Following [BK20], we introduce the following properties of ODEs.

Definition 3.5 (Systems of ODEs)**.** A system of ODEs has the form

$$\dot{x} = f(t, x), \quad t \in \mathbb{R},\ x = (x_1, \ldots, x_n)^T \in \mathbb{R}^n$$

and it consists of n ODEs $\dot{x}_i = f_i(t, x)$. We refer to it as an autonomous system, if f does not depend on t and thus, $\dot{x} = f(x)$.

In what follows, we consider a system of ODEs $\dot{x} = f(t, x)$ with the corresponding *initial value problem* $\dot{x} = f(t, x),\ x(t_0) = x_0$.

Definition 3.6 (Solution of a system)**.** Let $I \subset \mathbb{R}$ be an interval, $D \subset \mathbb{R} \times \mathbb{R}^n$ be open, and $f : D \to \mathbb{R}^n$. A function $x : I \to \mathbb{R}^n$ is a solution of the system of ODEs in the interval I, if x is differentiable in I and for all $t \in I$, it holds that $(t, x(t)) \in D$ and $\dot{x}(t) = f(t, x(t))$ are satisfied. If furthermore $(t_0, x_0) \in D$ with $t_0 \in I$ and $x(t_0) = x_0$ is given, then x is a solution of the corresponding initial value problem.

Definition 3.7 (Lipschitz continuity)**.** Let $D \subset \mathbb{R} \times \mathbb{R}^n$. A function $f : D \to \mathbb{R}^n$ is called Lipschitz continuous on D with respect to x, if there exists a constant $L > 0$ such that for all $(t, x), (t, y) \in D$, we have

$$\|f(t, x) - f(t, y)\|_\infty \leq L\|x - y\|_\infty.$$

L is called a Lipschitz constant for f on D. The function f is called locally Lipschitz continuous on D with respect to x, if for every $(t_0, x_0) \in D$, there is an open set $U \subset \mathbb{R} \times \mathbb{R}^n$ with $(t_0, x_0) \in U$ such that f on $U \subset D$ is Lipschitz continuous with respect to x.

The following theorem and lemma prove the existence and uniqueness of the solution of the initial value problem.

Theorem 3.1 (Picard-Lindelöf, local)**.** Let $D \subset \mathbb{R} \times \mathbb{R}^n$ be open, $(t_0, x_0) \in D$. Furthermore, let $f : D \to \mathbb{R}^n$ be continuous and locally Lipschitz continuous with respect to x. Then, there exists a $\delta > 0$ such that the initial value problem has a unique solution in the interval $[t_0 - \delta, t_0 + \delta]$.

Proof. A proof is provided in [cf. BK20, Theorem 2.4]. □

Lemma 3.1. Let $D \subset \mathbb{R} \times \mathbb{R}^n$ be open, $(t_0, x_0) \in D$. Further, let $f : D \to \mathbb{R}^n$ be continuous and locally Lipschitz continuous with respect to x. If x_1, $x_2 : J \to \mathbb{R}^n$ are solutions of the initial value problem on the intervall $J = (a, b)$, then $x_1 = x_2$ holds true on J.

Proof. A proof is provided in [cf. BK20, Lemma 2.5]. □

Theorem 3.2. Let $D \subset \mathbb{R} \times \mathbb{R}^n$ be open, $f : D \to \mathbb{R}^n$ be continuous and locally Lipschitz continuous with respect to x. Then, for every $(t_0, x_0) \in D$, there exists an open interval I and a solution x of the initial value problem in I such that for every solution y of the initial value problem on the interval J, we have that

$$J \subset I, \quad y = x|_J.$$

We refer to I as the maximal existence interval of the solution of the initial value problem.

Proof. A proof is provided in [cf. BK20, Theorem 2.6]. □

Theorem 3.3. Let $D \subset \mathbb{R} \times \mathbb{R}^n$ be open, $f : D \to \mathbb{R}^n$ be continuous and locally Lipschitz continuous with respect to x. Further, let x be the unique solution of the initial value problem and I be the maximal existence interval. Then, neither $\{(t, x(t)) : t \in I, t \geq t_0\}$ nor $\{(t, x(t)) : t \in I, t \leq t_0\}$ is contained in a compact subset of D.

Proof. A proof is provided in [cf. BK20, Theorem 2.7]. □

From the previous properties, it follows that if f is continuous on D and locally Lipschitz continuous with respect to x, then there exists a unique solution of the initial value problem where the corresponding graph extends to the boundary of D.

3.1.1 Linear systems and linearization

Equilibria and their stability behavior play an essential role in the dynamics of biological systems. In the following section, we will work with autonomous systems and provide a brief overview of some statements on the stability conditions of such systems. We first consider the linear case. In particular, the stability of a stationary point can be shown with the following theorem.

Theorem 3.4 (Linear system stability)**.** We consider the linear system

$$\dot{x} = Ax, \quad A \in \mathbb{R}^{n\times n}$$

and set $a = \max\{\mathrm{Re}(\lambda) : \lambda \text{ is an eigenvalue of } A\}$. For the stationary point $\bar{x} = 0$ of the system, it holds that

(i) $\bar{x}$ is asymptotically stable if $a < 0$, and

(ii) $\bar{x}$ is unstable if $a > 0$.

Proof. A proof is provided in [cf. Küh23, Theorem 2.10]. □

In what follows, we consider a non-linear autonomous system given by $\dot{x} = f(x)$ for $x \in \mathbb{R}^n$, where $f \in C^1$. An equilibrium $\bar{x} \in \mathbb{R}^n$ is called *hyperbolic*, if the Jacobian $Df(\bar{x})$ has no eigenvalues with vanishing real parts. In particular, hyperbolicity for equilibria implies that eigenvalues are not on the imaginary axis. Using Taylor's Theorem, we can write

$$f(\bar{x} + x) = Df(\bar{x})x + R(x),$$

where $R \in o(|x|)$. The corresponding linearized system is given by $\dot{z} = Az$, where $A = Df(\bar{x})$. Since $\bar{x}$ is hyperbolic, A is a hyperbolic matrix and therefore, there exists a splitting

$$\mathbb{R}^n = E^s(\bar{x}) \oplus E^u(\bar{x}),$$

where $E^s(\bar{x})$ and $E^u(\bar{x})$ denote the *stable* and *unstable eigenspace* of $\bar{x}$, respectively given by

$$E^s(\bar{x}) = \{y \in R^n : \lim_{t\to\infty} e^{tA}y = \bar{x}\},$$
$$E^u(\bar{x}) = \{y \in R^n : \lim_{t\to-\infty} e^{tA}y = \bar{x}\}.$$

By studying the behavior of the linearized system, we have the following result on the *stable* and *unstable manifolds* of the non-linear autonomous system.

Theorem 3.5. Suppose $Df(\bar{x})$ has k eigenvalues with negative real part and $n - k$ eigenvalues with positive real part. Further, let $E^s(\bar{x})$ and $E^u(\bar{x})$ denote the eigenspaces of the corresponding linearized system. Then, there exists a neighbourhood U of $\bar{x}$ with local stable and unstable manifolds denoted by $W^s_{loc}(\bar{x})$ and $W^u_{loc}(\bar{x})$, respectively, where

$$W^s_{\mathrm{loc}}(\bar{x}) = \{y \in U : \lim_{t\to\infty} \phi_t(y) = \bar{x} \text{ and } \phi_t(y) \in U \ \forall t \geq 0\},$$
$$W^u_{\mathrm{loc}}(\bar{x}) = \{y \in U : \lim_{t\to-\infty} \phi_t(y) = \bar{x} \text{ and } \phi_t(y) \in U \ \forall t \leq 0\}.$$

Furthermore, $W^s_{\mathrm{loc}}(\bar{x})$ and $W^u_{\mathrm{loc}}(\bar{x})$ are tangent to $E^s(\bar{x})$ and $E^u(\bar{x})$.

Proof. A proof is provided in [cf. Küh23, Theorem 3.8]. □

Before proceeding to the stability analysis of the non-linear autonomous system, we first consider the following concepts of *topological equivalence* and *conjugacy*.

Definition 3.8. A dynamical system (T, X, ϕ_t) is called topologically equivalent to a system (T, X, ψ_t) if there exists a homeomorphism $h : X \to X$ which maps orbits of the first system to orbits of the second system while preserving the direction of time. If the time parametrization is also preserved, then the systems are called conjugate.

Definition 3.9. A dynamical system (T, X, ϕ_t) with equilibrium $\bar{x}$ is called locally topologically equivalent to a system (T, X, ψ_t) near $\bar{x}$, if there exist neighbourhoods $U(\bar{x})$, $V(\bar{y})$ with $\psi_t(\bar{y}) = \bar{y}$ for all $t \in T$, and a homeomorphism $h : U(\bar{x}) \to V(\bar{y})$, which maps orbits of the first system to orbits of the second system while preserving the direction of time.

We thus have the following theorem on the stability analysis of non-linear autonomous systems.

Theorem 3.6 (Hartman-Grobman)**.** Consider the non-linear autonomous system $\dot{x} = f(x)$ with flow ϕ_t and the corresponding linearized system $\dot{z} = Az$. Further, let $\bar{x}$ be a hyperbolic equilibrium. Then ϕ_t is locally topologically conjugate to the flow $\exp(tA)$.

Proof. A proof is provided in [cf. Küh23, Theorem 4.5]. □

3.1.2 Two-dimensional systems

For a two dimensional system of differential equations, the following theorem allows us to exclude the occurrence of closed orbits lying entirely in a set D under certain circumstances.

Theorem 3.7 (Negative criterion of Bendixson-Dulac)**.** Let $D \subset \mathbb{R}^2$ be a simply connected region and $h_1, h_2, \rho \in C^1(D, \mathbb{R})$, such that $\rho(x, y) > 0$ for all $(x, y) \in D$ and $\operatorname{div}(\rho \cdot h_1, \rho \cdot h_2) = \frac{\partial}{\partial x}(\rho h_1) + \frac{\partial}{\partial y}(\rho h_2)$ is not the zero function and does not change sign. Then the system

$$\begin{aligned} \dot{x} &= h_1(x, y) \\ \dot{y} &= h_2(x, y) \end{aligned}$$

has no closed orbits lying entirely in D.

Proof. A proof is provided in [cf. Kut20, Proposition 7]. □

3.1.3 Hopf bifurcation

Following [Kut20], we present the Hopf bifurcation theorem, which can be used to establish the existence of periodic orbits. In particular, we refer to *bifurcation* as the appearance of a non-equivalent phase portrait under variation of a bifurcation parameter.

Theorem 3.8. Consider the system $\dot{x} = f(x;\mu)$, where $x \in \mathbb{R}^n$. Suppose that at μ_0, $\bar{x}$ is an equilibrium of the system, where the Jacobian $f'(\bar{x};\mu_0)$ has a simple pair of purely imaginary complex eigenvalues and no other eigenvalues with vanishing real parts. Then, there exists a (locally) smooth curve of equilibria $(x(\mu),\mu)$ with $x(\mu_0) = \bar{x}$. The eigenvalues $\lambda(\mu)$ and $\bar{\lambda}(\mu)$ of the Jacobian $f'(x(\mu);\mu)$, which are purely imaginary at $\mu = \mu_0$, depend smoothly on μ. If in addition,

$$d := \frac{d}{d\mu}(\mathrm{Re}(\lambda(\mu)))|_{\mu=\mu_0} \neq 0,$$

then there exists a unique three-dimensional center manifold passing through $(\bar{x},\mu_0)$ in $\mathbb{R}^n \times \mathbb{R}$ and a smooth system of coordinates (preserving the planes $\mu = const.$), for which the system can be formulated on the surface corresponding to the eigendirections of the pair of purely imaginary eigenvalues (depending on $(x,\mu) \in \mathbb{R}^n \times \mathbb{R}$) as follows:

$$\begin{aligned}\dot{x} &= (d\mu + a(x^2+y^2))x - (\omega + c\mu + b(x^2+y^2))y + \text{ higher order terms}\\ \dot{y} &= (\omega + c\mu + b(x^2+y^2))x + (d\mu + a(x^2+y^2))y + \text{ higher order terms}\end{aligned}$$

If $a \neq 0$, then there exists a surface of periodic solutions in the centre manifold, which has a quadratic tangency with the eigenspace of $\lambda(\mu_0)$ and $\bar{\lambda}(\mu_0)$ agreeing to second order with the paraboloid $\mu = -(a/d)(x^2+y^2)$. If $a < 0$, then these periodic solutions are stable limit cycles, while if $a > 0$, the periodic orbits are repelling.

3.2 Delay differential equations

In the following section, we provide an overview of the theory of DDEs. In a system of ODEs, the derivatives only depend on the current state of the system. However, in a system of DDEs, the derivatives can also depend on earlier states of the system. This allows us to model biological system, in which certain processes occur with a delay.

Let $x(t)$ be a function of time. Then, we can introduce a time delay r by considering $x(t-r)$. Such a delay is called a *constant discrete-time delay*. In the scope of this work, we will only deal with systems of DDEs with a single constant delay.

Furthermore, DDEs can be considered as elements of the general class of *retarded functional differential equations* (RFDEs). The notation and properties presented in the following section are adapted from [Kut22; Bar13; Hal77; Smi10; HL93; Die+95; RW03; Rua09].

Definition 3.10. Let $h > 0$ and $n \in \mathbb{N}$. We consider the following Banach spaces:

1. The set $C := C([-r, 0]; \mathbb{R}^n)$ of continuous functions $\phi : [-r, 0] \to \mathbb{R}^n$ with the norm $\|\phi\|_C := \sup_{-r \le t \le 0} |\phi(t)|$;
2. The set $C^1 := C^1([-r, 0]; \mathbb{R}^n)$ of continuously differentiable functions $\phi : [-r, 0] \to \mathbb{R}^n$ with the norm $\|\phi\|_{C^1} := \|\phi\|_C + \|\partial\phi\|_C$, where $\partial : C^1 \to C$ denotes the continuous linear operator of differentiation.

The general RFDE takes the form

$$\dot{x} = F(t, x_t),$$

where $F : D \to \mathbb{R}^n$ is a functional defined on an open subset $D \subset \mathbb{R} \times C$ and the function $x_t : [-r, 0] \to \mathbb{R}^n,\ s \mapsto x(t + s)$ indicates the piece of solution of the RFDE in the interval $[t - r, t]$. We refer to x_t as *solution segment* or *state of x at time t*. In particular, if x is a continuous function, then x_t is an element of C and the RFDE is well-defined. We say that a function x is a solution on an interval $[t_0 - r, t_0 + \delta]$ if there exist $t_0 \in \mathbb{R}$ and $\delta > 0$ such that $x \in C([t_0 - r, t_0 + \delta];\ \mathbb{R}^n)$ and for all $t \in [t_0, t_0 + \delta)$, we have $(t, x_t) \in D$ and $x(t)$ satisfies $\dot{x} = F(t, x_t)$. A RFDE is called *autonomous*, if the right-hand side does not explicitly depend on time, i.e. $\dot{x} = F(x_t)$, where $F : U \to \mathbb{R}^n$ is a functional defined on an open subset $U \subset C$. Solutions of autonomous RFDEs are invariant under time translation. In the scope of this work, we will mainly deal with autonomous RFDEs. Before moving on to the general theory of existence and uniqueness of solutions, let us first consider some properties of DDEs with a single constant discrete-time delay.

3.2.1 The method of steps for discrete delay equations

Let $t_0 \in \mathbb{R}$ be given and let $\phi : [t_0 - r, t_0] \to \mathbb{R}$ be continuous. Consider the non-linear DDE of the form

$$\dot{x}(t) = f(t, x(t), x(t - r)) \tag{3.1}$$

for $t \ge t_0$ and

$$x(t) = \phi(t) \tag{3.2}$$

for $t_0 - r \le t \le t_0$ with a single delay $r > 0$, where $f : \mathbb{R}^3 \to \mathbb{R}$ and its partial derivative $f_x(t, x, y)$ are both continuous. Note that we interpret $\dot{x}(t_0)$ as the right-hand derivative at t_0. The system given by (3.1) and (3.2) can be solved by the *method of steps* in the following manner. For $t_0 \le t \le t_0 + r$, $x(t)$ must satisfy

$$\begin{aligned} \dot{y}(t) &= f(t, y(t), \phi(t - r)) \\ y(t_0) &= \phi(t_0), \end{aligned} \tag{3.3}$$

which is an initial-value problem of an ODE. Since $g(t, y) := f(t, y, \phi(t - r))$ and $g_y(t, y)$ are continuous, a local solution of (3.3) is guaranteed from the theory of ODEs. If this local solution $x(t)$ exists for the entire interval $[t_0, t_0 + r]$, then the method applied above can be repeated to extend the solution farther. For $t_0 + r \leq t \leq t_0 + 2r$, a solution $x(t)$ must satisfy

$$\begin{aligned} \dot{y}(t) &= f(t, y(t), x(t - r)) \\ y(t_0 + r) &= x(t_0 + r). \end{aligned} \tag{3.4}$$

Once again, results from ODE theory guarantee the existence of a local unique solution for the problem (3.4). If the solution exists on the entire interval $[t_0 + r, t_0 + 2r]$, then the procedure can be repeated in an analogous way. We consider the following theorems from [Smi10].

Theorem 3.9. Let $f(t, x, y)$ and $f_x(t, x, y)$ be continuous on $\mathbb{R}^3$, $t_0 \in \mathbb{R}$, and let $\phi : [t_0 - r, t_0] \to \mathbb{R}$ be continuous. Then there exists $\sigma > t_0$ and a unique solution of the initial-value problem

$$\begin{aligned} \dot{x}(t) &= f(t, x(t), x(t - r)) && \text{for } t \geq t_0 \\ x(t) &= \phi(t) && \text{for } t_0 - r \leq t \leq t_0 \end{aligned}$$

on $[t_0 - r, \sigma]$.

Proof. We have seen earlier that for $t_0 \leq t \leq t_0 + r$, the initial-value problem is reduced to the initial-value problem given by (3.3). By Theorem 3.1 there exists a $\delta > 0$ such that the initial-value problem (3.3) has a unique solution in the interval $[t_0 - \delta, t_0 + \delta]$. Setting $\sigma := t_0 + \delta > t_0$ finishes the proof. □

Definition 3.11. Let x on $[t_0 - h, \beta_1)$ and y on $[t_0 - h, \beta_2)$ both be solutions of the same initial-value problem of a DDE. If $\beta_2 > \beta_1$, then y is said to be a continuation of x. A solution x is called non-continuable if it has no continuation.

In case of a single discrete-time delay, the following theorem gives a sufficient condition, which guarantees the continuability of solutions for all positive times.

Theorem 3.10. Let f satisfy the conditions of Theorem 3.9 and let $x : [t_0 - r, \sigma) \to \mathbb{R}$ be the non-continuable solution of the initial-value problem in Theorem 3.9. If $\sigma < \infty$, then

$$\lim_{t \to \sigma^-} |x(t)| = \infty.$$

Proof. A proof is provided in [cf. Smi10, Theorem 3.2]. □

Remark 3.1. Theorem 3.9 and Theorem 3.10 can be extended to the case of $x : \mathbb{R} \to \mathbb{R}^n$.

3.2.2 Positivity of solutions

In many biological applications, it is essential that the delay differential equations maintain non-negative quantities. Therefore, for the model to be biologically meaningful, it is important to guarantee that non-negative initial values result in non-negative solutions. We consider the following theorem from [Hal77].

Theorem 3.11. Let $f : \mathbb{R} \times \mathbb{R}^n_+ \times \mathbb{R}^n_+ \to \mathbb{R}^n$, such that $f(t, x, y)$ and $f_x(t, x, y)$ are continuous, $t_0 \in \mathbb{R}$, and let $\phi : [t_0 - r, t_0] \to \mathbb{R}^n$ be continuous. Further, let f satisfy

$$x_i = 0 \Rightarrow f_i(t, x, y) \geq 0$$

for all i, t and for all $x, y \in \mathbb{R}^n_+$. If the initial function in (3.2) satisfies $\phi \geq 0$, then the corresponding solution $x(t)$ of (3.1) satisfies $x(t) \geq 0$ for all $t \geq t_0$ where it is defined.

Proof. A proof is provided in [cf. Smi10, Theorem 3.4]. □

3.2.3 More general existence and uniqueness theory

For a more general setting, we consider the initial-value problem of a non-autonomous system

$$\begin{aligned} \dot{x}(t) &= F(t, x_t), \quad t \geq t_0 \\ x_{t_0} &= \phi, \end{aligned} \tag{3.5}$$

where F is a (with respect to t and x_t) continuous functional defined on a subset of $\mathbb{R} \times C$, $t_0 \in \mathbb{R}$, and $\phi \in C$ is the state of the system at time t_0. Besides continuity of F, we further assume it to be *locally Lipschitz continuous*.

Definition 3.12 ((Global) Lipschitz continuity)**.** Let $F : [t_0, t_f] \times C \to \mathbb{R}^n$ and $A \subset [t_0, t_f] \times C$. The functional F is (globally) Lipschitz continuous on A with constant K if there exists $K \geq 0$, such that

$$\|F(t, \phi) - F(t, \tilde{\phi})\| \leq K \|\phi - \tilde{\phi}\|_C$$

is satisfied for any (t, ϕ), $(t, \tilde{\phi}) \in A$.

Definition 3.13 (Local Lipschitz continuity)**.** Let $F : [t_0, t_f] \times C \to \mathbb{R}^n$. F is said to be locally Lipschitz continuous if for each given $(\tilde{t}, \tilde{\phi}) \in [t_0, t_f] \times C$, there exist $a, b > 0$, such that

$$B := \Big([\tilde{t} - a, \tilde{t} + a] \cap [t_0, t_f]\Big) \times \{\phi \in C : \|\phi - \tilde{\phi}\|_C \leq b\}$$

is a subset of $[t_0, t_f] \times C$ and F is Lipschitz continuous on B.

We further consider the following results on the existence and uniqueness of solutions and define $C_A = C([-r, 0]; A)$, where $A \subset \mathbb{R}^n$.

Theorem 3.12 (Uniqueness)**.** Assume $F : [t_0, \beta) \times C_D \to \mathbb{R}^n$ to be continuous and locally Lipschitz continuous. Then for any $\phi \in C_D$, system (3.5) has at most one solution on $[t_0 - r, \beta_1)$ for any $\beta_1 \in (t_0, \beta]$.

Proof. A proof is provided in [cf. Kut22, Theorem 3]. □

Theorem 3.13 (Local existence)**.** Assume $F : [t_0, \beta) \times C_D \to \mathbb{R}^n$ to be continuous and locally Lipschitz continuous. Then for any $\phi \in C_D$, system (3.5) has a unique solution on $[t_0 - r, t_0 + \sigma)$ for some $\sigma > 0$.

Proof. A proof is provided in [cf. Kut22, Theorem 4]. □

Theorem 3.14 (Global existence)**.** Let $D = \mathbb{R}^n$ and assume $F : [t_0, \beta) \times C_D \to \mathbb{R}^n$ to be continuous and locally Lipschitz continuous. Further, we assume that

$$\|F(t, \psi)\| \leq M(t) + N(t)\|\psi\|_C$$

holds on $[t_0, \beta) \times C$, where M and N are both continuous positive functions on the interval $[t_0, \beta)$. Then the unique non-continuable solution of system (3.5) exists on the whole interval $[t_0 - r, \beta)$.

Proof. A sketch of proof is provided in [cf. Kut22, Theorem 6]. □

3.2.4 Linear systems and linearization

Similar to the ODE case, one of the key concepts in analyzing DDEs is to determine the local stability of the equilibria. In particular, we linearize the system about the equilibrium and study the exponential growth and decay rates for the corresponding linearized system. We first consider the dynamics of linear autonomous DDEs before moving on to the general non-linear autonomous setting. Main results of this section are adapted from [Smi10; Kut22].

For autonomous systems, we can without loss of generality assume $t_0 = 0$. We consider the linear autonomous equation

$$\dot{x}(t) = Lx_t \tag{3.6}$$

for $t \geq 0$ and $x(t) = \phi(t)$ for $-r \leq 0$, where $L : C^C \to \mathbb{C}^n$ is a continuous linear map. Furthermore, we set $C^C := C([-h, 0]; \mathbb{C}^n)$ with a corresponding norm denoted by $\|\cdot\|$.

We derive the *characteristic equation* of (3.6) by seeking exponentially growing solutions of the form

$$x(t) = e^{\lambda t} v$$

for $\lambda \in \mathbb{C}$ and $0 \neq v \in \mathbb{C}^n$. We use the notation

$$\exp_\lambda : [-r, 0] \to \mathbb{C}, \ \exp_\lambda(s) = e^{\lambda s},$$

leading to $x_t(z) = x(t+z) = e^{\lambda(t+z)}v = e^{\lambda t}\exp_\lambda(z)v$. For $x(t)$ to be a solution of (3.6), it must satisfy $\dot{x}(t) = L(x_t)$, which is equivalent to $\lambda e^{\lambda t}v = e^{\lambda t}L(\exp_\lambda v)$ and further

$$\lambda v = L(\exp_\lambda v).$$

With $\{e_j\}_j$ being the standard basis for $\mathbb{C}^n$ and L being linear, we can write $v = \sum_{j=1}^n v_j e_j$ and $L(\exp_\lambda v) = \sum_{j=1}^n v_j L(\exp_\lambda e_j)$. Hence, we have $L(\exp_\lambda v) = L_\lambda v$, where L_λ is the $n \times n$ matrix defined by

$$L_\lambda = \left(L(\exp_\lambda e_1)\ L(\exp_\lambda e_2)\ \ldots\ L(\exp_\lambda e_{n-1})\ L(\exp_\lambda e_n)\right).$$

It follows that $x(t) = e^{\lambda t}v$ is a non-zero solution of (3.6) iff $\lambda \in \mathbb{C}^n$ is a solution of the characteristic equation given by

$$\det(\lambda I_n - L_\lambda) = 0. \tag{3.7}$$

Particularly, such a solution $\lambda \in \mathbb{C}$ is referred to as a *characteristic root*.

We now focus on the special case of a system of DDEs with a single constant discrete-time delay r given by

$$L(\phi) = A\phi(0) + B\phi(-r),$$

where A, B are $n \times n$ matrices and $\phi \in C^C$. We say that L is *bounded* if there is a constant $K > 0$, such that

$$\|L(\phi)\| \leq K\|\phi\|_C$$

holds for all $\phi \in C^C$. We can see that

$$\|L(\phi)\| = \|A\phi(0) + B\phi(-r)\| \leq \|A\|\|\phi\|_C + \|B\|\|\phi\|_C \leq (\|A\| + \|B\|)\|\phi\|_C,$$

which shows that L is bounded. Since L is linear and bounded, it is continuous and also satisfies the global Lipschitz condition in Definition 3.12, i.e. for $\phi, \psi \in C^C$, we have that

$$\|L(\phi) - L(\psi)\| = \|L(\phi - \psi)\| \leq K\|\phi - \psi\|_C,$$

where $K = \|A\| + \|B\|$. Further, with

$$\|F(t,\psi)\| \leq \|F(t,0)\| + \|F(t,\psi) - F(t,0)\| \leq \|F(t,0)\| + K\|\psi\|_C$$

the conditions in Theorem 3.14 are satisfied by choosing $M(t) = \|F(t,0)\|$ and $N(t) = K$. Thus, it follows that there exists a unique, non-continuable solution defined on the entire interval $[-r, \infty)$. Due to the linearity of L, we can apply the *superposition principle*, i.e. a linear combination of solutions is again a solution.

In case of a single discrete-time delay, (3.6) takes the form

$$\dot{x}(t) = Ax(t) + Bx(t-r).$$

with initial function

$$x(t) = \phi(t)$$

for $-r \leq t \leq 0$. The corresponding characteristic equation takes the form

$$\det\left(\lambda I_n - A - Be^{-\lambda r}\right) = 0. \tag{3.8}$$

Before proceeding to some properties of the characteristic equation and characteristic roots, we first introduce the concept of an analytic function. Consider a complex-valued function $f : D \to \mathbb{C}$, where $D \subset \mathbb{C}$ is open. The function f is said to be *analytic* on D if f is differentiable at each point of D. In particular, we say that f is an *entire* function if f is analytic on the entire domain $\mathbb{C}$. Coming back to the characteristic equation (3.7), one can prove that the function $h : \mathbb{C} \to \mathbb{C},\ \lambda \mapsto h(\lambda) := \det(\lambda I - L_\lambda)$ is an entire function [cf. Smi10, Lemma 4.1]. Following from some properties [Die+95; Bel+63; Kua93; Hal77] of non-trivial entire functions, the following holds for h:

(i) Each characteristic root has finite order.

(ii) There are at most countably many characteristic roots.

(iii) The set of characteristic roots has no finite accumulation point.

Particularly, the following lemma shows that there are only finitely many characteristic roots with positive real part.

Lemma 3.2. Given a value $\sigma \in \mathbb{R}$, there are at most finitely many characteristic roots with $\mathrm{Re}(\lambda) > 0$. Further, if there are infinitely many distinct characteristic roots $\{\lambda_n\}_n$, then

$$\lim_{n\to\infty} \mathrm{Re}(\lambda_n) \to -\infty$$

holds true.

Proof. A proof is provided in [cf. Smi10, Lemma 4.2]. □

Similar to the ODE case, we can analyze the stability of solutions of systems of linear autonomous DDEs by studying the corresponding characteristic roots. To that extend, we refer to $x(t_0, \phi)$ as the solution of (3.6) with initial function $x_{t_0} = \phi$. The solution $x = 0$ is said to be *stable* if for any $s \in \mathbb{R}$ and any $\varepsilon > 0$, there exists a value $\sigma = \sigma(s, \varepsilon)$ such that for all $\psi \in C$ with $\|\psi\| < \sigma$, we have that $\|x_t(s, \phi)\| < \varepsilon$ holds true. We say that it is *asymptotically stable* if it is stable and there exists $\rho(s) > 0$ such that for all $\psi \in C$ and $\|\psi\| < \rho(s)$, we have that

$\lim_{t\to\infty} x(s,\psi)(t) \to 0$. Finally, we say that $x = 0$ is *unstable* if it is not stable. The following lemma is discussed in [cf. Kut22, Proposition 2] and provides some information on the stability of the equilibrium $x = 0$ of (3.6), depending on the real part of the corresponding characteristic roots. The proof follows from properties given in [HL93, Chapter 7].

Lemma 3.3. Suppose that there exists a value μ such that $\mathrm{Re}(\lambda) < \mu$ for every characteristic root λ. Then for all $\phi \in C^C$, we have that for the solution $x(t_0, \phi)$ of (3.6) with initial function ϕ, there exists a value $K = K(\mu) > 0$ such that

$$\|x_t(t_0,\phi)\|_C \leq Ke^{\mu t}\|\phi\|_C$$

for all $t \geq t_0$. In particular, the trivial equilibrium $x = 0$ is asymptotically stable if $\mathrm{Re}(\lambda) < 0$ for all characteristic roots λ. It is unstable if there exists a characteristic root λ such that $\mathrm{Re}(\lambda) > 0$.

We now move on to some properties of a non-linear autonomous RFDE given by

$$\dot{x}(t) = f(x_t), \quad t \geq 0, \tag{3.9}$$

with initial function $\phi \in C$ and $f : U \to \mathbb{R}^n$, where $U \subset \mathbb{C}$ is open. Let $x^* \in C$, $x^*(t) = \bar{x} \in \mathbb{R}^n$ be an equilibrium of the system. Assume that there exists a linear bounded map $L : C \to \mathbb{R}^n$ and $\upsilon : C \to \mathbb{R}^n$ such that $|\upsilon| \in \mathcal{O}(\|\psi\|_C)$. Then, in proximity of the equilibrium, we can write $f(x^* + \psi) = f(x^*) + L(\psi) + \upsilon(\psi) = L(\psi) + \upsilon(\psi)$. The corresponding linearized system is given by

$$\dot{z} = L(z_t), \quad t \geq 0.$$

By studying the behavior of the linearized system, we have the following result on the local stability of the non-linear system (3.9).

Theorem 3.15 (Principle of linearized stability)**.** The equilibrium $x^* = \bar{x}$ of (3.9) is

(i) unstable if $\mathrm{Re}(\lambda) > 0$ for some root λ of the corresponding characteristic equation of the linearized system,

(ii) locally asymptotically stable if $\mathrm{Re}(\lambda) < 0$ for all roots λ of the corresponding characteristic equation of the linearized system.

Proof. A proof is provided in [cf. Die+95, Theorem 6.8]. □

3.2.5 Transcendental functions

In the following section, we will consider some properties of a type of transcendental functions, which we will later use in our model analysis in Chapter 7. Results of this chapter are adapted from [RW03; Rua09].

Theorem 3.16. Let $B \subset \mathbb{R}^n$ be an open connected set and $h(\lambda, \mu)$ be continuous in $(\lambda, \mu) \in \mathbb{C} \times B$ and analytic in $\lambda \in \mathbb{C}$. Further, assume that there exists a constant $c > 0$ such that the absolute values of the roots of $h(\lambda, \mu)$ in the right half plane $\{\lambda \in \mathbb{C} : \ \mathrm{Re}(\lambda) \geq 0\}$ are bounded by c for any μ. If for any $\mu \in B_1 \subset B$, where B_1 is bounded, closed, and connected, $h(\lambda, \mu)$ has no roots on the imaginary axis, then the sum of the orders of the roots of $h(\lambda, \mu)$ with $\mathrm{Re}(\lambda) > 0$ is a fixed number for B_1, i.e. it is independent of the parameter $\mu \in B_1$.

Proof. A proof is provided in [cf. RW03, Theorem 2.1]. □

Corollary 3.1. In particular, we observe that under the assumptions of Theorem 3.16, as the bifurcation parameter μ varies, the sum of the orders of the roots of $h(\lambda, \mu)$ in the open right half plane ($\mathrm{Re}(\lambda) > 0$) can change only if a root appears on the imaginary axis.

A special type of transcendental functions

Following [Rua09], we consider the transcendental function

$$\lambda^2 + p\lambda + a + (b\lambda + q)e^{-\lambda r} = 0, \tag{3.10}$$

where $p, a, b, q \in \mathbb{R}$ and $r \geq 0$. In case of $r = 0$, the function equals

$$\lambda^2 + (p + b)\lambda + (a + q). \tag{3.11}$$

Note that all roots of (3.11) have negative real parts iff

(H_1) $p + b > 0$;

(H_2) $a + q > 0$.

Assume that (H_1) and (H_2) are satisfied and let λ be a root of (3.10). Using r as the bifurcation parameter, we want to determine if $\mathrm{Re}(\lambda)$ reaches zero and eventually becomes positive as we vary r. To this end, we search for values of r, such that the corresponding roots take the form $i\omega$.

With $\exp(-\lambda r) = \exp(-\mathrm{Re}(\lambda)r)(\cos(\mathrm{Im}(\lambda)r) - i\sin(\mathrm{Im}(\lambda)r))$, inserting $\lambda = i\omega$ into (3.10) yields

$$-\omega^2 + ip\omega + a + (ib\omega + q)(\cos(\omega r) - i\sin(\omega r)) = 0.$$

By separating the real and the imaginary parts, we have

$$\begin{aligned} -\omega^2 + a &= -q\cos(\omega r) - b\omega\sin(\omega r) \\ p\omega &= -b\omega\cos(\omega r) + q\sin(\omega r). \end{aligned} \tag{3.12}$$

Squaring both equations and adding them together yields $\omega^4 - 2a\omega^2 + a^2 + p^2\omega^2 = q^2 + b^2\omega^2$, which gives

$$\omega^4 - (b^2 - p^2 + 2a)\omega^2 + (a^2 - q^2) = 0. \tag{3.13}$$

The possible real roots of (3.13) are given by $\omega_\pm$ and $-\omega_\pm$, which have to satisfy

$$\omega_\pm^2 = \frac{1}{2}(b^2 - p^2 + 2a) \pm \frac{1}{2}\sqrt{(b^2 - p^2 + 2a)^2 - 4(a^2 - q^2)}. \tag{3.14}$$

It follows that if

(H_3) $(b^2 - p^2 + 2a) < 0$ and $a^2 - q^2 > 0$, or $(b^2 - p^2 + 2a)^2 < 4(a^2 - q^2)$,

we have $\omega_\pm^2 < 0$, or $\omega_\pm^2$ is not real. Thus, (3.13) does not have any real roots, which shows that (3.10) has no purely imaginary roots. Further, since the assumptions (H_1) and (H_2) ensure that all roots of (3.11) have negative real parts, it follows from Corollary 3.1 that all roots of (3.10) have negative real parts. On the other hand, we observe that if

(H_4) $a^2 - q^2 < 0$, or $(b^2 - p^2 + 2a) > 0$ and $(b^2 - p^2 + 2a)^2 = 4(a^2 - q^2)$

then (3.13) has one positive root ω_+ and if

(H_5) $a^2 - q^2 > 0$, $(b^2 - p^2 + 2a) > 0$ and $(b^2 - p^2 + 2a)^2 > 4(a^2 - q^2)$,

then there are two positive roots ω_+ and ω_- for (3.13). In case of (H_5), (3.10) can only have a pair of purely imaginary roots $\pm i\omega_+$ or $\pm i\omega_-$ for $r = r_n^+$ or $r = r_n^-$, where

$$r_n^\pm = \frac{1}{\omega_\pm}\left(\arcsin\left(\frac{pq\omega_\pm + b\omega_\pm(\omega_\pm^2 - a)}{q^2 + b^2\omega_\pm^2}\right) + 2n\pi\right), \quad n \in \{0, 1, 2, \dots\}.$$

Furthermore, in case of (H_4), (3.10) can only have a pair of purely imaginary roots $\pm i\omega_+$ for $r = r_n^+$.

Next, we examine if the real part of the roots of (3.10) for $r \in \{r_n^+, r_n^-\}$ crosses the imaginary axis from left to right or vice versa in order to study the existence of roots with positive real part.

Differentiating (3.10) with respect to r gives

$$2\lambda\frac{d\lambda}{dr} + p\frac{d\lambda}{dr} + b\frac{d\lambda}{dr}e^{-\lambda r} + (b\lambda + q)e^{-\lambda r}\left(-\frac{d\lambda}{dr}r - \lambda\right) = 0,$$

which yields

$$\frac{d\lambda}{dr}\left(2\lambda + p + (b - r(b\lambda + q))e^{-\lambda r}\right) = \lambda(b\lambda + q)e^{-\lambda r}.$$

For any $n \in \{0, 1, 2, \dots\}$, we write $\lambda_n^+ = \alpha_n^+(r) + i\omega_n^+(r)$, which satisfy $\alpha_n^+(r_n^+) = 0$ and $\omega_n^+(r_n^+) = \omega_+$. Substituting $\lambda_n^+ = i\omega_n^+(r_n^+)$ leads to

$$\begin{aligned}\frac{d\lambda_n^+}{dr}(r_n^+) &= \frac{(-b\omega_+^2 + iq\omega_+)(\cos(\omega_+ r_n^+) - i\sin(\omega_+ r_n^+))}{2i\omega_+ + p + (b - ir_n^+ b\omega_+ - r_n^+ q)(\cos(\omega_+ r_n^+) - i\sin(\omega_+ r_n^+))} \\ &= \frac{\alpha_{\text{nom}} + i\beta_{\text{nom}}}{\alpha_{\text{denom}} + i\beta_{\text{denom}}} = \frac{(\alpha_{\text{nom}} + i\beta_{\text{nom}}) \cdot (\alpha_{\text{denom}} - i\beta_{\text{denom}})}{\alpha_{\text{denom}}^2 + \beta_{\text{denom}}^2},\end{aligned}$$

where

$$\begin{aligned}\alpha_{\text{nom}} &= -b\omega_+^2 \cos(\omega_+ r_n^+) + q\omega_+ \sin(\omega_+ r_n^+), \\ \beta_{\text{nom}} &= q\omega_+ \cos(\omega_+ r_n^+) + b\omega_+^2 \sin(\omega_+ r_n^+), \\ \alpha_{\text{denom}} &= p + (b - r_n^+ q)\cos(\omega_+ r_n^+) - r_n^+ b\omega_+ \sin(\omega_+ r_n^+), \\ \beta_{\text{denom}} &= 2\omega_+ - (b - r_n^+ q)\sin(\omega_+ r_n^+) - r_n^+ b\omega_+ \cos(\omega_+ r_n^+).\end{aligned}$$

We thus have

$$\frac{d\text{Re}(\lambda_n^+)}{dr}(r_n^+) = \frac{\alpha_{\text{nom}}\alpha_{\text{denom}} + \beta_{\text{nom}}\beta_{\text{denom}}}{\alpha_{\text{denom}}^2 + \beta_{\text{denom}}^2} = \frac{\omega_+^2\left(-(b^2 - p^2 + 2a) + 2\omega_+^2\right)}{\alpha_{\text{denom}}^2 + \beta_{\text{denom}}^2},$$

where the last equality follows from (3.12). With (3.14) and the fact that $\omega_+^2 > 0$, we thus have

$$\frac{d\text{Re}(\lambda_n^+)}{dr}(r_n^+) > 0 \quad \text{and} \quad \frac{d\text{Re}(\lambda_n^-)}{dr}(r_n^-) < 0,$$

where the case for ω_- follows from an analogous calculation. Following [CG82; Rua09], we have the following properties:

(i) If (H_1)-(H_3) hold, then all roots of (3.10) have negative real parts for all $r \geq 0$.

(ii) If (H_1), (H_2), and (H_4) hold, then for $r \in [0, r_0^+)$, all roots of (3.10) have negative real parts. When $r = r_0^+$, (3.10) has a pair of purely imaginary roots $\pm i\omega_+$, and if $r > r_0^+$, (3.10) has at least one root with positive real part.

(iii) If (H_1), (H_2), and (H_5) hold, then there exists a positive integer k such that

$$0 < r_0^+ < r_0^- < r_1^+ < \cdots < r_{k-1}^- < r_k^+$$

where for $r \in [0, r_0^+), (r_0^-, r_1^+), \dots, (r_{k-1}^-, r_k^+)$, all roots of (3.10) have negative real parts while for $r \in [r_0^+, r_0^-], [r_1^+, r_1^-], \dots, [r_{k-1}^+, r_{k-1}^-]$, and $r \geq r_k^+$, (3.10) has at least one root with non-negative real part.

3.2.6 Hopf bifurcation

The Hopf bifurcation theorem, which we will present in the following section, is one of the most important results for DDEs. The theorem can be used to establish the existence of periodic solutions, which are often relevant for applications. Following [Smi10; Kut22], we consider a family of autonomous delay equations

$$\dot{x}(t) = F(x_t; \mu), \tag{3.15}$$

where $F : C \times \mathbb{R} \to \mathbb{R}^n$ is twice continuous differentiable in its arguments and $x = 0$ is an equilibrium for all μ, i.e. $F(0; \mu) = 0$. We linearize F about $x = 0$ as described in Section 3.2.4, where the corresponding linearized system is given by $\dot{z}(t) = L(z_t; \mu)$. We assume the following condition on the corresponding characteristic equation to hold.

(H) For $\mu = 0$, the characteristic equation has a pair of simple roots $\pm i\omega_0$, where $\omega_0 \neq 0$ and no other root is an integer multiple of $i\omega_0$.

Let $h(\lambda, \mu) = 0$ denote this characteristic equation. In particular, (H) implies that for the partial derivative, $h_\lambda(i\omega_0, 0) \neq 0$ holds. From the implicit function theorem it follows that there exists a continuously differentiable family of roots $\lambda = \lambda(\mu) = \alpha(\mu) + i\omega(\mu)$ for small μ, which satisfy $\lambda(0) = i\omega_0$. We further assume that

$$\frac{d\mathrm{Re}(\lambda)}{d\mu}(0) = \frac{d\alpha}{d\mu}(0) > 0, \tag{3.16}$$

which implies that the roots cross the imaginary axis transversally as μ increases through zero. In particular, the pair of roots has negative real part for $\mu < 0$ and positive real part for $\mu > 0$. Note that if $\frac{d\alpha}{d\mu}(0) < 0$, we can consider the bifurcation parameter $\tilde{\mu} = -\mu$ such that (3.16) holds. The Hopf bifurcation theorem is formulated as follows.

Theorem 3.17. Let (H) and (3.16) hold true. Then, there exist $\varepsilon_0 > 0$, real-valued even functions $\mu(\varepsilon)$ and $T(\varepsilon) > 0$ with $\mu(0) = 0$ and $T(0) = \frac{2\pi}{\omega_0}$, and a non-constant $T(\varepsilon)$-periodic function $p(t, \varepsilon)$, with all functions being continuously differentiable in ε for $|\varepsilon| < \varepsilon_0$, such that the following holds.

(i) $p(t, \varepsilon)$ is a solution of the system (3.15) and

(ii) $p(t, \varepsilon) = \varepsilon q(t, \varepsilon)$, where $q(t, 0)$ is a $\frac{2\pi}{\omega_0}$-periodic solution of $\dot{q}(t) = L(0)q$.

Furthermore, there exist μ_0, β_0, $\delta > 0$, such that if (3.15) has a non-constant periodic solution $x(t)$ with period P for some μ satisfying $|\mu| < \mu_0$ with $\max_t |x(t)| < \beta_0$ and $|P - 2\pi/\omega_0| < \delta$, then $\mu = \mu(\varepsilon)$ and $x(t) = p(t + \theta, \varepsilon)$ for some $|\varepsilon| < \varepsilon_0$ and some θ.

If F is five times continuously differentiable, we then have

$$\mu(\varepsilon) = \mu_1 \varepsilon^2 + \mathcal{O}(\varepsilon^4)$$
$$T(\varepsilon) = \frac{2\pi}{\omega_0} \left(1 + \tau_1 \varepsilon^2 + \mathcal{O}(\varepsilon^4)\right).$$

If all other characteristic roots for $\mu = 0$ have strictly negative real parts except for $\pm i\omega_0$, then $p(t, \varepsilon)$ is asymptotically stable if $\mu_1 > 0$ and unstable if $\mu_1 < 0$.

4 A model by Kuznetsov et al.

In the work of [Kuz+94] in 1994, the authors present a mathematical model to describe a cell mediated response to a growing tumor cell population. The two-population model accounts for both the infiltration of the tumor by effector cells as well as the possibility of effector cell inactivation by the interaction with tumor cells. Additionally, the model is shown to exhibit oscillatory growth patterns in tumor cells, growth dormancy, as well as the "sneaking through" phenomenon. The latter describes the state where for high effector cell levels, the tumor cell population quickly approaches an apparent dormancy, in which the effector cell level gradually decreases leading to an eventual escape of the tumor. In particular, for two stimulated patients beginning with the same tumor cell level, the "sneaking through" phenomenon results in one having a progressive disease while the immune system of the other patient is able to keep the tumor in a dormancy state. Non-intuitively, the latter begins with a lower effector cell level than the former. This behavior can be explained by the presence of a *separatrix* in the phase plane of the system, where the stable manifold of the unstable, saddle equilibrium separates the basins of attraction of the two stable equilibria.

4.1 Model assumptions and formulation

The tumor-immune model is based on the "predator-prey" approach first proposed by Lotka in 1910, which is then used by Kolmogorov and subsequently by Volterra in year 1925 to study the dynamics of fish populations in the Adriatic. In the context of tumor-immune interaction, tumor cells play the role of the prey, while the effectors cells are the predators. Let T and E denote the tumor cell and effector cell population, respectively. The assumptions of the model are given as follows:

(1) In the absence of effector cells, the growth of the tumor cell population follows a logistic function.

(2) Interaction between tumor and effector cell populations is able to induce signals, such as released cytokines, which are able to recruit more effector cells to the site of the tumor. There is a limit at which the effector cells can be stimulated.

(3) In the absence of tumor cells, most effector cells undergo apoptosis.

(4) Each cytotoxic T cell will eventually become inactive after some number of interactions with tumor cells due to e.g. the aspect that effector cells can only produce a limited amount of proteins, which damage/kill tumor cells, and the ability of tumor cells to develop mechanisms to induce apoptosis of some nearby effector cells.

(5) The number of interactions between tumor and effector cells is proportional to the product of the two cell populations.

(6) Effector cells, such as NK cells and macrophages, are present even in the absence of a specific threat.

Putting these assumptions together and assuming Michaelis-Menten kinetics for the stimulated recruitment of effector cells by tumor cells yields the system of differential equations

$$\begin{aligned} \frac{dT}{dt} &= aT(1-bT) - \tilde{d}ET \\ \frac{dE}{dt} &= \sigma + \frac{\tilde{j}ET}{\tilde{g}+T} - \tilde{q}ET - \tilde{m}E, \end{aligned} \tag{4.1}$$

where all parameters are assumed to be positive. Table 4.1 contains the biological interpretation of the parameters, their units as well as the estimated values from [Kuz+94] based on experimental data in mice. Further, the stimulated recruitment rate by tumor cells per effector cell for $\tilde{j} = 0.8$ day^{-1} and $\tilde{g} = 1 \cdot 10^8$ cells is shown in Figure 4.1.

The interaction terms in the system (4.1) are derived from the law of mass-action, reflecting Assumption (5). This assumes a homogeneous environment, i.e. each tumor cell is equally likely to encounter an effector cell. In reality, this will not be the case, for example due to space limitations. In the later chapters, we will discuss various other approaches to describe the interaction term.

We further observe that the set $[0, b^{-1}] \times [0, \infty) \subset \mathbb{R}^2$ is positively invariant for the system (4.1) since the following is satisfied:

$$\begin{aligned} T = 0,\ E \geq 0: &\quad \frac{dT}{dt} = 0 \\ T = \frac{1}{b},\ E \geq 0: &\quad \frac{dT}{dt} = -\frac{dE}{b} \leq 0 \\ E = 0,\ T \in \left[0, \frac{1}{b}\right]: &\quad \frac{dE}{dt} = \sigma > 0. \end{aligned}$$

Further, for $(T, E) \in (0, b^{-1}) \times (0, \infty)$, which is a simply connected region, we have,

Table 4.1: Description of parameters in (4.1), their units, as well as the estimated parameter values from [Kuz+94].

Parameter	Unit	Description	Value in [Kuz+94]
a	day^{-1}	tumor growth rate	0.18
b	cells^{-1}	inverse of the carrying capacity of tumor cell population	$0.002 \cdot 10^{-6}$
$\tilde{d}$	$\text{day}^{-1}\ \text{cells}^{-1}$	tumor cell elimination rate caused by effector cells	$1.101 \cdot 10^{-7}$
σ	cells day^{-1}	constant source rate of effector cells	$0.013 \cdot 10^{6}$
$\tilde{j}$	day^{-1}	maximal recruitment rate of effector cells (stimulated by tumor cells)	$1.245 \cdot 10^{-1}$
$\tilde{g}$	cells	number of tumor cells at which the stimulated recruitment rate reaches its half-maximum (smaller $\tilde{g}$ implies a faster increase of effector cell stimulation)	$2.019 \cdot 10^{7}$
$\tilde{q}$	$\text{day}^{-1}\ \text{cells}^{-1}$	effector cell inactivation rate caused by tumor cells	$3.422 \cdot 10^{-10}$
$\tilde{m}$	day^{-1}	effector cell inactivation rate independent of tumor cells	$0.412 \cdot 10^{-1}$

by setting $\rho(T,E) = \frac{1}{ET} > 0$,

$$\begin{aligned}
&\operatorname{div}\left(\rho(T,E)\cdot\frac{dT}{dt},\ \rho(T,E)\cdot\frac{dE}{dt}\right)\\
=&\frac{\partial}{\partial T}\left(\frac{a(1-bT)}{E}-d\right)+\frac{\partial}{\partial E}\left(\frac{\sigma}{ET}+\frac{j}{g+T}-q-\frac{m}{T}\right)\\
=&-\left(\frac{\sigma}{TE^2}+\frac{ab}{E}\right)<0
\end{aligned}$$

and thus, the negative criterion of Bendixson-Dulac shows that the system described in (4.1) has no periodic orbits.

The equilibria of the model can be found by setting the right-hand-side of the equations in (4.1) to zero, which can, depending on the parameter values, yield up to four solutions. For the set of parameter values specified in Table 4.1, the system described in (4.1) has four equilibria denoted by A, B, C, and D, where A describes the tumor-free state with $T = 0$ and $E = \frac{\sigma}{m}$. The equilibrium B denotes the "dormant tumor" state, which is characterized by a relatively low tumor cell level, while the tumor cell level in D is relatively high and D is referred to as the

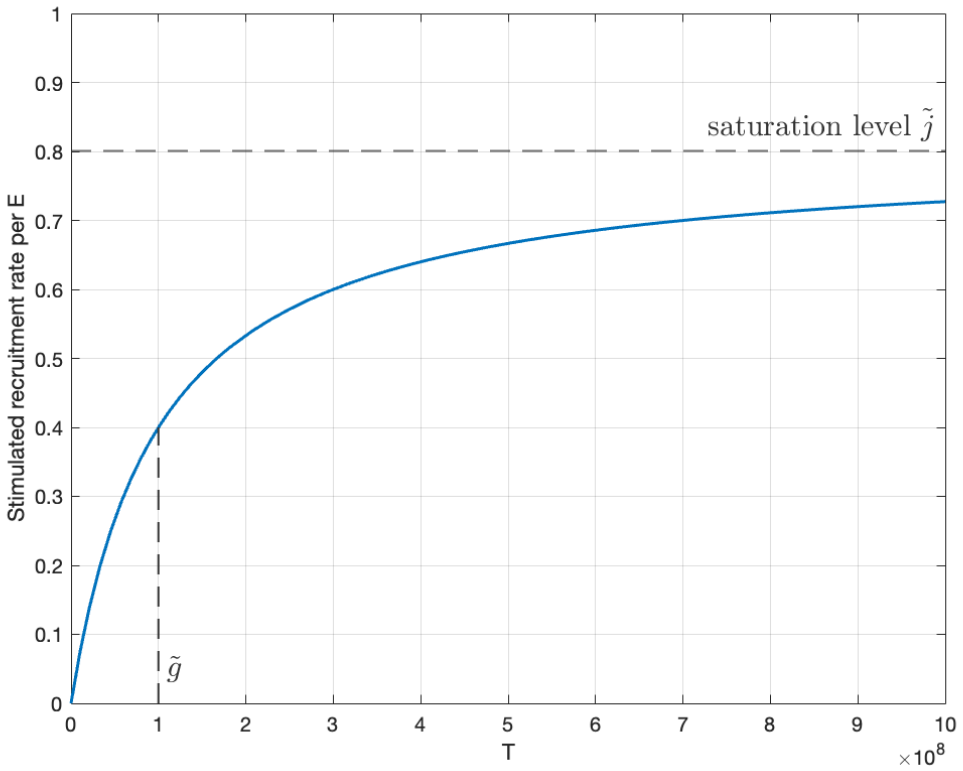


Figure 4.1: Stimulated recruitment rate by tumor cells with a saturation level at $\tilde{j} = 0.8$ day^{-1} and $\tilde{g} = 1 \cdot 10^8$ cells, at which the half-maximal value is obtained.

case of "tumor escape". The equilibria B and D are both locally asymptotically stable. For the same set of parameter values, all solutions beginning with a high level of effector cells and low level of tumor cells approach the dormant tumor state B asymptotically.

4.2 Existence of a heteroclinic bifurcation

In the work of [Kuz+94], Kuznetsov et al. showed that the system (4.1) establishes a *heteroclinic bifurcation*, where the boundaries of basins of attraction of the stable equilibria B and D dramatically change. In particular, the stable manifold of the unstable equilibrium C and the unstable manifold of the equilibrium A coincide. Before the heteroclinic bifurcation, the system establishes the phenomenon known as "sneaking through", which describes the situation where a tumor cell population seems to have reached an equilibrium, where it remains for some time, and then begins to proliferate. In particular, a trajectory with the same initial level of tumor cells but lower amount of effector cells results in a better outcome. One biological

interpretation is that a high amount of effector cells causes more tumor cells to be eliminated in the initial phase. However, while the tumor level is low, the immune response gradually drops until the tumor cell population is able to proliferate.

5 An ODE approach on the dynamics between tumor and cytotoxic T cells

In the model presented by Kuznetsov et al., the authors considered effector cell populations including cytotoxic T cells, NK cells, macrophages, or any other effector cells involved in the immune surveillance against tumor cells. In the following chapter, we want to focus on the interaction between antigenic tumor cells and tumor-specific cytotoxic T cells, which are only produced after an antigenic response of the naive forms of cytotoxic T cells. We therefore assume the constant, tumor-independent production rate of cytotoxic T cells σ to be zero. Furthermore, as mentioned before, Assumption (5) used in the model (4.1) is derived from the law of mass action, which may not always be appropriate in reality. Therefore, in the following chapters, we consider different functions for the elimination rate term in $\frac{dT}{dt}$, including the fractional kill rate term proposed in [dRW05] in 2005. For the rest of the chapter, let T and L denote the tumor cell and cytotoxic T cell population, respectively and assume Assumption (1)-(4) from the previous chapter to hold true.

5.1 Model assumptions and formulation

In 2006, Wiedemann et al. showed that an individual cytotoxic T cell is able to interact with multiple targets and eliminate them simultaneously in [Wie+06]. Further, in 2014, Roesch, Hasenclever, and Scholz presented a model to describe the tumor-immune interaction in large cell lymphoma and considered in [RHS14] the interaction of effector cells and tumor cells to be proportional to the tumor surface, which is proportional to $T^{2/3}$. Therefore, in the following section, we generalize the elimination rate term used in [Kuz+94] by choosing

$$g(T, L) = \tilde{d}LT^n, \tag{5.1}$$

where $n > 0$. The resulting system of differential equations is given by

$$\begin{aligned} \frac{dT}{d\tau} &= aT(1-bT) - \tilde{d}LT^n \\ \frac{dL}{d\tau} &= -\tilde{q}LT^n + \frac{\tilde{j}T^n}{\tilde{g}^n + T^n}L - \tilde{m}L, \end{aligned} \tag{5.2}$$

where all parameters are assumed to be positive. Table 5.1 contains the biological interpretation of the parameters as well as their units.

Table 5.1: Description of parameters in (5.2) and their units.

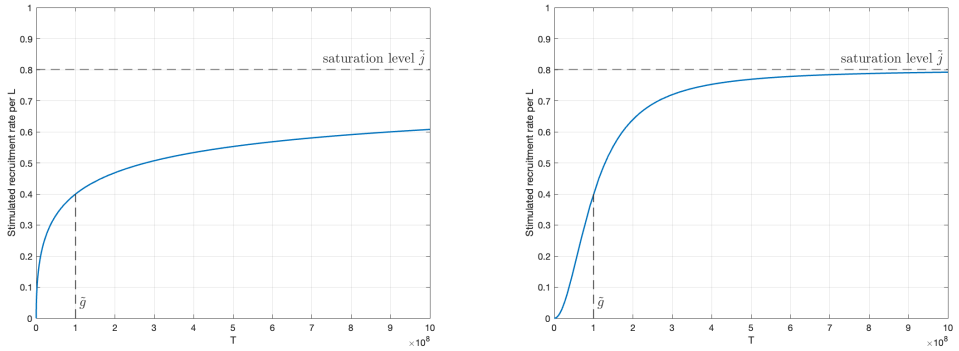
Parameter	Unit	Description
a	day^{-1}	tumor growth rate
b	cells^{-1}	inverse of the carrying capacity of tumor cell population
$\tilde{d}$	$\text{day}^{-1}\ \text{cells}^{-1}$	tumor cell elimination rate caused by cytotoxic T cells
$\tilde{j}$	day^{-1}	maximal recruitment rate of cytotoxic T cells (stimulated by tumor cells)
$\tilde{g}$	cells	number of tumor cells at which the stimulated recruitment rate reaches its half-maximum
$\tilde{q}$	$\text{day}^{-1}\ \text{cells}^{-1}$	cytotoxic T cell inactivation rate caused by tumor cells
$\tilde{m}$	day^{-1}	cytotoxic T cell inactivation rate independent of tumor cells
n	none	exponent in interaction terms of tumor and cytotoxic T cells

Note that the biological interpretation of the parameters $\tilde{j}$ and $\tilde{g}$ is not influenced by n. For $\tilde{j} = 0.8\ \text{day}^{-1}$, and $\tilde{g} = 1 \cdot 10^8$ cells, Figure 5.1 shows the stimulated recruitment rate per cytotoxic T cell for $n = 0.5$ and $n = 2$.

To simplify the model analysis, we re-parametrize the model by considering $x := bT$, $y := bL$, and $t := a\tau$. We associate $\frac{dx}{dt}$ and $\frac{dy}{dt}$ with $\dot{x}$ and $\dot{y}$, respectively and denote $d := \frac{1}{ab^n}\tilde{d}$, $q := \frac{1}{ab^n}\tilde{q}$, $j := \frac{1}{a}\tilde{j}$, $g := b\tilde{g}$, and $m := \frac{1}{a}\tilde{m}$ leading to the following re-parametrized model:

$$\begin{aligned} \dot{x} &= x(1-x) - dx^n y \\ \dot{y} &= -qx^n y + \frac{jx^n}{g^n + x^n}y - my \end{aligned} \tag{5.3}$$

We can verify that the parameters and variables in (5.3) are dimensionless.



(a) $n = 0.5$ (b) $n = 2$

Figure 5.1: Stimulated recruitment rate for model (5.2) with a saturation level of $\tilde{j} = 0.8$ day^{-1}, $\tilde{g} = 1 \cdot 10^8$ cells, and $n \in \{0.5, 2\}$.

5.2 Qualitative analysis

We analyze the qualitative behavior of the system (5.3) in a general setting. We first observe that the set $D := [0,1] \times [0,\infty) \subset \mathbb{R}^2$ is positively invariant for the system for all $n > 0$, as

$$\begin{aligned} x = 0,\ y \geq 0: &\quad \dot{x} = 0 \\ x = 1,\ y \geq 0: &\quad \dot{x} = -dy \leq 0 \\ y = 0,\ x \in [0,1]: &\quad \dot{y} = 0 \end{aligned}$$

holds true for all $n > 0$. Further, $\text{int}(D)$ is a simply connected region. With $h_1(x,y) = x(1-x) - dx^n y$, $h_2(x,y) = -qx^n y + \frac{jx^n y}{g+x^n} - my \in C^1(\text{int}(D), \mathbb{R})$ and $\rho(x,y) = \frac{1}{xy} > 0$ for $(x,y) \in \text{int}(D)$, we have that

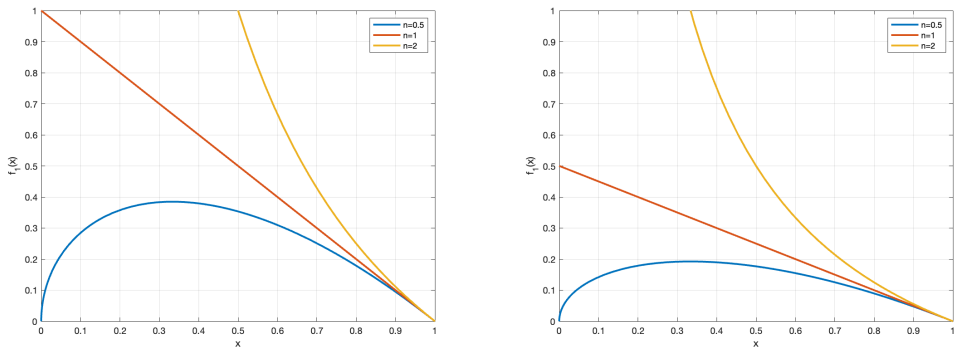
$$\begin{aligned} &\text{div}\left(\rho(x,y) \cdot h_1(x,y),\ \rho(x,y) \cdot h_2(x,y)\right) \\ =&\frac{\partial}{\partial x}\left(\frac{1-x}{y} - dx^{n-1}\right) + \frac{\partial}{\partial y}\left(-qx^{n-1} + \frac{jx^{n-1}}{g^n + x^n} - \frac{m}{x}\right) \\ =&-\left(\frac{1}{y} - (n-1)dx^{n-2}\right) < 0 \end{aligned}$$

for all $(x,y) \in \text{int}(D)$ and $n \geq 1$. Thus, from the negative criterion of Bendixson-Dulac, the system described in (5.3) has no closed orbits lying entirely in $\text{int}(D)$ for $n \geq 1$. In particular the system has no periodic orbits in D for $n \geq 1$. However, we will later see that the existence of a periodic orbit is possible for $n < 1$. The equilibria are found by determining the intersections of the nullclines $\dot{x} = 0$ and

$\dot{y} = 0$ in D. The nullclines are given by

$$\begin{aligned} \dot{x} = 0: \qquad & x = 0 \quad \text{or} \quad y = \frac{1-x}{dx^{n-1}} =: f_1(x) \\ \dot{y} = 0: \qquad & y = 0 \quad \text{or} \quad f_2(x) := -qx^n + \frac{jx^n}{g^n + x^n} - m = 0. \end{aligned} \tag{5.4}$$

Note that the equilibria $E_0 = (\bar{x}_0, \bar{y}_0) = (0,0)$ and $E_3 = (\bar{x}_3, \bar{y}_3) = (1,0)$ always exist. The steady state E_3 can be considered as the tumor-escape scenario while the steady state E_0 can be described as the tumor-free equilibrium. Note that for $n < 1$, the first equation in (5.3) is not differentiable in $x = 0$. Therefore, it is not possible to study the stability of this equilibrium E_0 by determining the eigenvalues of the linearized system around E_0. However, we note that for $y = 0$ and $x > 0$, $\dot{x} = x(1-x)$ is always positive. It thus follows that E_0 is unstable regardless of the parameter values chosen. The curve of the nullcline of x for different values of n and d is shown in Figure 5.2 and 5.3. We observe that $x = 1$ is always a root. The function f_1 has another root in $x = 0$ for $n < 1$ and intersects the $y-$axis only for $n = 1$. For $n > 1$, the function approaches infinity for $x \to 0$.



(a) $d = 1$ (b) $d = 2$

Figure 5.2: Graph of f_1 in (5.4) for $n \in \{0.5, 1, 2\}$.

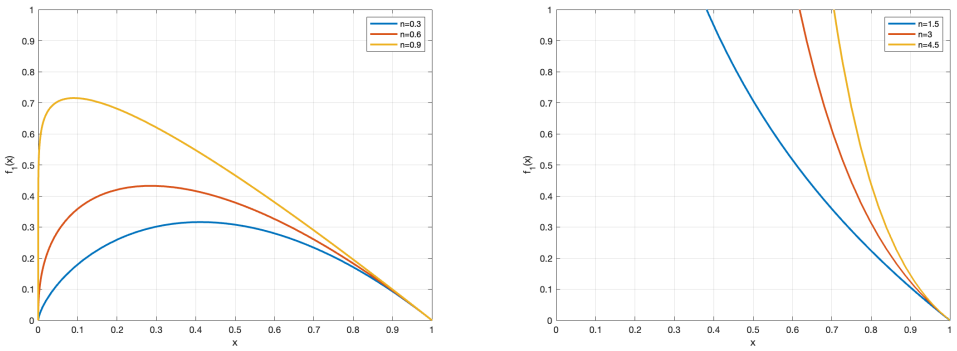
If f_1 is well-defined on the entire interval $(0,1)$, which is the case here, then the non-trivial equilibria are given by $(\bar{x}, \bar{y})$, where $\bar{x} \in (0,1)$ is a solution of $f_2(x) = 0$ on the interval $(0,1)$ and $\bar{y} = f_1(\bar{x})$. The following lemma allows us to determine the number of solutions of $f_2(x) = 0$ in $(0,1)$.

Lemma 5.1. Let n, q, j, g, and m be positive, and consider

$$f_2(x) = -qx^n + \frac{jx^n}{g + x^n} - m. \tag{5.5}$$

If $mg^n < q$ and

1. $j < qg^n + m + 2\sqrt{qg^n m}$, then f_2 has no roots in $(0,1)$;



(a) $n < 1$ (b) $n > 1$

Figure 5.3: Graph of f_1 in (5.4) for $d = 1$ and different n values.

2. $j = qg^n + m + 2\sqrt{qg^n m}$, then f_2 has one root in $(0, 1)$;
3. $qg^n + m + 2\sqrt{qg^n m} < j < qg^n + m + q + mg^n = (1 + g^n)(q + m)$, then f_2 has 2 roots in $(0, 1)$;
4. $j \geq (1 + g^n)(q + m)$, then f_2 has one root in $(0, 1)$.

If $mg^n \geq q$ and

1. $j \leq (1 + g^n)(q + m)$, then f_2 has no roots in $(0, 1)$;
2. $j > (1 + g^n)(q + m)$, then f_2 has one root in $(0, 1)$.

Further, for $x \in (\bar{x}_1, \bar{x}_2)$, $f_2(x) > 0$ and for $x \notin (\bar{x}_1, \bar{x}_2)$, we have that $f_2(x) < 0$.

Proof. Let $z := x^n$. For $f_2(x) = 0$, we have the following chain of equivalences:

$$\begin{aligned} & -qx^n + \frac{jx^n}{g^n + x^n} - m = 0 \\ \Leftrightarrow \quad & -qx^{2n} + (-qg^n - m + j)x^n - mg^n = 0 \\ \Leftrightarrow \quad & z^2 - \frac{-qg^n - m + j}{q} z + \frac{mg^n}{q} = 0 \\ \Leftrightarrow \quad & z_{1,2} = \frac{-qg^n - m + j \pm \sqrt{(-qg^n - m + j)^2 - 4qg^n m}}{2q} \end{aligned}$$

Note that $z \in (0, 1)$ iff $x \in (0, 1)$ and with $\bar{x}_{1,2} = z_{1,2}^{1/n}$, there are at most two roots in $(0, 1)$. We now analyze the conditions for which $z_{1,2} \in (0, 1)$ is satisfied. The solutions $z_{1,2}$ are real iff

$$\begin{aligned} 0 &\leq (-qg^n - m + j)^2 - 4qg^n m \\ &= (j^2 - 2(qg^n + m)j + (qg^n)^2 + m^2 + 2qg^n m) - 4qg^n m \\ &= j^2 - 2(qg^n + m)j + (qg^n)^2 + m^2 - 2qg^n m \\ &= j^2 - 2(qg^n + m)j + (qg^n - m)^2 \end{aligned} \tag{5.6}$$

is satisfied. For fixed parameters q, g^n, m and variable j, this is a parabola facing upward. Thus, (5.6) is fulfilled for all $0 < j \leq j_1$ and $j_2 \leq j$, where

$$\begin{aligned} j_{1,2} &= qg^n + m \pm \sqrt{(qg^n + m)^2 - (qg^n - m)^2} \\ &= qg^n + m \pm 2\sqrt{qg^n m}. \end{aligned}$$

The second equality follows from

$$\begin{aligned} (qg^n + m)^2 - (qg^n - m)^2 &= (qg^n)^2 + 2qg^n m + m^2 - (qg^n)^2 + 2qg^n m - m^2 \\ &= 4qg^n m. \end{aligned}$$

We first have a look at the case where $mg^n < q$, and consider the following scenarios:

(a) $0 < j < qg^n + m - 2\sqrt{qg^n m}$

(b) $j = qg^n + m - 2\sqrt{qg^n m}$

(c) $j = qg^n + m + 2\sqrt{qg^n m}$

(d) $qg^n + m + 2\sqrt{qg^n m} < j < qg^n + m + q + mg^n = (1 + g^n)(q + m)$

(e) $j = (1 + g^n)(q + m)$

(f) $j > (1 + g^n)(q + m)$

Recall that Scenario (a)-(f) guarantee that z_1 and z_2 are real. We will later also consider the same scenarios for $mg^n \geq q$. Note that for $mg^n \neq q$, we have $q + mg^n - 2\sqrt{qg^n m} = (\sqrt{q} - \sqrt{mg^n})^2 > 0$, which implies that $qg^n + m + 2\sqrt{qg^n m} < qg^n + m + q + mg^n$. Therefore, Scenario (d) is possible. On the other hand, $mg^n = q$ implies that $2\sqrt{qg^n m} = 2q = q + mg^n$ and thus, Scenario (c) and (e) fall together and Scenario (d) will never appear. We observe the following for $mg^n < q$:

Scenario (a) We have

$$\frac{-qg^n - m + j}{2q} < -\frac{2\sqrt{qg^n m}}{2q} = -\sqrt{\frac{mg^n}{q}} < 0$$

and $\sqrt{(-qg^n - m + j)^2 - 4qg^n m} < qg^n + m - j$. It follows that $z_1, z_2 < 0$ and thus, f_2 has no roots in $(0, 1)$.

Scenario (b) We have

$$z_1 = z_2 = \frac{-qg^n - m + j}{2q} = -\frac{2\sqrt{qg^n m}}{2q} = -\sqrt{\frac{mg^n}{q}} < 0$$

and thus, f_2 has no roots in $(0, 1)$.

Scenario (c) With

$$0 < z_1 = z_2 = \frac{-qg^n - m + j}{2q} = \frac{2\sqrt{qg^n m}}{2q} = \sqrt{\frac{mg^n}{q}} < 1,$$

f_2 has one root in $(0, 1)$.

Scenario (d) With $\sqrt{(-qg^n - m + j)^2 - 4qg^n m} < -qg^n - m + j$ and $-qg^n - m + j > 2\sqrt{qg^n m} > 0$, we have $z_1, z_2 > 0$. Further, with $-qg^n - m + j < q + mg^n$, it follows that

$$\begin{aligned}
& q(-qg^n - m + j) < q(q + mg^n) = q^2 + qg^n m \\
\Leftrightarrow\ & 4q(-qg^n - m + j) < 4q^2 + 4qg^n m \\
\Leftrightarrow\ & -4qg^n m < 4q^2 - 4q(-qg^n - m + j) \\
\Leftrightarrow\ & (-qg^n - m + j)^2 - 4qg^n m < 4q^2 - 4q(-qg^n - m + j) + (-qg^n - m + j)^2 \\
\Leftrightarrow\ & (-qg^n - m + j)^2 - 4qg^n m < (2q - (-qg^n - m + j))^2.
\end{aligned}$$

Since $2q - (-qg^n - m + j) > 2q - q - mg^n = q - mg^n > 0$ holds true, we have

$$\begin{aligned}
& \sqrt{(-qg^n - m + j)^2 - 4qmg^n} < 2q - (-qg^n - m + j) \\
\Leftrightarrow\ & -qg^n - m + j + \sqrt{(-qg^n - m + j)^2 - 4qg^n m} < 2q \\
\Leftrightarrow\ & z_2 = \frac{-qg^n - m + j + \sqrt{(-qg^n - m + j)^2 - 4qg^n m}}{2q} < 1.
\end{aligned}$$

and particularly, since $z_1 < z_2$ holds, $z_1 < 1$ holds true as well. Therefore, $z_{1,2}$ are both in $(0, 1)$ and f_2 has two roots in $(0, 1)$.

Scenario (e) With $\sqrt{(-qg^n - m + j)^2 - 4qg^n m} < -qg^n - m + j$ and $-qg^n - m + j = q + mg^n > 0$, we have $z_1, z_2 > 0$. Further, we observe that $(-qg^n - m + j)^2 - 4qg^n m = (q + mg^n)^2 - 4qg^n m = (q - mg^n)^2$ and since $mg^n < q$ holds, we have

$$\begin{aligned}
z_1 &= \frac{-qg^n - m + j - q + mg^n}{2q} = \frac{q + mg^n - q + mg^n}{2q} = \frac{mg^n}{q} < 1 \\
z_2 &= \frac{-qg^n - m^n + j + q - mg^n}{2q} = \frac{q + mg^n + q - mg^n}{2q} = 1.
\end{aligned}$$

Thus, f_2 has one root in $(0, 1)$.

Scenario (f) With $\sqrt{(-qg^n - m + j)^2 - 4qg^n m} < -qg^n - m + j$ and $-qg^n - m + j > q + mg^n > 0$, we have $z_1, z_2 > 0$. Further, with $-(-qg^n - m + j) < -q - mg^n$, we have

$$\begin{aligned}
& -4q(-qg^n - m + j) < -4q^2 - 4qg^n m \\
\Leftrightarrow\ & (-qg^n - m + j)^2 - 4q(-qg^n - m + j) + 4q^2 < (-qg^n - m + j)^2 - 4qg^n m \\
\Leftrightarrow\ & ((-qg^n - m + j) - 2q)^2 < (-qg^n - m + j)^2 - 4qg^n m.
\end{aligned}$$

With $\sqrt{(-qg^n - m + j)^2 - 4qg^n m} > |(-qg^n - m + j) - 2q| \geq (-qg^n - m + j) - 2q$, it follows that

$$\begin{aligned} & \sqrt{(-qg^n - m + j)^2 - 4qg^n m} > (-qg^n - m + j) - 2q \\ \Leftrightarrow \quad & -\sqrt{(-qg^n - m + j)^2 - 4qg^n m} < -(-qg^n - m + j) + 2q \\ \Leftrightarrow \quad & (-qg^n - m + j) - \sqrt{(-qg^n - m + j)^2 - 4qg^n m} < 2q \\ \Leftrightarrow \quad & z_1 = \frac{(-qg^n - m + j) - \sqrt{(-qg^n - m + j)^2 - 4qg^n m}}{2q} < 1. \end{aligned}$$

On the other hand, with $\sqrt{(-qg^n - m + j)^2 - 4qg^n m} > |(-qg^n - m + j) - 2q| \geq -(-qg^n - m + j) + 2q$, we have

$$\begin{aligned} & \sqrt{(-qg^n - m + j)^2 - 4qg^n m} > -(-qg^n - m + j) + 2q \\ \Leftrightarrow \quad & (-qg^n - m + j) + \sqrt{(-qg^n - m + j)^2 - 4qg^n m} > 2q \\ \Leftrightarrow \quad & z_2 = \frac{(-qg^n - m + j) + \sqrt{(-qg^n - m + j)^2 - 4qg^n m}}{2q} > 1. \end{aligned}$$

Thus, f_2 has one root in $(0, 1)$.

We note that the arguments for Scenario (a), (b), and (f) do not depend on the relation between q and mg^n and can be performed in an analogous way for $mg^n \geq q$.

For $mg^n = q$, we have the following:

Scenario (c) and (e) We have

$$z_1 = z_2 = \frac{-qg^n - m + j}{2q} = \frac{2q}{2q} = 1$$

and thus, f_2 has no roots in $(0, 1)$.

Lastly, for $mg^n > q$, we have the following:

Scenario (c) We have

$$z_1 = z_2 = \frac{-qg^n - m + j}{2q} = \frac{2\sqrt{qg^n m}}{2q} = \sqrt{\frac{mg^n}{q}} > 1.$$

Thus, f_2 has no roots in $(0, 1)$.

Scenario (d) Similar as before, we have

$$\begin{aligned} & 4q(-qg^n - m + j) < 4q^2 + 4qg^n m \\ \Leftrightarrow \quad & (-qg^n - m + j)^2 - 4qg^n m < (-qg^n - m + j)^2 - 4q(-qg^n - m + j) + 4q^2 \\ \Leftrightarrow \quad & (-qg^n - m + j)^2 - 4qg^n m < (2q - (-qg^n - m + j))^2. \end{aligned}$$

and since $2\sqrt{qg^n m} < -qg^n - m + j < q + mg^n$ and $mg^n > q$ hold true, we observe that

$$2q - (-qg^n - m + j) < 2q - 2\sqrt{qg^n m} < 2q - 2q = 0,$$

which leads to

$$\begin{aligned} & \sqrt{(-qg^n - m + j)^2 - 4qg^n m} < (-qg^n - m + j) - 2q \\ \Leftrightarrow \quad & -\sqrt{(-qg^n - m + j)^2 - 4qg^n m} > -(-qg^n - m + j) + 2q \\ \Leftrightarrow \quad & (-qg^n - m + j) - \sqrt{(-qg^n - m + j)^2 - 4qg^n m} > 2q \\ \Leftrightarrow \quad & z_1 = \frac{(-qg^n - m + j) - \sqrt{(-qg^n - m + j)^2 - 4qg^n m}}{2q} > 1. \end{aligned}$$

Since $z_2 > z_1 > 1$, f_2 has no roots in $(0, 1)$.

Scenario (e) We observe that $(-qg^n - m + j)^2 - 4qg^n m = (q + mg^n)^2 - 4qg^n m = (mg^n - q)^2$ and since $mg^n > q$ holds true, we have

$$\begin{aligned} z_1 &= \frac{-qg^n - m + j - mg^n + q}{2q} = \frac{q + mg^n - mg^n + q}{2q} = \frac{q}{q} = 1, \\ z_2 &= \frac{-qg^n - m + j + mg^n - q}{2q} = \frac{q + mg^n + mg^n - q}{2q} = \frac{mg^n}{q} > 1. \end{aligned}$$

Hence, f_2 has no roots in $(0, 1)$.

From the previous analysis, we can have the following cases for the position of the roots $\bar{x}_{1,2}$, where $\bar{x}_1 \leq \bar{x}_2$:

1. $\bar{x}_{1,2} \leq 0$
2. $\bar{x}_1 \in (0, 1)$ and $\bar{x}_2 \geq 1$
3. $\bar{x}_{1,2} \in (0, 1)$
4. $\bar{x}_{1,2} \geq 1$

Furthermore, we note that f_2 is continuous in $[0, 1]$, where $f_2(0) = -m < 0$. A change of sign occurs only at $\bar{x}_{1,2}$ and since $\bar{x}_1 \leq \bar{x}_2$, we have that $f_2(x) > 0$ for $x \in (\bar{x}_1, \bar{x}_2)$. In particular, for case 1 and 4, $f_2(x) < 0$ for all $x \in (0, 1)$. □

We can now formulate the following theorem on the number of equilibria of system (5.3) in $\text{int}(D)$.

Theorem 5.1. Let n, d, q, j, g, and m be positive and consider the system (5.3). Let f_1 be the non-zero component of the x nullcline. If $f_1 : (0, 1) \to [0, \infty)$ is well-defined, then the following holds. If $mg^n < q$ and

1. $j < qg^n + m + 2\sqrt{qg^n m}$, then system (5.3) has no equilibria in $\text{int}(D)$;

2. $j = qg^n + m + 2\sqrt{qg^n m}$, then system (5.3) has one additional equilibrium in $\mathrm{int}(D)$;

3. $qg^n + m + 2\sqrt{qg^n m} < j < qg^n + m + q + mg^n = (1 + g^n)(q + m)$, then system (5.3) has two additional equilibria in $\mathrm{int}(D)$;

4. $j \geq (1 + g^n)(q + m)$, then system (5.3) has one additional equilibrium in $\mathrm{int}(D)$.

If $mg^n \geq q$ and

1. $j \leq (1 + g^n)(q + m)$, then system (5.3) has no additional equilibria in $\mathrm{int}(D)$;

2. $j > (1 + g^n)(q + m)$, then system (5.3) has one additional equilibrium in $\mathrm{int}(D)$.

Proof. From Lemma 5.1, we know the number of roots of f_2 in $(0, 1)$ and since f_1 in (5.4) is defined on the interval $(0, 1)$, we have

$$\bar{y}_{1,2} = \frac{1 - \bar{x}_{1,2}}{d\bar{x}_{1,2}^{n-1}} > 0$$

if $\bar{x}_{1,2} \in (0, 1)$, where $\bar{x}_{1,2}$ are the roots of f_2. □

We recall that the dimensionless parameters m, g, and q denote the cytotoxic T cell inactivation rate independent of tumor cells, amount of tumor cells at which the stimulated recruitment rate is at its half-maximal value, and cytotoxic T cell inactivation rate due to tumor cells, respectively. Furthermore, j describes the maximal stimulated recruitment rate of cytotoxic T cells. If the immune system is able to recruit enough cytotoxic T cells fast enough, i.e. $j \geq qg^n + m + 2\sqrt{qg^n m}$ for $mg^n < q$ and $j > (1 + g^n)(q + m)$ for $mg^n \geq q$, the system (5.3) can establish a non-trivial equilibrium. However, if the maximal stimulated recruitment rate of cytotoxic T cells is too small, i.e. $j < qg^n + m + 2\sqrt{qg^n m}$ for $mg^n < q$ and $j \leq (1 + g^n)(q + m)$ for $mg^n \geq q$, the existence of a tumor dormant state will not be possible.

Moreover, in reality it is rather unlikely to observe parameter combinations such that equality in Theorem 5.1 holds. Thus, in the following, we only consider the cases where inequality is satisfied.

5.2.1 Local stability

We denote the non-trivial equilibria as $E_{1,2} = (\bar{x}_{1,2}, \bar{y}_{1,2})$, where $\bar{x}_1 < \bar{x}_2$ and $\bar{y}_{1,2} = \frac{1-\bar{x}_{1,2}}{d\bar{x}_{1,2}^{n-1}}$. For the linearized system of (5.3), the general Jacobian matrix for $x > 0$ reads

$$J(x, y) = \begin{pmatrix} 1 - 2x - ndx^{n-1}y & -dx^n \\ -nqx^{n-1}y + ng^n \frac{jx^{n-1}}{(g^n + x^n)^2} y & -qx^n + \frac{jx^n}{g^n + x^n} - m \end{pmatrix}.$$

For $(x, y) = (1, 0) = E_3$, we have

$$J(1,0) = \begin{pmatrix} -1 & -d \\ 0 & -q + \frac{j}{g^n+1} - m \end{pmatrix}.$$

The eigenvalues are given by -1 and $-q + \frac{j}{g^n+1} - m$. Since we have excluded $j = (1+g^n)(q+m)$ earlier, the eigenvalues have a non-zero real part. In particular, E_3 is locally asymptotically stable, if

$$-q + \frac{j}{g^n + 1} - m < 0$$

is satisfied, which is equivalent to

$$j < (q + m)(g^n + 1) = qg^n + m + q + mg^n.$$

As we have seen previously, this implies the case where there are either no or two additional equilibria in $\text{int}(D)$. If $(q + m)(g^n + 1) < j$ holds true, then the system (5.3) has only one additional equilibrium in $\text{int}(D)$ and E_3 becomes unstable. For a non-trivial equilibrium $(\bar{x}, \bar{y}) \in \{E_1, E_2\}$, we have that

$$\begin{aligned} J(\bar{x}, \bar{y}) &= \begin{pmatrix} 1 - 2\bar{x} - nd\bar{x}^{n-1}\bar{y} & -d\bar{x}^n \\ -nq\bar{x}^{n-1}\bar{y} + n\frac{jg^n\bar{x}^{n-1}}{(g^n+\bar{x}^n)^2}\bar{y} & 0 \end{pmatrix} \\ &= \begin{pmatrix} 1 - 2\bar{x} - n(1-\bar{x}) & -dz \\ n\frac{1-\bar{x}}{d}\left(-q + \frac{jg^n}{(g^n+z)^2}\right) & 0 \end{pmatrix}, \end{aligned}$$

where $z = \bar{x}^n$. The corresponding characteristic equation reads

$$\lambda^2 - (1 - 2\bar{x} - n(1 - \bar{x})) \cdot \lambda + nz(1 - \bar{x})\left(-q + \frac{jg^n}{(g^n + z)^2}\right) = 0,$$

which yields the eigenvalues

$$\begin{aligned} \lambda_1(\bar{x}) &= \frac{1 - 2\bar{x} - n(1 - \bar{x})}{2} \\ &\quad - \frac{\sqrt{(1 - 2\bar{x} - n(1 - \bar{x}))^2 - 4nz(1 - \bar{x})\left(-q + \frac{jg}{(g+z)^2}\right)}}{2}, \\ \lambda_2(\bar{x}) &= \frac{1 - 2\bar{x} - n(1 - \bar{x})}{2} \\ &\quad + \frac{\sqrt{(1 - 2\bar{x} - n(1 - \bar{x}))^2 - 4nz(1 - \bar{x})\left(-q + \frac{jg}{(g+z)^2}\right)}}{2}. \end{aligned}$$

We now study the stability of the equilibria E_1 and E_2 in the following theorem.

Theorem 5.2. Consider the system (5.3) and assume the parameters to be chosen in such a way that $1 - 2z_1^{1/n} - n(1 - z_1^{1/n}) < 0$. If $E_1 \in \mathrm{int}(D)$, then it is locally asymptotically stable. If $E_2 \in \mathrm{int}(D)$, then it is unstable.

Proof. We begin with the equilibrium $E_1 \in \mathrm{int}(D)$. For $\lambda_1(\bar{x}_1)$, we observe that the real part is, by assumption, always negative. Further, $\mathrm{Re}(\lambda_2(\bar{x}_1)) < 0$ is fulfilled iff

$$\begin{aligned}&(1 - 2\bar{x}_1 - n(1 - \bar{x}_1))^2 - 4nz_1(1 - \bar{x}_1)\left(-q + \frac{jg^n}{(g^n + z_1)^2}\right)\\ &< (1 - 2\bar{x}_1 - n(1 - \bar{x}_1))^2\end{aligned}$$

is satisfied. Since $4nz_1(1 - \bar{x}_1) > 0$, this is equivalent to

$$-q + \frac{jg^n}{(g^n + z_1)^2} > 0. \tag{5.7}$$

Since $E_1 \in \mathrm{int}(D)$, Theorem 5.1 yields $j > qg^n + m + 2\sqrt{qg^n m}$ and hence, we have $C := -qg^n - m + j > 0$. With the expression for z_1 derived in the proof of Lemma 5.1, we have

$$\begin{aligned}(g^n + z_1)^2 &= \left(\frac{2qg^n + (-qg^n - m + j) - \sqrt{(-qg^n - m + j)^2 - 4qg^n m}}{2q}\right)^2\\ &= \left(\frac{2qg^n + C - \sqrt{C^2 - 4qg^n m}}{2q}\right)^2\end{aligned}$$

and it follows that

$$-q + \frac{jg^n}{(g^n + z_1)^2} = \frac{-q\left(2qg^n + C - \sqrt{C^2 - 4qg^n m}\right)^2 + 4q^2 jg^n}{\left(2qg^n + C - \sqrt{C^2 - 4qg^n m}\right)^2},$$

which has the same sign as

$$\begin{aligned}&-\left(2qg^n + C - \sqrt{C^2 - 4qg^n m}\right)^2 + 4qjg^n\\ =&-\left(4q^2 (g^n)^2 + C^2 + C^2 - 4qg^n m + 4qg^n C - 4qg^n\sqrt{C^2 - 4qg^n m}\right.\\ &\left.-2C\sqrt{C^2 - 4qg^n m}\right) + 4qjg^n,\end{aligned}$$

since $q > 0$. We recall that $C = -qg^n - m + j$, which leads to

$$\begin{aligned}&-4q^2 (g^n)^2 - 2C^2 + 4qg^n m - 4qg^n C + 4qg^n\sqrt{C^2 - 4qg^n m} + 2C\sqrt{C^2 - 4qg^n m}\\ &+ 4qjg^n \underbrace{-4qg^n m + 4qg^n m}_{=0}\\ =\ &4qg^n(-qg^n - m + j) - 4qg^n C - 2C^2 + 8qg^n m + 4qg^n\sqrt{C^2 - 4qg^n m} + 2C\sqrt{C^2 - 4qg^n m}\\ =\ &-2C^2 + 8qg^n m + 4qg^n\sqrt{C^2 - 4qg^n m} + 2C\sqrt{C^2 - 4qg^n m}\\ =\ &2\left(-C^2 + 4qg^n m + 2qg^n\sqrt{C^2 - 4qg^n m} + C\sqrt{C^2 - 4qg^n m}\right).\end{aligned}$$

We can see that

$$\begin{aligned} & - \underbrace{(C^2 - 4qg^n m)}_{>0 \text{ since } j > qg^n + m + 2\sqrt{qg^n m}} + 2qg^n\sqrt{C^2 - 4qg^n m} + C\sqrt{C^2 - 4qg^n m} \\ = & -\left(\sqrt{C^2 - 4qg^n m}\right)^2 + 2qg^n\sqrt{C^2 - 4qg^n m} + C\sqrt{C^2 - 4qg^n m} \\ = & \sqrt{C^2 - 4qg^n m}\left(2qg^n + \underbrace{C - \sqrt{C^2 - 4qg^n m}}_{>C-C=0}\right) > 0 \end{aligned}$$

and thus, (5.7) is satisfied, which yields the local asymptotic stability of E_1.

Next, we consider the case where E_2 is also in $\text{int}(D)$. By Theorem 5.1, this is only the case if $mg^n < q$ and $qg^n + m + 2\sqrt{qg^n m} < j < qg^n + m + q + mg^n$. In particular, this implies $C > 0$.

In the following, we will prove the instability of E_2 by showing that

$$-q + \frac{jg^n}{(g^n + z_2)^2} < 0,$$

which implies $\text{Re}(\lambda_2(\bar{x}_2)) > 0$. Following the same calculations as before, we see that

$$-q + \frac{jg^n}{(g^n + z_2)^2}$$

has the same sign as

$$\begin{aligned} & -2C^2 + 8qg^n m - 4qg^n\sqrt{C^2 - 4qg^n m} - 2C\sqrt{C^2 - 4qg^n m} \\ = & \sqrt{C^2 - 4qg^n m}(-2C - 4qg^n) + 8qg^n m - 2C^2, \end{aligned}$$

which is smaller than zero, as $8qg^n m - 2C^2 < 0$ since $C^2 > 4qg^n m$. It follows that $\text{Re}(\lambda_2(\bar{x}_2)) > 0$ and that E_2 is unstable. □

Remark 5.1. In order to see when the condition $1 - 2z^{1/n} - n(1 - z^{1/n}) < 0$ is fulfilled, consider $l_n(z) = 1 - 2z^{1/n} - n(1 - z^{1/n}) = 1 - n + (n-2)z^{1/n}$ for a fixed $n > 0$. Since $z \mapsto z^{1/n}$ is strictly monotone on $(0, 1)$, it follows that l_n is strictly monotone on $(0, 1)$ as well. For $n \geq 1$, we note that $l_n(0) = 1 - n \leq 0$ and $l_n(1) = -1 < 0$. Hence, for $E_1 \in \text{int}(D)$, it follows that $l_n(z_1) < 0$ always holds true. However, for $n \in (0, 1)$, we have that $l_n(0) = 1 - n > 0$ and $l_n(1) = -1 < 0$ and thus, using n as a bifurcation parameter, it is possible to observe a Hopf bifurcation around E_1, which results in a possible existence of a periodic orbit around E_1. We will further study this situation in the next section.

In particular, if $E_2 \in \text{int}(D)$, the equilibrium E_2 is an unstable saddle. With $\bar{x}_1 < \bar{x}_2$, the stable equilibrium $E_1 \in \text{int}(D)$ corresponds to the dormant state. If we recall the three phases of cancer immunoediting, we find that the equilibrium

E_0 would correspond to the elimination phase, where the tumor cell population is successfully destructed. The equilibrium phase can be represented by the non-trivial equilibrium E_1, in which the tumor cell population is kept in a dormant state. Lastly, the equilibrium E_3 describes the escape phase, which is characterized by the progressive growth of tumor cell populations. Following the stability analysis, we observe that the equilibrium E_0 is always unstable, which would mean that the immune system is never able to destroy tumor cells completely. However, depending on the parameter values, the x component of the stable equilibrium E_1, which corresponds to the dimensionless tumor cell population, can get very close to zero, such that the tumor cell population becomes clinically undetectable.

5.3 Analysis of Hopf bifurcation

For the existence of a Hopf bifurcation, the Jacobian matrix of the linearized system around an equilibrium needs to establish a pair of purely complex eigenvalues.

Recall that the eigenvalues of the Jacobian matrix for the linearized system of (5.3) around E_1 read

$$\lambda_{1,2}(n) = \frac{1 - 2z_1^{1/n} - n(1 - z_1^{1/n})}{2} \pm \frac{\sqrt{\left(1 - 2z_1^{1/n} - n(1 - z_1^{1/n})\right)^2 - 4nz_1(1 - z_1^{1/n})\left(-q + \frac{jg^n}{(g^n + z_1)^2}\right)}}{2},$$

where

$$z_1 = \frac{-qg^n - m + j - \sqrt{(-qg^n - m + j)^2 - 4qg^n m}}{2q},$$

which is independent of n. Note that $\mathrm{Re}(\lambda_{1,2}(n)) = 1 - 2z_1^{1/n} - n(1 - z_1^{1/n})$ iff

$$\left(1 - 2z_1^{1/n} - n(1 - z_1^{1/n})\right)^2 - 4nz_1(1 - z_1^{1/n})\left(-q + \frac{jg^n}{(g^n + z_1)^2}\right) \leq 0. \tag{5.8}$$

In the proof of Theorem 5.2, we have shown that

$$-q + \frac{jg^n}{(g^n + z_1)^2} > 0$$

and thus we have,

$$4nz_1(1 - z_1^{1/n})\left(-q + \frac{jg^n}{(g^n + z_1)^2}\right) > 0.$$

It follows that (5.8) is equivalent to

$$|1 - 2z_1^{1/n} - n(1 - z_1^{1/n})| \leq \sqrt{4nz_1(1 - z_1^{1/n})\left(-q + \frac{jg^n}{(g^n + z_1)^2}\right)} =: Z(n). \quad (5.9)$$

Note that for $n \geq 1$, we have $l_{z_1}(n) := 1 - 2z_1^{1/n} - n(1 - z_1^{1/n}) < 0$ and following the proof of Theorem 5.2, we can see that $\mathrm{Re}(\lambda_{1,2}(n)) < 0$ holds true and hence, for $n \geq 1$, the system does not exhibit a Hopf bifurcation.

For $n \in (0, 1)$, l_{z_1} is continuous. With $\lim_{n\to 0} l_{z_1}(n) = 1 > 0$ and $l_{z_1}(1) = -z_1 < 0$, if follows from the Intermediate value theorem that there exists an $n_0 \in (0, 1)$ such that $l_{z_1}(n_0) = 0$. Further, for $z_1 \in (0, 1)$ and $n \in (0, 1)$, we have that

$$l'_{z_1}(n) = -\frac{(n-2)z_1^{1/n}\ln(z_1)}{n^2} + z_1^{1/n} - 1 < -\frac{(n-2)z_1^{1/n}\ln(z_1)}{n^2} < 0. \quad (5.10)$$

Hence, n_0 is the only root of l_{z_1} in $(0, 1)$. Since Z is continuous, there exists a neighbourhood around n_0, where (5.9) is satisfied. Particularly, for such n, the real part of the eigenvalues of $J_n(\bar{x}_1, \bar{y}_1)$ equals

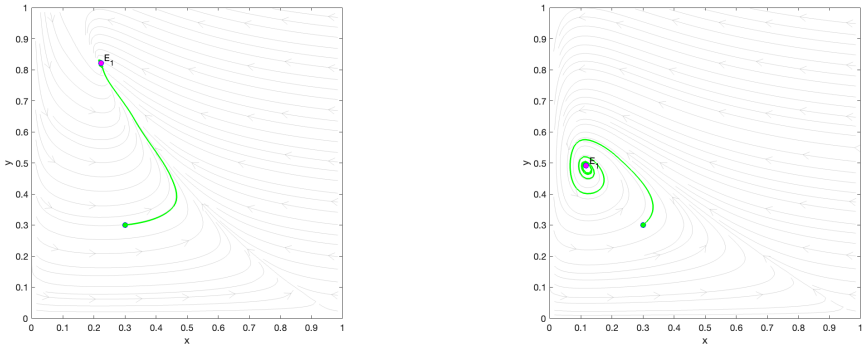
$$\frac{1 - 2z_1^{1/n} - n(1 - z_1^{1/n})}{2}.$$

Since $l'_{z_1}(n_0) < 0$, $J_n(\bar{x}_1, \bar{y}_1)$ has exactly one pair of purely imaginary complex eigenvalues at $n = n_0$, where $\mathrm{Re}(\lambda_{1,2}(n)) < 0$ for $n > n_0$ and $\mathrm{Re}(\lambda_{1,2}(n)) > 0$ for $n < n_0$. Moreover, we have

$$\frac{d}{dn}\mathrm{Re}(\lambda_{1,2}(n))|_{n=n_0} \neq 0$$

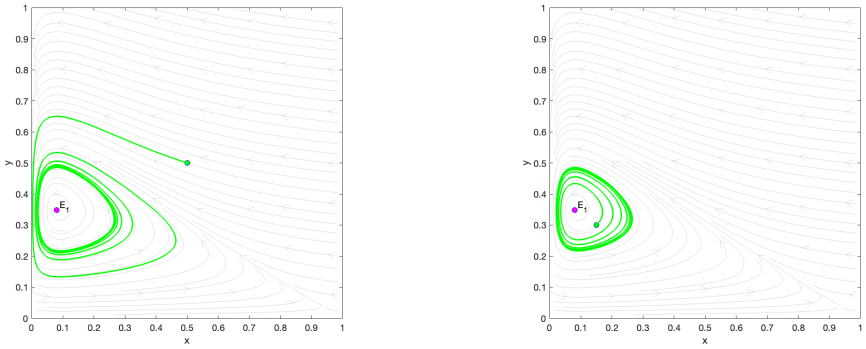
and thus, the conditions for the Hopf bifurcation theorem are satisfied. However, it is not possible to find an analytical solution for n_0 such that $l(n_0) = 0$ for a general set of parameter values. Nevertheless, we illustrate this behavior for the parameter values $q = 0.5$, $j = 1.6$, $g^n = 1$, $m = 0.1$, and $d = 2$. Using the "fzero" function in MATLAB [BB19], we obtain an approximate solution of $n_0 \approx 0.9082$. For $n \in \{1.5, 1.05, 0.8\}$, Figure 5.4 and 5.5 show the corresponding phase planes, where E_1 is locally asymptotically stable for $n > n_0$ and unstable for $n < n_0$. At the same time, a locally stable periodic orbit appear around E_1.

The existence of a stable periodic orbit may be in contradiction to what is typically observed in tumor-immune interactions on a large scale. One likely reason, which is provided by Kareva et al. in [Kar+21], is that the threat of autoimmune responses can make the cytotoxic T cells very inefficient in eliminating tumor cells, which is not accounted for in our model. However, it is possible that there exist some small-scale oscillations between the elimination and the equilibrium phase, which might be missed due to its occurrence in the early stage of tumor progression. As we have seen in the simulation above, the dampening of the oscillation around the stable equilibrium E_1 can be controlled by the parameter n, which emphasizes the importance of considering a more general interaction term between tumor and cytotoxic T cell populations.



(a) $n = 1.5 > n_0$ (b) $n = 1.05 > n_0$

Figure 5.4: Phase plane of the system (5.3), where $q = 0.5$, $j = 1.6$, $g^n = 1$, $m = 0.1$, and $d = 2$. Magenta circle: Stable equilibrium E_1. Green circle: Initial value for the green trajectory.



(a) Initial value outside. (b) Initial value inside.

Figure 5.5: Phase plane of the system (5.3), where $q = 0.5$, $j = 1.6$, $g^n = 1$, $m = 0.1$, and $d = 2$. and $n = 0.89 < n_0$. Magenta circle: Unstable equilibrium E_1. Green circle: Initial value for the green trajectory, which tends to the stable periodic orbit asymptotically. Left: Initial value outside of the periodic orbit. Right: Initial value inside the periodic orbit.

5.4 Analysis of the stable manifold of E_2

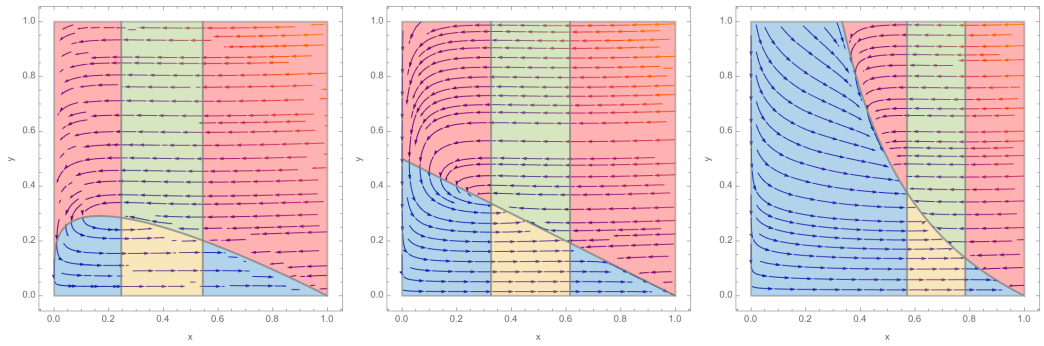
In the following, we assume that the condition in Theorem 5.2 is satisfied, i.e. the equilibrium E_1 is locally asymptotically stable and the equilibrium E_2 is an unstable saddle. We analyze the behavior of the stable manifold of E_2 by numerical simulations. From Theorem 3.5, we know that in proximity of the unstable equilibrium E_2, its stable manifold is tangent to the stable eigenspace of the corresponding linearized system. Thus, close to E_2, we can approximate the corresponding stable manifold as follows:

1. Compute the Jacobian matrix of the linearized system evaluated in E_2 and the eigenvector v that corresponds to the negative eigenvalue.

2. For the initial values $E_2 \pm 1 \cdot 10^{-10} \cdot \frac{v}{\|v\|}$, solve backwards in time to approximate the stable manifold of E_2 using the "ode45" function in MATLAB [BB19].

In addition, we define an event function for the ODE solver to specify the final time in the interval of integration, at which the dimensionless variable x reaches a value of $1 \cdot 10^{-8}$. This is especially important when $n > 1$, where one side of the stable manifold of E_2 asymptotically approaches the unstable manifold of $E_0 = (0, 0)$, which is the y-axis. The corresponding MATLAB scripts are provided in Appendix A.

Let us consider the parameters $q = 0.5$, $j = 1.07$, $g^n = 1$, and $m = 0.1$. By using the "fzero" function in MATLAB [BB19], the root of $l_{z_1}(n) = 1 - 2z_1^{1/n} - n(1 - z_1^{1/n})$ is found to be approximately $n_0 \approx 0.728$. Thus, for our analysis, we only consider $n \geq 0.75$. For $d = 4$, the phase portrait of the system (5.3) is illustrated in Figure 5.6 and is computed using Mathematica [Wol23].

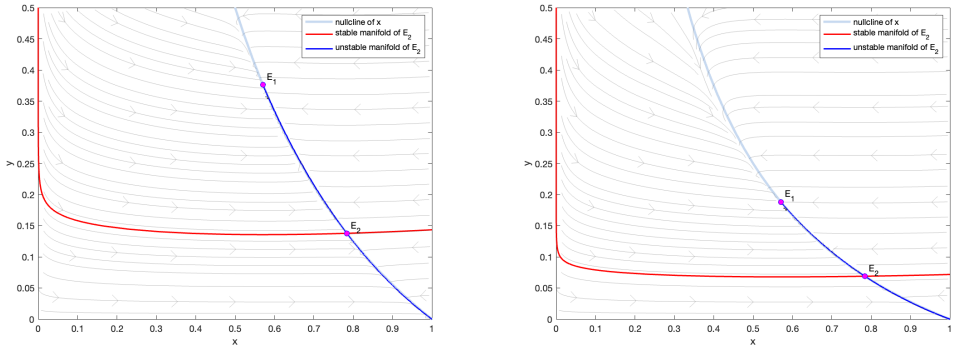


(a) $n = 0.8$ (b) $n = 1$ (c) $n = 2$

Figure 5.6: Phase plane of the system (5.3), where $q = 0.5$, $j = 1.07$, $g^n = 1$, $m = 0.1$, $d = 4$, and $n \in \{0.8, 1, 2\}$. The regions colored in red, blue, green, and yellow represent the cases $\dot{x} < 0$, $\dot{y} < 0$, $\dot{x} > 0$, $\dot{y} < 0$, $\dot{x} < 0$, $\dot{y} > 0$, and $\dot{x} > 0$, $\dot{y} > 0$, respectively.

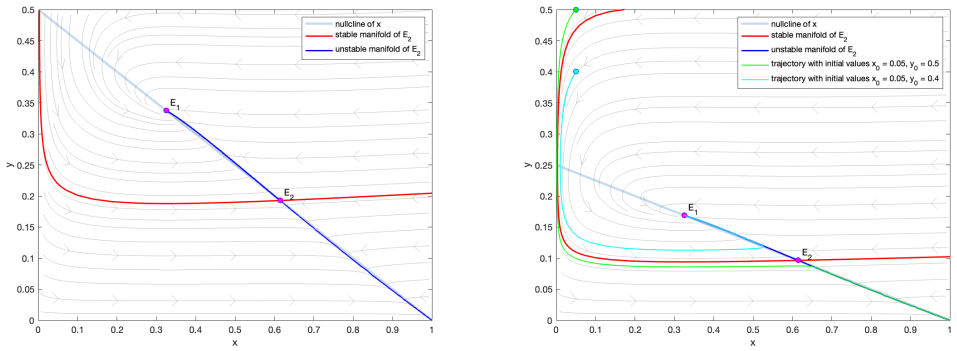
For $n > 1$, we can see in Figure 5.3 that f_1, which is one of the components of the nullcline of x, tends towards infinity for $x \to 0$. Particularly, it is strictly monotonic decreasing without intersecting the y-axis. This leads to the observation that the side of the stable manifold of the equilibrium E_2 corresponding to $x < \bar{x}_2$ will never intersect the graph of f_1 on $(0, 1)$. In particular, there exists a T such that for $t < -T$, this side of the stable manifold will always stay in the blue domain in Figure 5.6c, where $\dot{x} > 0$ and $\dot{y} < 0$. For the set of parameter values chosen in the beginning of the section and for $n = 2$, Figure 5.7 shows in red the stable manifold of the unstable equilibrium E_2. For $n \leq 1$, the nullcline of x does intersect the y-axis. In Figure 5.6a and 5.6b, we observe that the stable manifold of the

equilibrium E_2 corresponding to $x < \bar{x}_2$ will eventually cross the graph of f_1 for $t \to -\infty$, leading to a transition from the blue domain into the red domain, where $\dot{x} < 0$ and $\dot{y} < 0$. Interestingly, for $t \to -\infty$ the stable manifold of E_2 will enter the red domain on the left-hand side in Figure 5.6a and 5.6b.



(a) $d = 2$ (b) $d = 4$

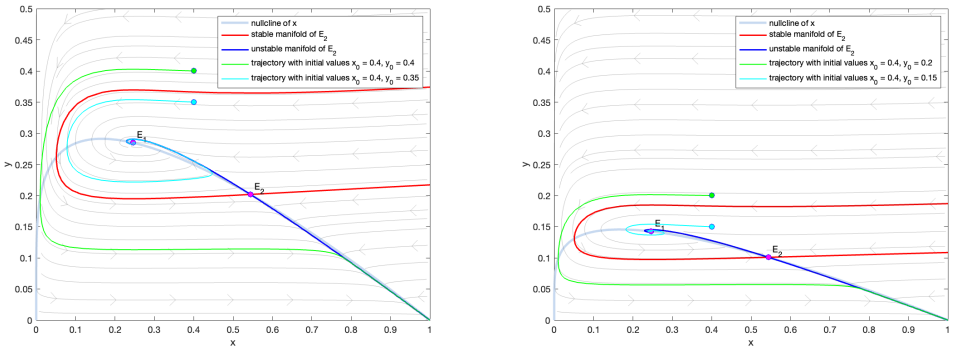
Figure 5.7: Phase plane of the system (5.3), where $q = 0.5$, $j = 1.07$, $g^n = 1$, $m = 0.1$, and $n = 2$.



(a) $d = 2$ (b) $d = 4$

Figure 5.8: Phase plane of the system (5.3), where $q = 0.5$, $j = 1.07$, $g^n = 1$, $m = 0.1$, and $n = 1$.

For the set of parameter values chosen in the beginning of the section, the system exhibits the "sneaking through" phenomenon discussed in the beginning of Chapter 4. This is illustrated in Figure 5.8 and 5.9. In particular, the green trajectories have the same initial level of tumor cells as the trajectories in light blue. However, the initial amount of cytotoxic T cells for the green trajectories is higher. We observe in Figure 5.8 and 5.9 that while the light blue trajectories asymptotically approach the stable equilibrium E_1, the green trajectories asymptotically tend to the stable equilibrium E_3, which represents the tumor-escape scenario.



(a) $d = 2$ (b) $d = 4$

Figure 5.9: Phase plane of the system (5.3), where $q = 0.5$, $j = 1.07$, $g^n = 1$, $m = 0.1$, and $n = 0.8$.

6 Model variations

We consider the model from Chapter 5 and once again let T and L denote the tumor cell and the cytotoxic T cell population, respectively. In the following chapter, we study the effect of other functional types to describe the elimination of tumor cells by tumor-infiltrating cytotoxic T cells and consider the system of differential equations given by

$$\begin{aligned} \frac{dT}{d\tau} &= aT(1-bT) - g(T,L) \\ \frac{dL}{d\tau} &= -\tilde{q}LT^n + \frac{\tilde{j}T^n}{\tilde{g}^n + T^n}L - \tilde{m}L, \end{aligned} \tag{6.1}$$

where $g(T,L)$ describes the elimination of tumor cells by the interaction with cytotoxic T cells. We note that the second equation in (6.1) remains the same as in (5.2) and thus, all other parameters maintain their biological interpretations and units as given in Table 5.1.

6.1 Model variation including T cell exhaustion

As we have seen in Chapter 2.3, a continuous antigenic stimulation of immune cells may induce a state called exhaustion. This describes a functional but yet hyporesponsive state of cytotoxic T cells.

In the following section, we aim to adapt this aspect into our current model by assuming that in the early stage of tumor growth, we would not expect many cytotoxic T cells to be present in the TME. In particular, we assume that a large amount of cytotoxic T cells would be related to a longer exposure of the cytotoxic T lymphocytes to the tumor cells. Consider the following elimination term

$$g(T,L) = \tilde{d}\frac{L^\lambda}{\tilde{s}^\lambda + L^\lambda}T^n, \tag{6.2}$$

where $\tilde{d}$, $\tilde{s}$, n, $\lambda > 0$. Table 6.1 contains the biological description of the parameters in (6.2) and their units.

In the following, we consider $n = 1$. In our current model, the parameter $\tilde{d}$ describes the maximal tumor cell elimination rate that is induced by the cytotoxic

Table 6.1: Description of parameters in (6.2) and their units.

Parameter	Unit	Description
n	none	exponent in interaction terms of tumor and cytotoxic T cells
$\tilde{d}$	day^{-1}	maximal tumor cell elimination rate caused by cytotoxic T cells
$\tilde{s}$	cells	number of cytotoxic T cells, at which the tumor cell elimination rate reaches its half-maximum
λ	none	exponent in tumor cell elimination term induced by cytotoxic T cells

T cells. Particularly, if $\tilde{d} < a$, the tumor cell elimination will always be less efficient compared to the growth of tumor cells. Therefore, in the following, we assume $\tilde{d} \geq a$ to hold.

With $x = bT$, $y = bL$, and $\tau = at$, we re-parametrize the system and associate $\frac{dx}{dt}$ and $\frac{dy}{dt}$ with $\dot{x}$ and $\dot{y}$, respectively leading to the dimensionless system of differential equations

$$\begin{aligned} \dot{x} &= x(1-x) - d\frac{y^\lambda}{s^\lambda + y^\lambda}x \\ \dot{y} &= -qxy + \frac{jx}{g+x}y - my, \end{aligned} \tag{6.3}$$

where $d = \frac{1}{a}\tilde{d}$ and $s = b\tilde{s}$. In a similar way as before, we can show that the set $D = [0,1] \times [0,\infty) \subset \mathbb{R}^2$ is positively invariant for the system (6.3) and in particular, $\text{int}(D)$ is a simply connected region. With $h_1(x,y) = x(1-x) - d\frac{y^\lambda}{s^\lambda+y^\lambda}x$, $h_2(x,y) = -qxy + \frac{jx}{g+x}y - my$, and $\rho(x,y) = \frac{1}{xy} > 0$ for $(x,y) \in \text{int}(D)$, we have

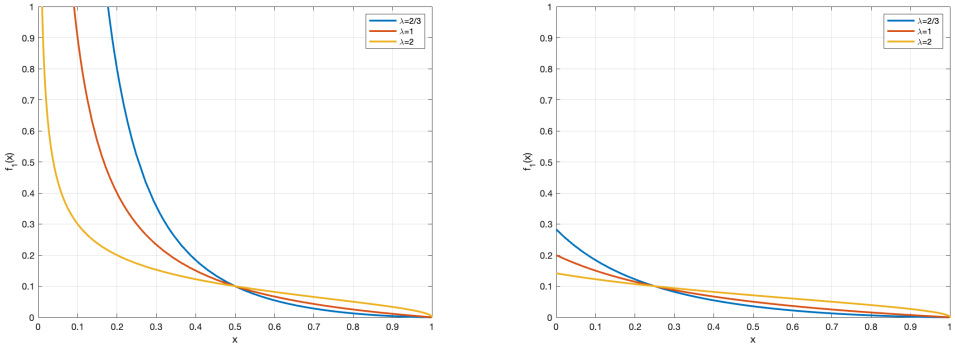
$$\begin{aligned} \text{div}\left(\rho(x,y)\cdot h_1(x,y),\ \rho(x,y)\cdot h_2(x,y)\right) &= \frac{\partial\left(\frac{1-x}{y} - \frac{dy^{\lambda-1}}{s^\lambda+y^\lambda}\right)}{\partial x} + \frac{\partial\left(-q + \frac{j}{g+x} - \frac{m}{x}\right)}{\partial y} \\ &= -\frac{1}{y} < 0. \end{aligned}$$

It follows from the negative criterion of Bendixson-Dulac that the system (6.3) has no closed orbits lying entirely in $\text{int}(D)$.

Setting the right hand side of the equations in (6.3) to zero and considering f_2 from Lemma 5.1 yields the nullclines

$$\begin{aligned} \dot{x} = 0: &\qquad x = 0 \quad \text{or} \quad y = s\left(\frac{(1-x)}{d-(1-x)}\right)^{1/\lambda} =: f_1(x) \\ \dot{y} = 0: &\qquad y = 0 \quad \text{or} \quad -qx + \frac{jx}{g+x} - m = f_2(x) = 0, \end{aligned} \tag{6.4}$$

where the equilibria $E_0 = (\bar{x}_0, \bar{y}_0) = (0,0)$ and $E_3 = (\bar{x}_3, \bar{y}_3) = (1,0)$ always exist. As discussed in the previous chapter, the equation $f_2(x) = 0$ yields up to two solutions $\bar{x}_1$ and $\bar{x}_2$ in $(0,1)$, which are represented by two vertical lines in the x,y-plane. The assumption $\tilde{d} \geq a$ implies that $d = \tilde{d}/a \geq 1$ holds true and thus, for $x \in (0,1)$, $y = \left(\frac{s(1-x)}{d-(1-x)}\right)^{1/\lambda} > 0$ is defined on the entire interval $(0,1)$. Particularly, Theorem 5.1 holds and if $\bar{x}_{1,2} \in (0,1)$, then the non-trivial equilibria in $\mathrm{int}(D)$ are given by $E_1 = (\bar{x}_1, \bar{y}_1)$ and $E_2 = (\bar{x}_2, \bar{y}_2)$, where $\bar{y}_1 = f_1(\bar{x}_1)$ and $\bar{y}_2 = f_1(\bar{x}_2)$. Figure 6.1 illustrates the graph of f_1 for $d = 1$ and $d > 1$.



(a) $d = 1$ (b) $d = 1.5$

Figure 6.1: Graph of f_1 in (6.4) for $s = 0.1$ and different values of d and λ.

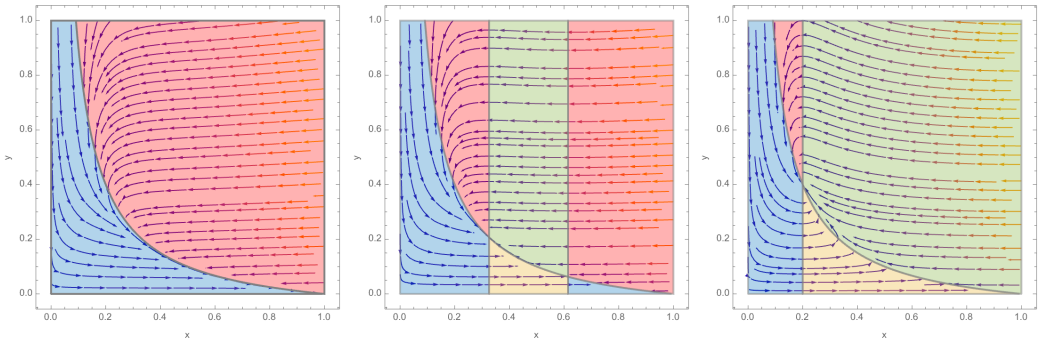
In case of $d = 1$, we observe that the maximal tumor cell elimination rate induced by cytotoxic T cells is given by the parameter value a, which denotes the tumor growth rate. Note that, for $x \to 0$, the system would require $y \to \infty$ in order to have an elimination rate approximating the growth rate of tumor cells. With

$$\begin{aligned} \dot{x} < 0 \quad &\Leftrightarrow \quad 1 - x - d\frac{y^\lambda}{s^\lambda + y^\lambda} < 0 \\ &\Leftrightarrow \quad y > f_1(x) \\ \dot{y} < 0 \quad &\Leftrightarrow \quad f_2(x) < 0 \\ &\Leftrightarrow \quad x < \bar{x}_1 \ \vee \ x > \bar{x}_2, \end{aligned}$$

the region in which $x < \bar{x}_1$ and $y < f_1(x)$, extends to infinity along the y-axis for x towards 0.

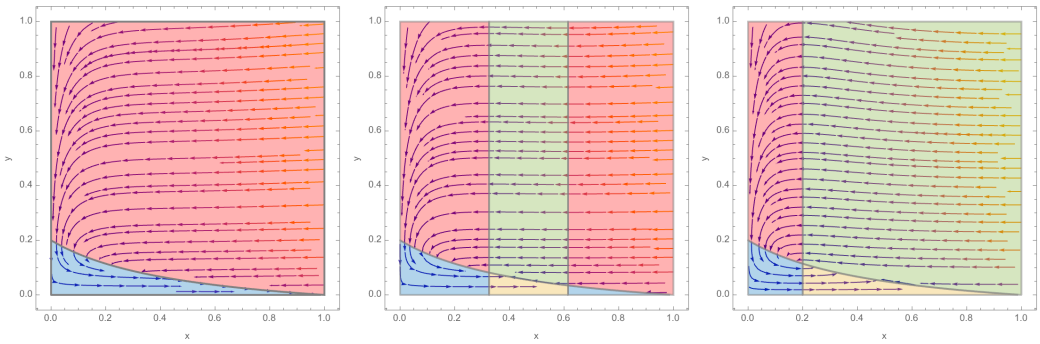
From the biological point of view, this implies that in the initial stage of the tumor development, where the amount of tumor cells is small, cancer cells will grow regardless of the amount of tumor-specific cytotoxic T cells that is present in the TME, as the elimination is not efficient enough to overcome the growth rate of tumor cells. This behavior is illustrated in the blue domain of the phase portraits of the system for the parameter values $q = 0.5$, $g = 1$, $m = 0.1$, $\lambda = 1$, $s = 0.1$, and $j \in \{1, 1.07, 1.2\}$ in Figure 6.2. For the same set of parameter values, Figure

6.3 shows the phase portraits of the system for $d = 1.5$. Particularly, we observe that f_1 intersects the y-axis. The phase portraits are computed using Mathematica [Wol23].



(a) $j = 1$ (b) $j = 1.07$ (c) $j = 1.2$

Figure 6.2: Phase plane of the system (6.3), where $q = 0.5$, $g = 1$, $m = 0.1$, $\lambda = 1$, $s = 0.1$, and $d = 1$. The regions colored in red, blue, green, and yellow represent the cases $\dot{x} < 0,\ \dot{y} < 0$, $\dot{x} > 0,\ \dot{y} < 0$, $\dot{x} < 0,\ \dot{y} > 0$, and $\dot{x} > 0,\ \dot{y} > 0$, respectively.



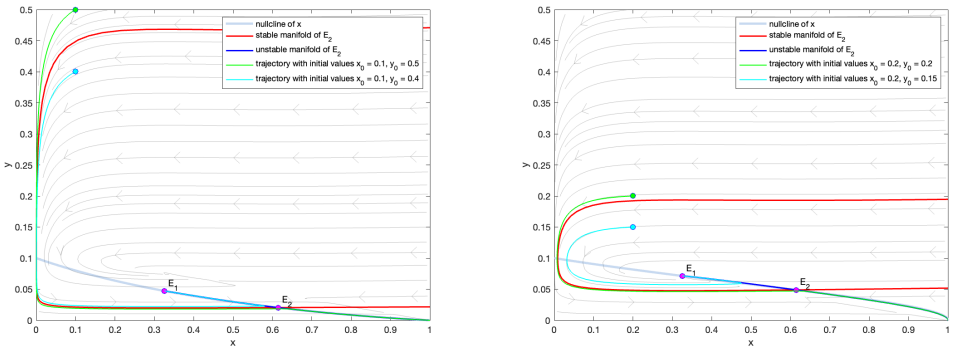
(a) $j = 1$ (b) $j = 1.07$ (c) $j = 1.2$

Figure 6.3: Phase plane of the system (6.3), where $q = 0.5$, $g = 1$, $m = 0.1$, $\lambda = 1$, $s = 0.1$, and $d = 1.5$. The regions colored in red, blue, green, and yellow represent the cases $\dot{x} < 0,\ \dot{y} < 0$, $\dot{x} > 0,\ \dot{y} < 0$, $\dot{x} < 0,\ \dot{y} > 0$, and $\dot{x} > 0,\ \dot{y} > 0$, respectively.

In the current model, we may also observe the "sneaking through" phenomenon discussed previously for $d > 1$, where the non-zero nullcline of x intersects the y-axis. For the parameter values $q = 0.5$, $j = 1.07$, $g = 1$, $m = 0.1$, $s = 0.1$, and $d = 2$, Figure 6.4 illustrates this for $\lambda = 0.9$ and $\lambda = 2$.

For a general $n > 0$, the re-parametrized model is given by

$$\begin{aligned} \dot{x} &= x(1-x) - d\frac{y^\lambda}{s^\lambda + y^\lambda}x^n \\ \dot{y} &= -qx^n y + \frac{jx^n}{g^n + x^n}y - my, \end{aligned} \tag{6.5}$$



(a) $\lambda = 0.9$ (b) $\lambda = 2$

Figure 6.4: Phase plane of the system (6.3), where $q = 0.5$, $j = 1.07$, $g = 1$, $m = 0.1$, $s = 0.1$, and $d = 2$.

where the parameters are defined analogously as before. We observe that the nullclines of the system (6.3) are given by

$$\begin{aligned} \dot{x} = 0: &\qquad x = 0 \quad \text{or} \quad y = s\left(\frac{(1-x)}{dx^{n-1} - (1-x)}\right)^{1/\lambda} =: f_1(x) \\ \dot{y} = 0: &\qquad y = 0 \quad \text{or} \quad f_2(x) = -qx^n + \frac{jx^n}{g^n + x^n} - m = 0. \end{aligned} \tag{6.6}$$

In order to apply Theorem 5.1 on the number of equilibria in $\text{int}(D)$, f_1 has to be defined on the entire interval $(0, 1)$. For all $n > 0$, the denominator of f_1, which is given by $h_n(x) := dx^{n-1} - 1 + x$, is continuous on the interval $(0, 1)$. In the case of $n > 1$, we can extend the interval to $[0, 1]$ and with

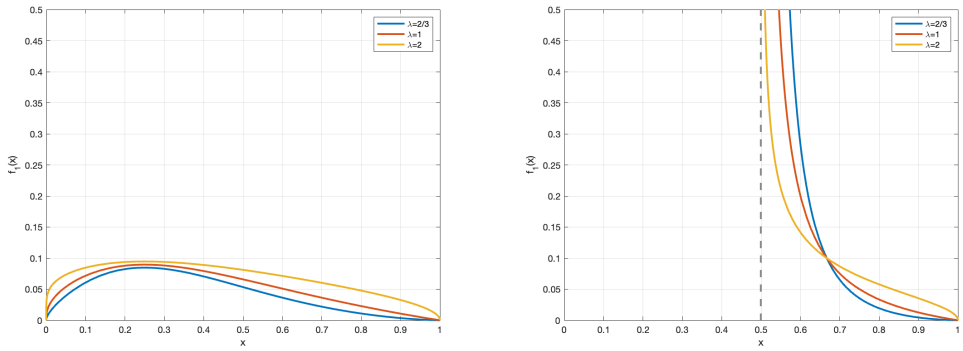
$$h_n'(x) = (n-1)dx^{n-2} + 1 > 0 \quad \forall x \in [0, 1],$$

h_n is strictly monotone on $[0, 1]$. Further, with $h_n(0) = -1 < 0$ and $h_n(1) = d > 0$, the Intermediate value theorem states that h has a root x^* in the interval $(0, 1)$. Thus, f_1 is not defined in x^* for $n > 1$. On the other hand, for $n < 1$, we have

$$h_n(x) = \frac{d}{x^{1-n}} - 1 + x \geq d - 1 + x = h_1(x).$$

With $d \geq 1$, it follows that $h_1(x) > 0$ for all $x \in (0, 1)$. Thus, h_n has no root in the interval $(0, 1)$ for $n \leq 1$. It follows that for $n \leq 1$, f_1 is defined on the whole interval $(0, 1)$, while this is not the case for $n > 1$. For $d = 1$ and $s = 0.1$, Figure 6.5 shows the graph of f_1 on the interval $(0, 1)$ for $n = 2/3$ and $n = 2$. Particularly, we observe an asymptote for $n = 2$, which is illustrated by the grey dashed line in Figure 6.5b.

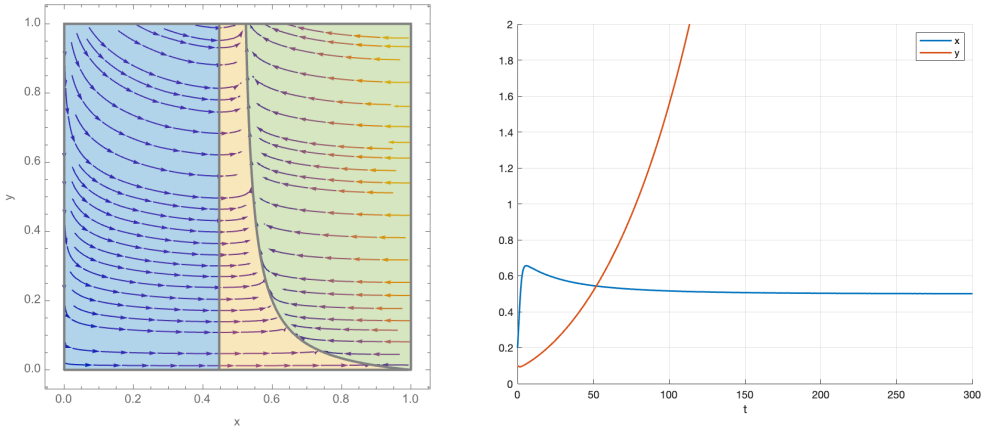
In terms of the dynamics of the system, it is possible to observe a situation, where the tumor cell population approaches an equilibrium while the cytotoxic T



(a) $n = 2/3$ (b) $n = 2$

Figure 6.5: Graph of f_1 in (6.6) for $d = 1$, $s = 0.1$ and different values of n and λ.

cell population tends to infinity. For $q = 0.5$, $j = 1.2$, $n = 2$, $g^n = 1$, $m = 0.1$, $\lambda = 1$, $s = 0.1$, and $d = 1$, Figure 6.6 shows the phase portrait of the system as well as the long-term behavior of the x and y trajectories with initial values $x_0 = 0.2$ and $y_0 = 0.1$.



(a) (b)

Figure 6.6: Situation for the system (6.5), where $\bar{x}_1 \in (0, 1)$, but $f_1(\bar{x}_1)$ is not defined. The parameters are set to $q = 0.5$, $j = 1.2$, $n = 2$, $g^n = 1$, $m = 0.1$, $\lambda = 1$, $s = 0.1$, and $d = 1$. The phase portrait of the system is illustrated in (a) while (b) shows the trajectories of x and y with initial values $x_0 = 0.2$ and $y_0 = 0.1$.

From the biological perspective, this situation implies that the immune system would need to produce infinitely many cytotoxic T cells to retain the tumor in a dormant state. However, in reality, this is not possible due to various factors, such as space limitation. Thus, the model (6.5) for $n > 1$ might not always be suitable to describe the tumor-immune interactions. We move on to examine the effect of the de Pillis-Radunskaya Law [dR14] on our model (6.1).

6.2 Model variation including the de Pillis-Radunskaya Law

In 2005, de Pillis, Radunskaya, and Wiseman presented a mathematical model in [dRW05], which focuses on the role of natural killer and CTL cells in tumor surveillance. Similar to the model in [Kuz+94], the authors describe the rate of change of tumor cell population as the difference between the growth and death rate of tumor cells and the cell-cell elimination rate. The cell kill rate for the NK cells was assumed to have the same form as in the model in [Kuz+94]. On the other hand, de Pillis, Radunskaya, and Wiseman introduced a new form for the elimination term of tumor cells by cytotoxic T cells, which takes the form

$$\tilde{d}\frac{(L/T)^\lambda}{s^\lambda + (L/T)^\lambda}T = \tilde{d}\frac{L^\lambda}{s^\lambda T^\lambda + L^\lambda}T, \tag{6.7}$$

where $\tilde{d}$, s, $\lambda > 0$. In accordance with the work in [dRW05], we refer to this as the "fractional cell kill". By fitting their model to experimental data from [Die+01], de Pillis, Radunskaya, and Wiseman were able to describe the tumor cell elimination via cytotoxic T cells more accurate using (6.7). In the following section, we adapt the fractional cell kill (6.7) into our model by considering

$$g(T, L) = \tilde{d}\frac{(L/T)^\lambda}{s^\lambda + (L/T)^\lambda}T^n = d\frac{L^\lambda}{s^\lambda T^\lambda + L^\lambda}T^n, \tag{6.8}$$

where $n > 0$ and examine the dynamics of the system. Table 6.2 provides an overview of the biological interpretation and unit of the parameters in (6.8).

Table 6.2: Description of parameters in (6.8) and their units.

Parameter	Unit	Description
s	none	ratio of cytotoxic T cells to tumor cells, at which the tumor cell elimination rate reaches its half-maximum
λ	none	exponent in ratio of cytotoxic T cells to tumor cells, which represents how the lysis rate depends on the ratio
n	none	exponent in interaction terms of tumor and cytotoxic T cells
$\tilde{d}$	day^{-1}	maximal tumor cell elimination rate caused by cytotoxic T cells

With $x = bT$, $y = bL$, and $t := a\tau$, we re-parametrize the system and associate $\frac{dx}{dt}$ and $\frac{dy}{dt}$ with $\dot{x}$ and $\dot{y}$, respectively. This leads to the non-dimensionalized system of equations

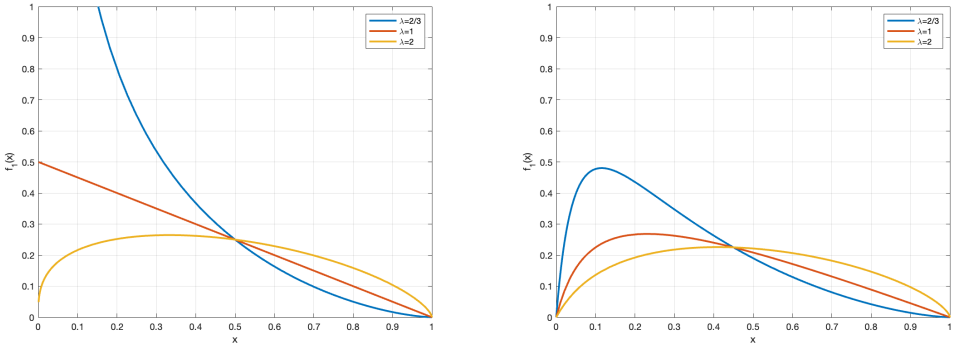
$$\begin{aligned} \dot{x} &= x(1-x) - d\frac{y^\lambda}{s^\lambda x^\lambda + y^\lambda}x^n \\ \dot{y} &= -qx^n y + \frac{jx^n}{g^n + x^n}y - my, \end{aligned} \tag{6.9}$$

where $d = \frac{1}{a}\tilde{d}$, $q := \frac{1}{ab^n}\tilde{q}$, $j := \frac{1}{a}\tilde{j}$, $g := b\tilde{g}$, and $m := \frac{1}{a}\tilde{m}$. In a similar way as in Section 5.2, we can show that the set $D = [0,1]\times[0,\infty) \subset \mathbb{R}^2$ is positively invariant.

In the following, we consider $n = 1$ and assume, similar to Section 6.1, that $\tilde{d} \geq a$ holds true. Setting the right-hand side of (6.9) to zero and considering f_2 from Lemma 5.1 yields the nullclines

$$\begin{aligned} \dot{x} = 0: \qquad & x = 0 \quad \text{or} \quad y = sx\left(\frac{1-x}{d-(1-x)}\right)^{1/\lambda} =: f_1(x) \\ \dot{y} = 0: \qquad & y = 0 \quad \text{or} \quad f_2(x) = -qx + \frac{jx}{g+x} - m = 0, \end{aligned} \tag{6.10}$$

where similar as before, the equilibria $E_0 = (\bar{x}_0, \bar{y}_0) = (0,0)$ and $E_3 = (\bar{x}_0, \bar{y}_0) = (1,0)$ always exist. The equation $f_2(x) = 0$ yields up to two solutions $\bar{x}_1$ and $\bar{x}_2$ in $(0,1)$, where $\bar{x}_1 < \bar{x}_2$. The assumption $\tilde{d} \geq a$ implies that $d = \tilde{d}/a \geq 1$ holds true and thus, for $x \in (0,1)$, we have $d - 1 + x > 0$ for $x \in (0,1)$. It follows that f_1 is defined on the entire interval $(0,1)$ and particularly, we can apply Theorem 5.1 on the number of equilibria in $\mathrm{int}(D)$. For $s = 0.5$, $d \in \{1, 1.1\}$, Figure 6.7 illustrates the graph of f_1 on $(0,1)$.



(a) $d = 1$ (b) $d = 1.1$

Figure 6.7: Graph of f_1 in (6.10) for $s = 0.5$ and different values of d and λ.

For $d > 1$, $f_1(0) = 0$ always holds true, which was not the case in the previous model (6.3). However, for $d = 1$, we have

$$f_1(x) = sx\left(\frac{1-x}{x}\right)^{1/\lambda} = s\left(\frac{x^\lambda(1-x)}{x}\right)^{1/\lambda}$$

for $x \in (0,1)$. If $\lambda = 1$, $f_1(0)$ is simply s. For $\lambda \neq 1$, L'Hôpital's rule yields

$$\lim_{x\to 0} \frac{x^\lambda(1-x)}{x} = \lim_{x\to 0} \frac{\lambda x^{\lambda-1} - (\lambda+1)x^\lambda}{1}.$$

For $\lambda < 1$, we thus have

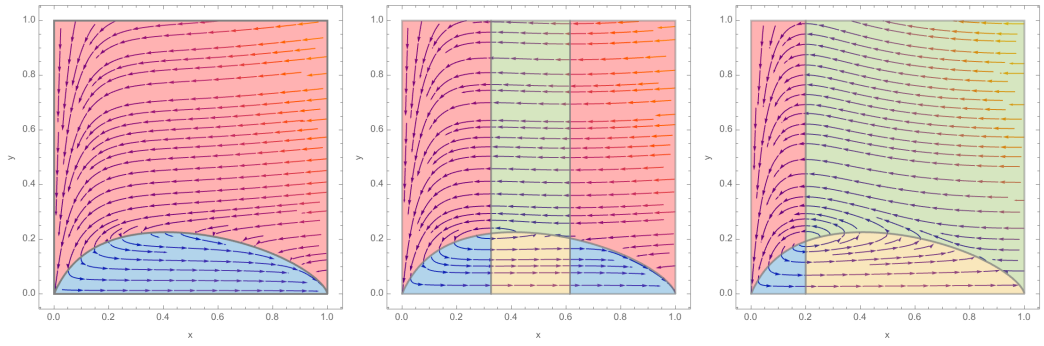
$$\lim_{x \to 0} \frac{\frac{\lambda}{x^{1-\lambda}} - (\lambda + 1)x^{\lambda}}{1} = \infty$$

and for $\lambda > 1$,

$$\lim_{x \to 0} \frac{\lambda x^{\lambda - 1} - (\lambda + 1)x^{\lambda}}{1} = 0$$

holds true. It follows that if $d = 1$ and $\lambda \geq 1$, f_1 intersects the y-axis while if $d = 1$ and $\lambda < 1$, we have $\lim_{x \to 0} f_1(x) = \infty$. The latter is always the case in the previous model approach. In an analogous way as before, this situation would mean that in the initial stage of tumor progression, where the number of tumor cells is low, cancer cells will grow independent of the available amount of cytotoxic T cells in the TME due to the inefficient elimination of cytotoxic T cells. By increasing the parameter value d, this phenomenon can be avoided.

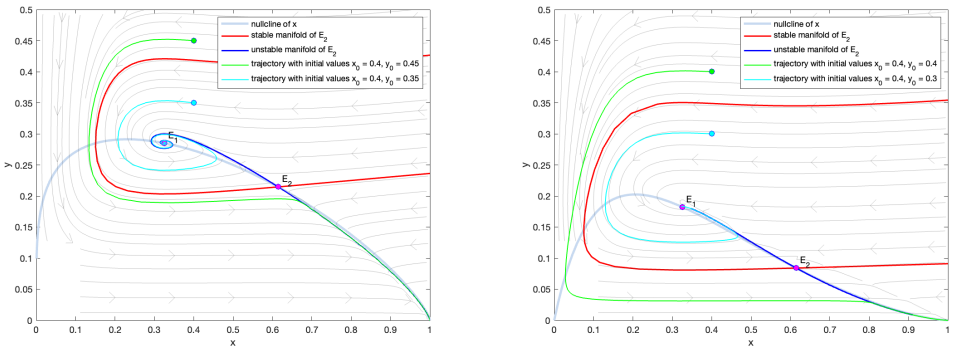
The phase portrait of the system for the parameter values $q = 0.5$, $g = 1$, $m = 0.1$, $s = 0.5$, $\lambda = 1.5$, $d = 1.1$, and $j \in \{1, 1.07, 1.2\}$ is illustrated in Figure 6.8, in which we see that f_1 intersects the y-axis. Particularly, the blue domain, where $\dot{x} > 0$ and $\dot{y} < 0$, does not stretch to infinity along the y-axis. The phase portraits are computed using Mathematica [Wol23].



(a) $j = 1$ (b) $j = 1.07$ (c) $j = 1.2$

Figure 6.8: Phase plane of the system (6.3), where $q = 0.5$, $g = 1$, $m = 0.1$, $\lambda = 1.5$, $s = 0.5$, and $d = 1.1$. The regions colored in red, blue, green, and yellow represent the cases $\dot{x} < 0,\ \dot{y} < 0$, $\dot{x} > 0,\ \dot{y} < 0$, $\dot{x} < 0,\ \dot{y} > 0$, and $\dot{x} > 0,\ \dot{y} > 0$, respectively.

In the current model, the system again establishes the "sneaking through" phenomenon for parameter values, where the non-zero nullcline of x intersects the y-axis. For the parameter values $q = 0.5$, $j = 1.07$, $g = 1$, $m = 0.1$, $s = 0.5$, and $d = 1$, Figure 6.9 illustrates this for $\lambda = 1.3$, $d = 1$ and $\lambda = 2/3$, $d = 1.3$.



(a) $\lambda = 1.3$, $d = 1$ (b) $\lambda = 2/3$, $d = 1.3$

Figure 6.9: Phase plane of the system (6.9), where $n = 1$, $q = 0.5$, $j = 1.07$, $g = 1$, $m = 0.1$, and $s = 0.5$.

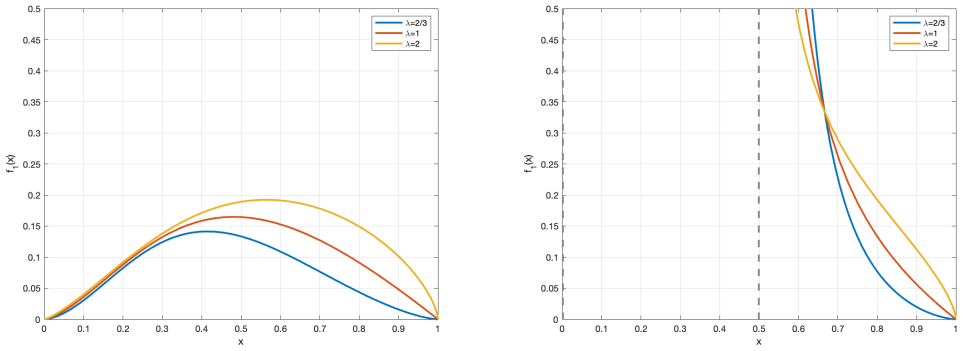
For a general $n > 0$, the nullclines of the system (6.9) are given by

$$\begin{aligned} \dot{x} = 0: &\qquad x = 0 \quad \text{or} \quad y = sx\left(\frac{1-x}{dx^{n-1}-(1-x)}\right)^{1/\lambda} =: f_1(x) \\ \dot{y} = 0: &\qquad y = 0 \quad \text{or} \quad f_2(x) = -qx^n + \frac{jx^n}{g^n + x^n} - m = 0. \end{aligned} \tag{6.11}$$

The denominator of f_1 in (6.11) has the same form as the denominator of f_1 in (6.6). Thus, using the same arguments as before, system (6.9) is able to establish a phenomenon, in which the immune system would require infinitely many cytotoxic T cells to control the tumor cells in a dormant state. For $n = 2/3$ and $n = 2$, Figure 6.10 illustrates the graph of f_1 with $d = 1$, where we observe that for $n = 2$, there is an asymptote (dashed line in grey). Analogously to Section 6.1, we argue that the model (6.9) for $n > 1$ might not always be suitable to describe the tumor-immune interactions. For the parameter values $n = 2$, $q = 0.5$, $g^n = 1$, $m = 0.1$, $\lambda = 1$, $s = 0.5$, and $d = 1$, Figure 6.11 illustrates the possible asymptotic behavior.

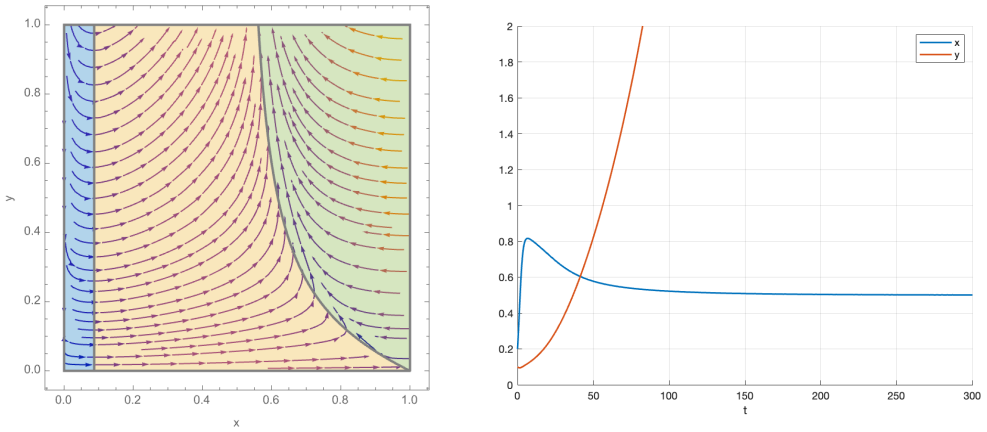
The model approaches discussed in the current chapter allow different variations of the nullcline of x. We argued that for $n > 1$, it is important to keep the asymptotic behavior in mind when using the models to describe the dynamics between tumor and cytotoxic T cell populations. In order to qualitatively conclude which of the models best describes the interaction between tumor cells and cytotoxic T cells, we further need to fit the models to real-world data of human patients, where the level of tumor and cytotoxic T cells can be measured.

Up to now, we only used systems of ordinary differential equations to model the interaction between tumor and cytotoxic T cells. Particularly, we did not account for the possible time delay in the stimulation and inactivation of cytotoxic T cells. In the next chapter, we incorporate this aspect in a model described by a system of delay differential equations.



(a) $n = 2/3$ (b) $n = 2$

Figure 6.10: Graph of f_1 in (6.10) for $d = 1$, $s = 0.5$, and different values of n and λ.



(a) (b)

Figure 6.11: Situation for the system (6.9) with $n = 2$, where $\bar{x}_1 \in (0, 1)$, but $f_1(\bar{x}_1)$ is not defined. The parameters are set to $q = 0.5$, $j = 1.2$, $g^n = 1$, $m = 0.1$, $\lambda = 1$, $s = 0.5$, and $d = 1$. The phase portrait of the system is illustrated in (a) while (b) shows the trajectories of x and y with initial values $x_0 = 0.2$ and $y_0 = 0.1$.

7 A DDE approach on the dynamics between tumor and cytotoxic T cells

In many biological systems, time delay plays an important role. With a time delay in the model, the system may not only depend on the current state, but also on the past states. In tumor-immune dynamics, time delays also appear in many aspects, such as cell differentiation and proliferation, activation of the adaptive immune system, stimulation of effector cells, etc. Further, one of the countermeasures by tumor cells is the release of soluble forms of FasL, which activate the apoptosis of nearby cytotoxic T cells upon binding with their Fas receptors.

In this chapter, we adapt the model from Chapter 5 for $n = 1$ by introducing a discrete-time delay in the stimulation of matured T cell proliferation and in the deactivation of matured T cells through the interaction with tumor cells. In particular, we consider both processes to depend on signals released by tumor cells, where the resulting effect, i.e. T cell proliferation and deactivation, occur with a time lag and depend on the current cytotoxic T cell population size.

7.1 Model assumptions and formulation

Let T and L once again denote the tumor cell and cytotoxic T cell population, respectively and consider Assumption (1)-(5) from Chapter 4. In addition, we introduce a discrete-time delay in the inactivation of cytotoxic T cells induced by the interaction with tumor cells as well as in the stimulation of cytotoxic T cell proliferation.

The resulting system of delay differential equations reads

$$\begin{aligned} \frac{dT(\tau)}{d\tau} &= aT(\tau)(1 - bT(\tau)) - \tilde{d}T(\tau)L(\tau) \\ \frac{dL(\tau)}{d\tau} &= -\tilde{q}L(\tau)T(\tau - \tilde{r}) + \frac{\tilde{j}T(\tau - \tilde{r})}{\tilde{g} + T(\tau - \tilde{r})}L(\tau) - mL(\tau), \end{aligned} \tag{7.1}$$

for $\tau \geq 0$, where $\tilde{r} \geq 0$ describes the time lag between the signal transmission by tumor cells and the occurrence of the stimulation and inactivation of cytotoxic T

cells. All other parameters are assumed to be positive, where their biological interpretation and unit remain the same as in Table 5.1. System (7.1) is an autonomous system with a constant discrete-time delay. Thus, without loss of generality, we can assume $\tau_0 = 0$. We further assume the initial function $\phi(\tau) = (T_0(\tau), L_0(\tau))$ for $\tau \in [-\tilde{r}, 0]$ to be continuous and to satisfy $\phi(\tau) \geq 0$ component-wise for all $\tau \in [-\tilde{r}, 0]$.

Similar as in Chapter 5, we use the dimensionless variables $x = bT$, $y = bL$, $t = a\tau$, and $r = a\tilde{r}$ and parameters $d = \frac{1}{ab}\tilde{d}$, $q = \frac{1}{ab}\tilde{q}$, $j = \frac{1}{a}\tilde{j}$, $g = b\tilde{g}$, and $m = \frac{1}{a}\tilde{m}$. Associating $\frac{dx}{dt}$ and $\frac{dy}{dt}$ with $\dot{x}$ and $\dot{y}$, respectively yields the system of equations

$$\begin{aligned} \dot{x}(t) &= x(t)(1 - x(t)) - dx(t)y(t) \\ \dot{y}(t) &= y(t)\left(-qx(t-r) + \frac{jx(t-r)}{g + x(t-r)} - m\right). \end{aligned} \tag{7.2}$$

Note that due to biological reasons, we only consider non-negative initial functions that lie within $[0, 1]$ for x and $[0, \infty)$ for y.

7.2 Qualitative analysis

Since $x(t) = 0$ and $y(t) = 0$ imply $\dot{x}(t) = 0$ and $\dot{y}(t) = 0$, respectively, it follows from Theorem 3.11 that the corresponding solution of (7.2) is non-negative for all $t > 0$ where it is defined.

7.2.1 Boundedness of solutions

In what follows, we consider the following theorem on the boundedness of solutions of (7.2), which guarantees the continuability of solutions for all positive times.

Theorem 7.1. Solutions of (7.2) are bounded for positive time.

Proof. First, we note that the non-dimensional variable x lies within the interval $[0, 1]$, if the initial functions are chosen as previously discussed, since $\dot{x} \geq 0$ for $x = 0$ and $\dot{x} \leq 0$ for $x = 1$. If $mg < q$ and $j < qg + m + 2\sqrt{qgm}$, or $mg \geq q$ and $j \leq (1 + g)(q + m)$, it follows from Lemma 5.1 that for all $x \in [0, 1]$, we have

$$-qx + \frac{jx}{g + x} - m \leq 0$$

and thus,

$$\dot{y}(t) = y(t)\left(-qx(t-r) + \frac{jx(t-r)}{g + x(t-r)} - m\right) \leq 0$$

holds for all $t > 0$, which implies the boundedness of y since y is non-negative. In the case of $mg < q$ and $j \geq qg + m + 2\sqrt{qgm}$, or $mg \geq q$ and $j > (1+g)(q+m)$, Lemma 5.1 states that the equation

$$-qx + \frac{jx}{g+x} - m = 0$$

has at least one solution in $(0,1)$, denoted by $\bar{x}_1$, where for $x < \bar{x}_1$ we have

$$-qx + \frac{jx}{g+x} - m < 0 \tag{7.3}$$

and for $\min\{\bar{x}_2, 1\} > x > \bar{x}_1$,

$$-qx + \frac{jx}{g+x} - m > 0.$$

Note that (7.3) implies that $\dot{y}(t) \leq 0$ holds true. Particularly, there exists a x^* with $\bar{x}_1 < x^* \leq 1$, such that

$$-qx^* + \frac{jx^*}{g+x^*} - m \geq -qx + \frac{jx}{g+x} - m$$

holds true for all $x \in [0,1]$, which implies

$$\begin{aligned}\dot{y}(t) &= y(t)\left(-qx(t-r) + \frac{jx(t-r)}{g+x(t-r)} - m\right) \\ &\leq y(t)\left(-qx^* + \frac{jx^*}{g+x^*} - m\right).\end{aligned}$$

The second equation in (7.2) can be expressed in integral form given by

$$y(t) = y(t_0)\exp\left(\int_{t_0}^{t}\left(-qx(s-r) + \frac{jx(s-r)}{g+x(s-r)} - m\right)ds\right)$$

and therefore we have

$$y(t_2) \leq y(t_1)\exp\left(\left(-qx^* + \frac{jx^*}{g+x^*} - m\right)(t_2 - t_1)\right)$$

for all $t_2 \geq t_1 \geq 0$, which is equivalent to

$$t_2 - t_1 \geq \frac{1}{-qx^* + \frac{jx^*}{g+x^*} - m}\ln\left(\frac{y(t_2)}{y(t_1)}\right). \tag{7.4}$$

We further observe that if $y(t) \geq \frac{2-\bar{x}_1}{2d}$ for some $t \geq 0$, it then follows that

$$\begin{aligned}\dot{x} &= x(t)(1 - x(t) - dy(t)) \leq x(t)\left(1 - x(t) - \left(1 - \frac{\bar{x}_1}{2}\right)\right) \\ &\leq 1 - x(t) - \left(1 - \frac{\bar{x}_1}{2}\right) \leq -x(t) + \frac{\bar{x}_1}{2},\end{aligned} \tag{7.5}$$

which has a unique positive root given by $\tilde{x} = \bar{x}_1/2 < \bar{x}_1 < x^*$. Let (7.5) be satisfied for $t \geq t_0 \geq 0$. We observe that solutions of

$$\dot{u}(t) = -u(t) + \tilde{x} \tag{7.6}$$

with initial value $u(t_0) \in [0, 1]$ have the form

$$u(t) = (u(t_0) - \tilde{x}) \exp(-t) + \tilde{x},$$

which converges to $\tilde{x}$ for $t \to \infty$. Note that $(u(t_0) - \tilde{x}) \exp(-t) + \tilde{x} \leq (1 - \tilde{x}) \exp(-t) + \tilde{x}$ holds for all $t_0 \geq 0$. Thus, independent of t_0, there exists a time $\hat{T} > 0$, for which $u(t) < \bar{x}_1$ for $t \geq t_0 + \hat{T}$. This implies that $x(t) < \bar{x}_1$ for $t \geq t_0 + \hat{T}$.

We now assume that $y(t)$ is unbounded and consider the following two possible cases.

1. There exists a time $T > 0$, such that for $t \geq T$ the solution $y(t)$ stays above $\frac{2-\bar{x}_1}{2d}$. In this case, (7.5) is satisfied for $t \geq T$. Comparing this with (7.6) states that for $t \geq T + \hat{T}$, we have $x(t) < \bar{x}_1$ and analogously for $t \geq T + \hat{T} + r$, we have $x(t - r) < \bar{x}_1$. It then follows from (7.3) and $y(t) > 0$ that $\dot{y}(t) < 0$, which contradicts the assumption that $y(t)$ is unbounded.

2. The solution $y(t)$ does not stay above a certain value for all large times. Particularly, there exist sequences of time points $(s_n)_n$ and $(t_n)_n$ with $s_n, t_n \to \infty$, $y(s_n) < \frac{2-\bar{x}_1}{2d}$, $y(t_n) > \frac{2-\bar{x}_1}{2d}$, $y(t_n) \to \infty$, $\dot{y}(t_n) = 0$, and $t_{n-1} < s_n < t_n$ for $n > 1$. Next, we choose a sequence of time points $(l_n)_n$, such that $s_n < l_n < t_n$, $y(l_n) = \frac{2-\bar{x}_1}{2d}$, and $y(t) > \frac{2-\bar{x}_1}{2d}$ for $l_n < t < t_n$. Since $y(t_n)$ gets arbitrarily large, there exists a $\tilde{n}$ such that $y(t_{\tilde{n}}) \geq \exp\left(\left(-qx^* + \frac{jx^*}{g+x^*} - m\right)(\hat{T} + r)\right) \cdot \frac{2-\bar{x}_1}{2d}$. With $y(l_{\tilde{n}}) = \frac{2-\bar{x}_1}{2d}$ it follows from (7.4) that

$$\begin{aligned} t_{\tilde{n}} - l_{\tilde{n}} &\geq \frac{1}{-qx^* + \frac{jx^*}{g+x^*} - m} \ln\left(\frac{y(t_{\tilde{n}})}{y(l_{\tilde{n}})}\right) \\ &\geq \frac{1}{-qx^* + \frac{jx^*}{g+x^*} - m} \ln\left(\frac{\exp\left(\left(-qx^* + \frac{jx^*}{g+x^*} - m\right)(\hat{T} + r)\right) \cdot \frac{2-\bar{x}_1}{2d}}{\frac{2-\bar{x}_1}{2d}}\right) \\ &= \hat{T} + r. \end{aligned}$$

   Particularly, $t_{\tilde{n}} \geq l_{\tilde{n}} + \hat{T} + r$.

   By setting $t_0 = l_{\tilde{n}}$, we know from the argumentation conducted with (7.5) and (7.6) that $x(t) < \bar{x}_1$ for $l_{\tilde{n}} + \hat{T} + r \leq t \leq t_{\tilde{n}}$ and analogously, for $l_{\tilde{n}} + \hat{T} \leq t - r \leq t_{\tilde{n}} - r$, we have $x(t - r) < \bar{x}_1$. However, by the definition of $\bar{x}_1$, this implies that

$$\dot{y}(t_{\tilde{n}}) = y(t_{\tilde{n}}) \left(-qx(t_{\tilde{n}} - r) + \frac{jx(t_{\tilde{n}} - r)}{g + x(t_{\tilde{n}} - r)} - m\right) < 0,$$

   which contradicts $\dot{y}(t_{\tilde{n}}) = 0$.

Thus, $y(t)$ is bounded. □

7.2.2 Analysis of Hopf bifurcation

For $r = 0$, system (7.2) was discussed in Chapter 5 by setting $n = 1$. As time delay does not affect the existence conditions of equilibria, Theorem 5.1 applies for (7.2) as well. Further, from Section 5.2, we know that the system without delay has no periodic solutions.

Consider $mg < q$ and $j \geq qg + m + 2\sqrt{qgm}$. According to Theorem 5.1, system (7.2) has a non-trivial equilibrium $E_1 = (\bar{x}_1, \bar{y}_1) \in \text{int}(D)$, where $D = [0,1] \times [0,\infty) \subset \mathbb{R}^2$ and $\bar{y}_1 = (1-\bar{x}_1)/d$. In Section 5.2, we have shown that E_1 is locally asymptotically stable for $r = 0$. We set $u := x - \bar{x}_1$ and $v := y - \bar{y}_1$ and write $\gamma(x) = \frac{jx}{g+x}$. The corresponding system, where the equilibrium E_1 is shifted into the origin, is given by

$$\begin{aligned} \dot{u}(t) =& (u(t) + \bar{x}_1)(1 - u(t) - \bar{x}_1) - d(u(t) + \bar{x}_1)(v(t) + \bar{y}_1) \\ \dot{v}(t) =& -q(u(t-r) + \bar{x}_1)(v(t) + \bar{y}_1) + \gamma(u(t-r) + \bar{x}_1)(v(t) + \bar{y}_1) \\ & - m(v(t) + \bar{y}_1). \end{aligned} \tag{7.7}$$

With $\gamma(u(t-r) + \bar{x}_1) = \sum_{i=0}^{\infty} \frac{u(t-r)^i}{i!}\gamma^i(\bar{x}_1) = \gamma(\bar{x}_1) + \gamma'(\bar{x}_1)u(t-r) + \ldots$, the linearized system is given by

$$\begin{aligned} \dot{u}(t) &= -\bar{x}_1 u(t) - d\bar{x}_1 v(t) \\ \dot{v}(t) &= -q\bar{y}_1 u(t-r) - q\bar{x}_1 v(t) + \frac{j\bar{x}_1}{g+\bar{x}_1} v(t) + \frac{jg}{(g+\bar{x}_1)^2}\bar{y}_1 u(t-r) - mv(t) \\ &= \left(-q\bar{x}_1 + \frac{j\bar{x}_1}{g+\bar{x}_1} - m\right) v(t) + \frac{1-\bar{x}_1}{d}\left(-q + \frac{jg}{(g+\bar{x}_1)^2}\right) u(t-r). \end{aligned} \tag{7.8}$$

Note that $-q\bar{x}_1 + \frac{j\bar{x}_1}{g+\bar{x}_1} - m = 0$ and recall from the proof of Lemma 5.1 that $-q + \frac{jg}{(g+\bar{x}_1)^2} > 0$. For the matrices A and B from Section 3.2.4, we have

$$A = \begin{pmatrix} -\bar{x}_1 & -d\bar{x}_1 \\ 0 & 0 \end{pmatrix}, \quad B = \begin{pmatrix} 0 & 0 \\ \frac{1-\bar{x}_1}{d}\left(-q + \frac{jg}{(g+\bar{x}_1)^2}\right) & 0 \end{pmatrix}.$$

Furthermore, with $\beta := \bar{x}_1(1-\bar{x}_1)\left(-q + \frac{jg}{(g+\bar{x}_1)^2}\right) > 0$, the characteristic equation reads

$$\begin{aligned} 0 &= \det\left(\lambda I - A - B\exp(-\lambda r)\right) \\ &= \det\begin{pmatrix} \lambda + \bar{x}_1 & d\bar{x}_1 \\ -\frac{1-\bar{x}_1}{d}\left(-q + \frac{jg}{(g+\bar{x}_1)^2}\right)\exp(-\lambda r) & \lambda \end{pmatrix} \\ &= \lambda^2 + \bar{x}_1\lambda + \bar{x}_1(1-\bar{x}_1)\left(-q + \frac{jg}{(g+\bar{x}_1)^2}\right)\exp(-\lambda r) \\ &= \lambda^2 + \bar{x}_1\lambda + \beta\exp(-\lambda r). \end{aligned} \tag{7.9}$$

We observe that the graph of $h_1(\lambda) = \lambda^2 + \bar{x}_1\lambda$ does not intersect the graph of $h_2(\lambda) = -\beta\exp(-\lambda r)$ for $\lambda \geq 0$, since $h_1(0) = 0$ and $h_1(\lambda) > 0$ for $\lambda > 0$ while

$h_2'(\lambda) > 0$, $h_2(0) = -\beta < 0$, and $\lim_{\lambda\to\infty} h_2(\lambda) = 0$. Therefore, there are no real solutions of (7.9) satisfying $\lambda \geq 0$. Further, the characteristic equation has the form of (3.10) with $p = \bar{x}_1$, $a = b = 0$, and $q = \beta$. In particular, (H_1) and (H_2) from Section 3.2.5 are satisfied.

Let $\lambda = \alpha + i\omega$ be a solution of (7.9). From Section 3.2.5 we know that if $\alpha = 0$ and $\omega > 0$, we have

$$\omega_\pm^2 = -\frac{\bar{x}_1^2}{2} \pm \frac{\sqrt{\bar{x}_1^4 + 4\beta^2}}{2}.$$

Since $-\bar{x}_1^2 < 0$, we have that (H_4) from Section 3.2.5 holds and thus, $\omega_-^2 < 0$ and $\omega_+^2 > 0$. We calculate

$$\omega_+ = \sqrt{-\frac{\bar{x}_1^2}{2} + \frac{\sqrt{\bar{x}_1^4 + 4\beta^2}}{2}}$$

and

$$\cos(\omega_+ r) = \frac{\omega_+^2}{\beta} > 0, \quad \sin(\omega_+ r) = \frac{\omega_+ \bar{x}_1}{\beta} > 0$$

and set

$$r_n = \frac{1}{\omega_+}\left(\arcsin\left(\frac{\omega_+\bar{x}_1}{\beta}\right) + 2n\pi\right)$$

for $n \in \{0, 1, 2, \dots\}$. Recall from Section 3.2.5 that (7.9) can only have a pair of purely imaginary solutions $\pm i\omega_+$ if $r = r_n$ for some n. We consider the inverse of the increasing branch $\sin : (-\frac{\pi}{2}, \frac{\pi}{2}) \to (-1, 1)$, and since $\cos(\omega_+ r) = \frac{\omega_+^2}{\beta} > 0$ and $\sin(\omega_+ r) = \frac{\omega_+\bar{x}_1}{\beta} > 0$, we have that $0 < \sin(\omega_+ r) < \frac{\pi}{2}$. Thus, the smallest delay for which there is a pair of purely imaginary roots $\pm i\omega_+$ is

$$r_0 = \frac{1}{\omega_+}\arcsin\left(\frac{\omega_+\bar{x}_1}{\beta}\right).$$

From Section 3.2.5 it follows that for $r \in [0, r_0)$, all roots of (7.9) have negative real parts and for $r > r_0$, (7.9) has at least one root with positive real part. Thus, for $r > r_0$, Theorem 3.15 yields that the equilibirum E_1 is unstable.

We now check if a Hopf bifurcation occurs at $r = r_0$. To keep the notation from Section 3.2.6, we consider $r = r_0 + \mu$, which implies $\mu = r - r_0$. The characteristic equation (7.9) takes the form

$$h(\lambda, \mu) := \lambda^2 + \bar{x}_1\lambda + \beta e^{-\lambda(r_0+\mu)} = 0.$$

In particular, we have $h(i\omega_+, 0) = 0$ and

$$h_\lambda(i\omega_+, 0) = \bar{x}_1 - r_0\omega_+^2 + i(2\omega_+^2 r_0 \bar{x}_1) \neq 0,$$

where h_λ is the partial derivative of h with respect to λ. Thus, it follows from the Implicit function theorem, that there exists an open interval $W \subset \mathbb{R}$ with $0 \in W$ and a function $\lambda : W \to \mathbb{C}$, $\lambda = \lambda(\mu) = \alpha(\mu) + i\omega(\mu)$, such that

$$\alpha(0) = 0,\ \alpha'(0) = \frac{d\mathrm{Re}(\lambda)}{d\mu}(0) = \frac{d\mathrm{Re}(\lambda)}{dr}(r_0) > 0,\ \text{and } \omega(0) = \omega_+.$$

The last inequality follows from the computation in Section 3.2.5. We observe that this root crosses the imaginary axis at $\mu = 0$ from left to right, i.e. $\alpha < 0$ for $\mu < 0$, which is equivalent to $r < r_0$. We have now verified all the conditions for a Hopf bifurcation.

We further note that for $r = 0$, system (7.1) has no periodic solutions. Therefore, we conclude that for $r > r_0$, there exists a periodic solution.

7.3 Numerical simulations

In the following section, we consider the dimensionless parameter values given in Table 7.1 and study the dynamics of the system (7.2) by varying the parameter j and the delay r.

Table 7.1: Dimensionless parameter values.

Dimensionless parameter	Value
$d = \tilde{d}/(ab^n)$	5
$q = \tilde{q}/(ab^n)$	0.5
$g = b\tilde{g}$	0.5
$m = \tilde{m}/a$	0.1

For the initial function, we assume a tumor cell population that proliferates following a logistic growth function with $x_0 := x(-r)$. For simplicity, we assume a positive constant level of cytotoxic T cells, which do not have a negative effect on the tumor cells. Thus, for $-r \le t \le 0$, we consider the initial function of the form

$$\begin{aligned} x_0(t) &= \frac{1}{\frac{1}{x_0}\exp(-t) + 1} \\ y_0(t) &= y_0. \end{aligned} \tag{7.10}$$

With $qg+m+2\sqrt{qgm} \approx 0.666$ and $(q+m)(g+1) = 0.9$, it follows from Theorem 5.1 that if $0.666 < j < 0.9$, we have $E_1, E_2 \in \mathrm{int}(D)$ and if $j > 0.9$, only $E_1 \in \mathrm{int}(D)$ holds.

For the initial function in (7.10), solutions of the system (7.2) are solved using the "dde23" function in MATLAB [BB19].

Existence of two non-trivial equilibria

We first analyze the case, where both equilibria $E_1 = (\bar{x}_1, \bar{y}_1)$ and $E_2 = (\bar{x}_2, \bar{y}_2)$ are in $\text{int}(D)$.

We set $j = 0.75$. Then, the equilibria E_1 and E_2 are given by $(0.155, 0.169)$ and $(0.645, 0.071)$, respectively. With $\beta = \bar{x}_1(1 - \bar{x}_1)\left(-q + \frac{jg}{(g+\bar{x}_1)^2}\right) \approx 0.049$, it follows that

$$\omega_+ = \sqrt{-\frac{\bar{x}_1^2}{2} + \frac{\sqrt{\bar{x}_1^4 + 4\beta^2}}{2}} \approx 0.196$$

and thus, we have

$$r_0 = \frac{1}{\omega_+} \sin^{-1}\left(\frac{\omega_+ \bar{x}_1}{\beta}\right) \approx 3.412.$$

In case of no delay, the system (7.2) is reduced to the ODE case in (5.3). For the set of parameter values given in Table 7.1, the corresponding phase plane is illustrated in Figure 7.1. Let (x_0, y_0) denote the initial state of the system. We observe that if x_0 is small enough such that x_0 is on the left-hand side of the stable manifold of the equilibrium E_2, the tumor cell population will eventually grow into the "uncontrolled" state regardless of the initial available cytotoxic T cell population.

For $x_0 = 1 \cdot 10^{-4}$ and $y_0 \in \{0.2, 0.5\}$, Figure 7.2 illustrates the corresponding trajectories. We observe that the tumor cell population size is kept low for some time after the initialization, while the size of the cytotoxic T cell population decreases until the remaining tumor cells are able to grow and the cytotoxic T cells are no longer able to control the growing tumor cell population.

We now study the behavior of the system near the equilibrium E_1 when varying the delay r. We consider an initial state $(x_0(-r), y_0(-r)) = (0.15, 0.16)$. For $r \in \{0, 1.5, 3, 4.5\}$, Figure 7.3 illustrates the corresponding solution curves.

In particular, we observe that for $r < r_0$, the solutions curves correspond to a dampened oscillation around the locally asymptotically stable equilibrium. However for a delay that is slightly larger than r_0, the system establishes a locally stable periodic orbit, which is illustrated in Figure 7.3d. Next, we consider the case where $E_2 \notin \text{int}(D)$ and $E_3 = (1, 0)$ becomes unstable.

Existence of one non-trivial equilibrium

For $j = 1$, we find $E_1 = (\bar{x}_1, \bar{y}_1) = (0.082, 0.184)$ and $E_2 \notin \text{int}(D)$. For $r = 0$ and the same set of initial values chosen as in Figure 7.2, Figure 7.4 illustrates the corresponding solution curves of the system (7.2). Further, we calculate $\beta \approx 0.073$ and thus, it follows that $\omega_+ \approx 0.264$ and $r_0 \approx 1.140$.

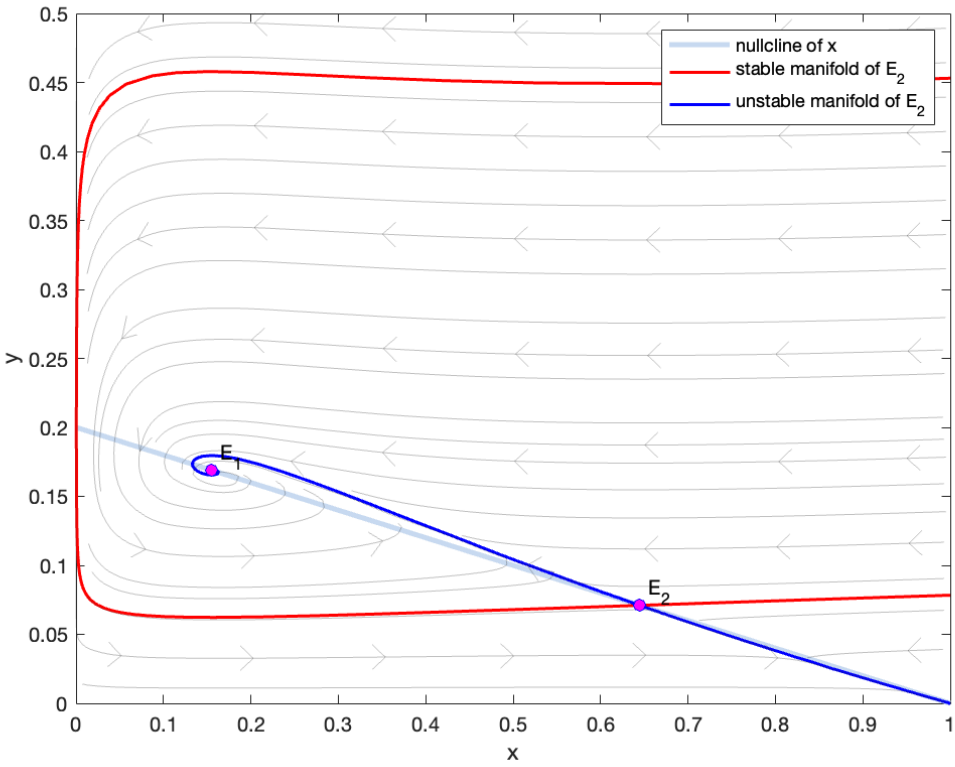
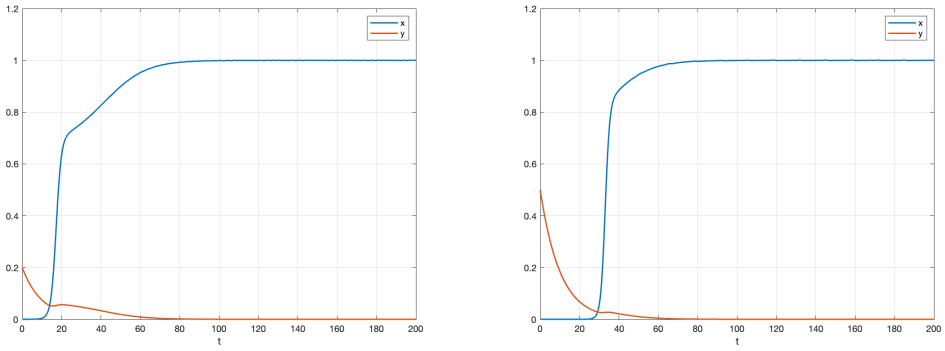


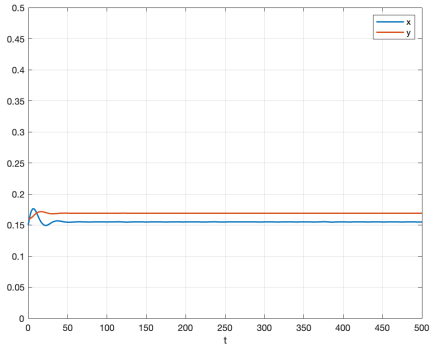
Figure 7.1: Phase plane of the system (7.2), where $q = 0.5$, $j = 0.75$, $g = 0.5$, $m = 0.1$, $d = 5$, and there is no delay, i.e. $r = 0$.



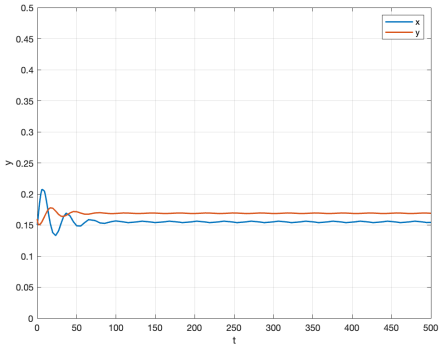
(a) $y_0 = 0.2$ (b) $y_0 = 0.5$

Figure 7.2: Solution curves of the system (7.2) with $r = 0$, $q = 0.5$, $j = 0.75$, $g = 0.5$, $m = 0.1$, $d = 5$, $x_0 = 1 \cdot 10^{-4}$, and $y_0 \in \{0.2, 0.5\}$.

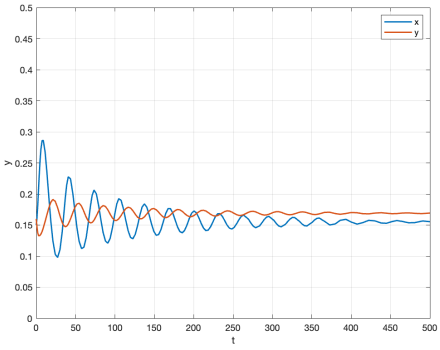
We study the behavior of the system near the equilibrium E_1 when varying the delay r. We consider an initial state $(x_0(-r), y_0(-r)) = (0.1, 0.2)$. For $r \in$



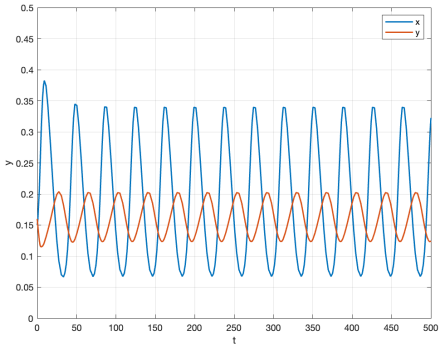
(a) $r = 0$



(b) $r = 1.5 < r_0$

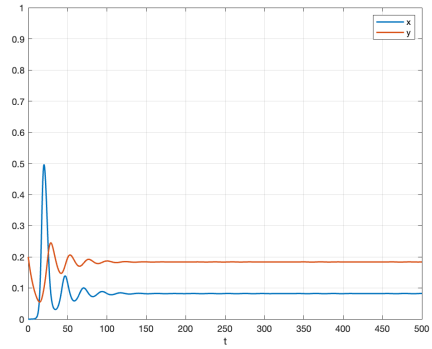


(c) $r = 3 < r_0$

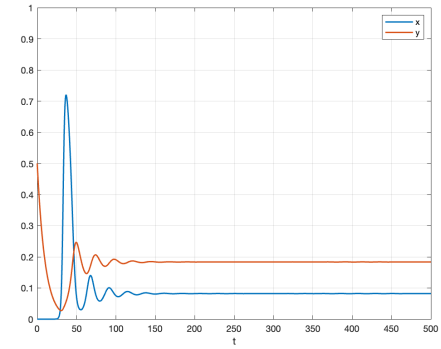


(d) $r = 4.5 > r_0$

Figure 7.3: Solution curves of the system (7.2) with $q = 0.5$, $j = 0.75$, $g = 0.5$, $m = 0.1$, $d = 5$, $x_0(-r) = 0.15$, and $y_0 = 0.16$.



(a) $y_0 = 0.2$

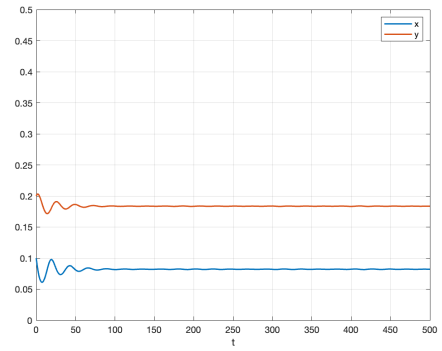


(b) $y_0 = 0.5$

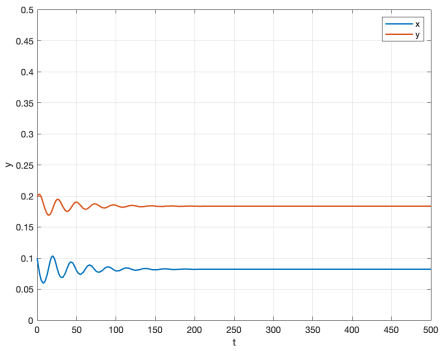
Figure 7.4: Solution curves of the system (7.2) with $r = 0$, $q = 0.5$, $j = 1$, $g = 0.5$, $m = 0.1$, $d = 5$, $x_0 = 1 \cdot 10^{-4}$, and $y_0 \in \{0.2, 0.5\}$.

$\{0, 0.5, 1, 1.5\}$, Figure 7.5 illustrates the corresponding solution curves.

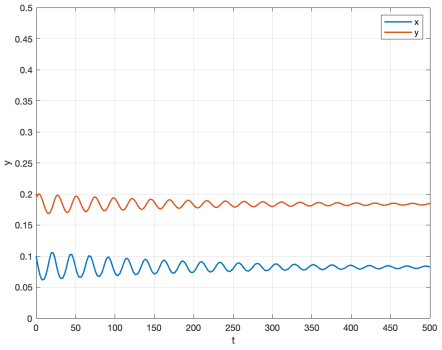
Furthermore, we observe that by further increasing $r > r_0$, the period and the



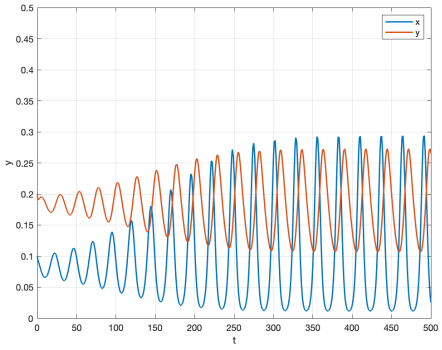
(a) $r = 0$



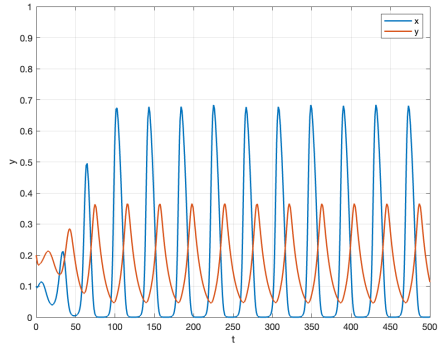
(b) $r = 0.5 < r_0$



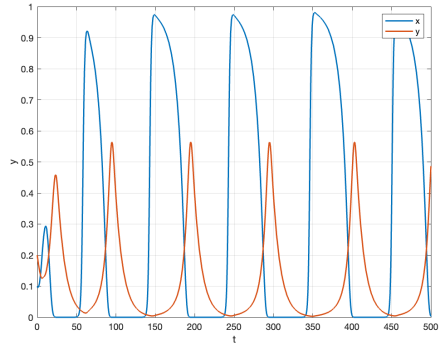
(c) $r = 1 < r_0$



(d) $r = 1.5 > r_0$



(e) $r = 3 > r_0$



(f) $r = 6 > r_0$

Figure 7.5: Solution curves of the system (7.2) with $q = 0.5$, $j = 1$, $g = 0.5$, $m = 0.1$, $d = 5$, $x_0(-r) = 0.1$, and $y_0 = 0.2$.

amplitude of the periodic orbit increases. Particularly, the solution curve for the dimensionless tumor cell population in Figure 7.5f is nearly zero at $t \approx 50$. From the biological perspective, this would describe the case of an elimination of tumor cells and the process can be terminated at this point.

8 Conclusion

In this work we analyzed various mathematical models to describe the dynamics of the interaction between cancer and effector cells. These models are based on the approach used to describe predator-prey dynamics and include systems of ordinary differential equations and delay differential equations. Using the two-population model introduced by Kuznetsov et al. as a basis, we further examined three model variations based on systems of differential equations, which account for different aspects in the tumor-immune system. All three variations focused on the tumor-specific cytotoxic T cells as part of the adaptive immune system, which are usually not present in absence of antigenic tumor cells. In the analysis of the first model, we included an exponent in the terms describing the interaction between tumor and immune cell populations to also allow interactions that are not derived from the law of mass action. In particular, when the tumor size increases, a linear interaction might no longer be appropriate due to space limitation such that not all tumor cells are accessible by newly recruited cytotoxic T cells. The second and third model used different functional terms to describe the elimination of tumor cells induced by immune cells. Particularly, the second model took into account the aspect of T cell exhaustion due to long-term exposure to virus cells, while the third model examined the effect of the de Pillis-Radunskaya Law on the dynamics of our model. Notably, all three models can have up to four equilibria. Three of those equilibria correspond to the three stages of cancer immunoediting. Interestingly, all three models exhibit the "sneaking through" effect observed both in reality and in the model by Kuznetsov et al. The effect of different functional terms is especially reflected in the position of the non-trivial equilibria and the "shape" of the nullcline of the tumor cell population. Besides the mathematical analysis of the models, we also conducted numerical simulations to examine the theoretical results. However, we further need to validate these models to make a statement about their performance in describing the tumor-immune dynamics. Moreover, the restriction to only consider the adaptive immune system simplifies the complex system dramatically. Indeed, the extension to a three-population model by accounting for immune cells, such as NK cells, which are part of the innate system, might lead to further interesting aspects.

Using our first model approach as a basis, we additionally extended the model to account for time delay effects in immune cell differentiation, proliferation, and inactivation due to the interaction with tumor cells. We observed that the delay model exhibits the existence of a Hopf bifurcation, leading to the existence of pe-

riodic orbits, which were not observed in the model without delay. However, the presented delay model considered the same constant delay for both the process of immune cell differentiation and proliferation, as well as the process of inactivation of cytotoxic T cell due to tumor cells, which is a very simplified assumption. We can further extend the model to consider two discrete-time delays as the time needed for immune cell differentiation and proliferation might be different compared to the time required until apoptosis signals induced by tumor cells "reach" the immune cells. Moreover, the assumption of a discrete-time delay can be extended by using a distributed delay, since the time lag in the processes might also depend on other factors.

In many applications of mathematical models of tumor-immune interactions, the effect of treatment on the dynamics plays an essential role, especially when trying to predict the outcome of a patient. Thus, our models can also be further extended by including different immunotherapy aspects.

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A MATLAB scripts

Script descriptions

manifold_E2.m This script file can be used to plot stable and unstable manifolds of the unstable equilibrium E_2. It calls the following scripts:

- f2.m: Computes the values of $\bar{x}_{1,2}$.
- f1.m: Computes the nullcline of x.
- equilibrium.m: Computes the non-trivial equilibria E_1 and E_2.
- jacobian.m: Computes the Jacobian matrix of the equilibria E_1 and E_2.
- model_dimensionless: Contains the dimensionless ODE systems.
- outside_domain.m: Event function for ODE solver.

Script files

manifold_E2.m

```
% analysis of stable manifold of E_2 for ODE model in
   chapter 5 and model variations in chapter 6

%% Parameter values
model = 1;
% takes value 1 (ODE model in chapter 6), 2 (model
   including T cell exhaustion), and 3 (model including
   de Pillis-Radunskaya Law)

j = 1.07;
n = 0.8;
q = 0.5;
m = 0.1;
```

```
gn = 1;
d = 4;
s = 0.5;
lambda = 2/3;
par = [model j n q m gn d s lambda];

equil = manifold(par);

% add trajectories to plot
% uncomment to add trajectories to plot
%{
init_1 = [0.4, 0.4];
init_2 = [0.4, 0.3];
tspan = [0 500];

[~, traj_1]=ode45(@(t, traj_1) model_dimensionless(t,
   traj_1, par), tspan, init_1);
[~, traj_2]=ode45(@(t, traj_2) model_dimensionless(t,
   traj_2, par), tspan, init_2);

p7 = plot(traj_1(:,1), traj_1(:,2),'g', 'LineWidth', 1, '
   DisplayName','trajectory with initial values x_0 =
   0.4, y_0 = 0.4');
p8 = plot(traj_2(:,1), traj_2(:,2),'Color', "#00FFFF", '
   LineWidth', 1, 'DisplayName','trajectory with initial
   values x_0 = 0.4, y_0 = 0.3');
p9 = plot(init_1(1), init_1(2), 'bo', 'MarkerFaceColor',
   'g', HandleVisibility='off');
p10 = plot(init_2(1), init_2(2), 'bo', 'MarkerFaceColor',
    "#00FFFF", HandleVisibility='off');
%}

%% Define function to compute and plot the stable
   manifold of E_2
function equil = manifold(par)

xbar = f2(par);
equil = equilibrium(xbar, par);

% compute corresponding Jacobian matrix of E_2
J1 = jacobian(equil(1, :), par);
[~, D] = eig(J1);
real1 = real(D(1, 1));
```

```
real2 = real(D(2, 2));

% check if the equilibrium E_1 is locally asymptotically
   stable
if real1 < 0 && real2 < 0
    disp('Equilibrium E_1 is locally asymptotically
       stable.')
else
    disp('Equilibrium E_1 is not stable.')
end

% check if 0 < xbar_1 < 1
if xbar(2) < 1 && xbar(2) > 0

    % determine an appropriate time to stop the solution
    options = odeset('Events', @outside_domain);

    % compute corresponding Jacobian matrix of E_2
    J = jacobian(equil(2, :), par);
    [V, L] = eig(J);

    % find stable eigenvector
    [~, ind_s] = min(diag(L));
    s_right_0 = equil(2, :) + 1e-10 .* V(:, ind_s)' /
       norm(V(:, ind_s));

    tspan_s = [500 0];

    % check if the initial state is already outside of
       the domain
    [val, ~] = outside_domain(0, s_right_0, []);
    if val ~= 0
        % solve backwards for one side of the stable
           manifold
        [~, sr] = ode45(@model_dimensionless, tspan_s,
           s_right_0, options, par);
    else
        sr = s_right_0;
    end

    s_left_0 = equil(2,:) - 1e-10 .* V(:, ind_s)'/norm(V
       (:, ind_s));
```

```
% check if the initial state is already outside of
   the domain
[val, ~] = outside_domain(0, s_left_0, []);
if val ~= 0
    % solve backwards for the other side of the
       stable manifold
    [~, sl] = ode45(@model_dimensionless, tspan_s,
       s_left_0, options, par);
else
    sl = s_left_0;
end

% find unstable eigenvector
[~, ind_u] = max(diag(L));
u_right_0 = equil(2, :) + 1e-5 .* V(:, ind_u)' / norm
   (V(:, ind_u));

tspan_u = [0 500];

% check if the initial state is already outside of
   the domain
[val, ~] = outside_domain(0, u_right_0, []);
if val ~= 0
    % solve forward for one side of the unstable
       manifold
    [~, ur] = ode45(@model_dimensionless, tspan_u ,
       u_right_0, options, par);
else
    ur = u_right_0;
end

u_left_0 = equil(2, :) - 1e-5 .* V(:, ind_u)' / norm(
   V(:, ind_u));

% check if the initial state is already outside of
   the domain
[val, ~] = outside_domain(0, u_left_0, []);
if val ~= 0
    % solve forward for the other side of the
       unstable manifold
    [~, ul] = ode45(@model_dimensionless, tspan_u ,
       u_left_0, options, par);
else
```

```
    ul = u_left_0;
end

% add streamlines
x1 = linspace(0, 1, 10);
x2 = linspace(0, 0.5, 5);

[x,y] = meshgrid(x1, x2);

u = zeros(size(x));
v = zeros(size(x));

t=0;
for i = 1:numel(x)
    Xprime = model_dimensionless(t, [x(i); y(i)], par
       );
    u(i) = Xprime(1);
    v(i) = Xprime(2);
end

% plots
% add nullcline of x
p1 = fplot(@(x) f1(x, par), [0 1],'Linewidth', 2.5, '
   Color', '#C7D9F0', 'DisplayName', 'nullcline of x'
   );
axis manual
axis([0 1 0 0.5])
xlabel('x')
ylabel('y')
hold on
p2 = plot(sr(:, 1), sr(:, 2),'r', 'LineWidth', 1.5, '
   DisplayName', 'stable manifold of E_2');
p3 = plot(sl(:, 1), sl(:, 2),'r', 'LineWidth', 1.5);
p4 = plot(ur(:, 1), ur(:, 2),'b', 'LineWidth', 1.5, '
   DisplayName', 'unstable manifold of E_2');
p5 = plot(ul(:, 1), ul(:, 2),'b', 'LineWidth', 1.5);
l = streamslice(x, y, u, v, "arrows");
set(l, 'Color', [0.2 0.2 0.2 0.3]);

p6 = plot(equil(:,1), equil(:,2), 'bo', '
   MarkerFaceColor', 'm');
text(equil(1,1)+0.01,equil(1,2)+0.01,'E_1');
text(equil(2,1)+0.01,equil(2,2)+0.01,'E_2');
```

```
    legend([p1 p2 p4])
else
    disp('Equilibrium E_2 is not in D.')
end
end
```

f2.m

```
function xbar = f2(par)
model = par(1);
j = par(2);
n = par(3);
q = par(4);
m = par(5);
gn = par(6);
d = par(7);
s = par(8);
lambda = par(9);

z1 = (- q * gn - m + j - sqrt((- q * gn - m + j)^2 - 4 *
   q * gn * m)) / (2 * q);
z2 = (- q * gn - m + j + sqrt((- q * gn - m + j)^2 - 4 *
   q * gn * m)) / (2 * q);

xbar(1) = z1^(1/n);
xbar(2) = z2^(1/n);
end
```

f1.m

```
function y = f1(x, par)
model = par(1);
j = par(2);
n = par(3);
q = par(4);
m = par(5);
gn = par(6);
d = par(7);
s = par(8);
lambda = par(9);
```

```
if model == 1
    y = (1 - x) ./ (d .* x .^ (n - 1));
elseif model == 2
    y = s .* ((1 - x) ./ (d .* x .^ (n - 1) - 1 + x)) .^
       (1 / lambda);
else
    y = s .* x .* ((1 - x) ./ (d .* x .^ (n - 1) - 1 + x)
       ) .^ (1 / lambda);
end
end
```

equilibrium.m

```
function equil = equilibrium(xbar, par)
model = par(1);
j = par(2);
n = par(3);
q = par(4);
m = par(5);
gn = par(6);
d = par(7);
s = par(8);
lambda = par(9);

equil(1,1) = xbar(1);
equil(2,1) = xbar(2);

if model == 1
    equil(1,2) = (1 - equil(1,1)) / (d * equil(1,1)^(n -
       1));
    equil(2,2) = (1 - equil(2,1)) / (d * equil(2,1)^(n -
       1));
elseif model == 2
    if n > 1
        disp('Asymptotic behavior in phase portrait
           possible!')
    end
    equil(1,2) = s * ((1 - equil(1,1)) / (d * equil(1,1)
       ^(n-1) - 1 + equil(1,1)))^(1 / lambda);
    equil(2,2) = s * ((1 - equil(2,1)) / (d * equil(2,1)
       ^(n-1) - 1 + equil(2,1)))^(1 / lambda);
```

```
else
    if n > 1
        disp('Asymptotic behavior in phase portrait
           possible!')
    end
    equil(1,2) = s * equil(1,1) * ((1 - equil(1,1)) / (d
       * equil(1,1)^(n-1) - 1 + equil(1,1)))^(1 / lambda)
       ;
    equil(2,2) = s * equil(2,1) * ((1 - equil(2,1)) / (d
       * equil(2,1)^(n-1) - 1 + equil(2,1)))^(1 / lambda)
       ;
end
end
```

jacobian.m

```
function J = jacobian(equil, par)
model = par(1);
j = par(2);
n = par(3);
q = par(4);
m = par(5);
gn = par(6);
d = par(7);
s = par(8);
lambda = par(9);

xbar = equil(1);
ybar = equil(2);

if model == 1
    J(1,1) = 1 - 2 * xbar - n * d * xbar^(n - 1) * ybar;
    J(1,2) = - d * xbar^n;
    J(2,1) = - n * q * xbar^(n - 1) * ybar + n * gn * j *
        xbar^(n - 1) * ybar / ((gn + xbar^n)^2);
    J(2,2) = - q * xbar^n + j * xbar^n / (gn + xbar^n) -
       m;
elseif model == 2
    J(1,1) = 1 - 2 * xbar - n * d * xbar^(n - 1) * ybar^
       lambda / (s^lambda + ybar^lambda);
    J(1,2) = - d * xbar^n * ((lambda * s^lambda * ybar^(
       lambda - 1)) / (s^lambda + ybar^lambda)^2);
```

```
    J(2,1) = - n * q * xbar^(n - 1) * ybar + n * gn * j *
        xbar^(n - 1) * ybar / ((gn + xbar^n)^2);
    J(2,2) = - q * xbar^n + j * xbar^n / (gn + xbar^n) -
       m;
else
    J(1,1) = 1 - 2 * xbar - d * ybar^lambda * ((n -
       lambda) * s^lambda * xbar^(n - 1 + lambda) + n *
       xbar^(n - 1) * ybar^lambda / (s^lambda * xbar^
       lambda + ybar^lambda)^2);
    J(1,2) = - d * xbar^n * ((lambda * s^lambda * xbar^
       lambda * ybar^(lambda - 1)) / (s^lambda * xbar^
       lambda + ybar^lambda)^2);
    J(2,1) = - n * q * xbar^(n - 1) * ybar + n * gn * j *
        xbar^(n - 1) * ybar / ((gn + xbar^n)^2);
    J(2,2) = - q * xbar^n + j * xbar^n / (gn + xbar^n) -
       m;
end
end
```

model_dimensionless.m

```
function xdot = model_dimensionless(t, x, par)
model = par(1);
j = par(2);
n = par(3);
q = par(4);
m = par(5);
gn = par(6);
d = par(7);
s = par(8);
lambda = par(9);

if model == 1
    xdot = [x(1,:) * (1 - x(1,:)) - d * x(2,:) * x(1,:)^n
       ;
        -q * x(2,:) * x(1,:)^n + j * x(1,:)^n / (gn + x
           (1,:)^n) * x(2,:) - m * x(2,:)];
elseif model == 2
    xdot = [x(1,:) * (1 - x(1,:)) - d * x(1,:)^n * x(2,:)
       ^lambda / (s^lambda + x(2,:)^lambda);
        -q * x(2,:) * x(1,:)^n + j * x(1,:)^n / (gn + x
           (1,:)^n) * x(2,:) - m * x(2,:)];
```

```
else
    xdot = [x(1,:) * (1 - x(1,:)) - d * x(1,:)^n * x(2,:)
       ^lambda / (s^lambda * x(1,:)^lambda + x(2,:)^
       lambda);
         -q * x(2,:) * x(1,:)^n + j * x(1,:)^n / (gn + x
            (1,:)^n) * x(2,:) - m * x(2,:)];
end
end
```

outside_domain.m

```
function [position, isterminal, direction] =
   outside_domain(t , y, flag)
% check if to stop the ode solver when solution is
   outside of the domain = [xmin xmax ymin ymax]

domain = [1e-8 1 0 2];
is_out = min([y(1) - domain(1) domain(2)-y(1) y(2)-domain
   (3) domain(4)-y(2)]);
position = is_out >= 0;
isterminal = 1;
direction = 0;
end
```