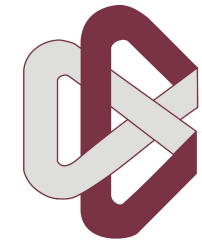

CIMAT

CENTRO DE INVESTIGACIÓN EN MATEMÁTICAS

DOCTORADO EN CIENCIAS CON ORIENTACIÓN EN MATEMÁTICAS APLICADAS

DISCRETE MODELING OF AN AGGRESSIVE-INVASIVE CANCER UNDER CHEMOTHERAPY

TESIS

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Dedicatoria

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Contents

Summary

Cancer is an important disease due to its high mortality rate in the modern world. It has been amply studied and modeled mathematically by the scientific community using different theoretical approaches and computational tools. Such models have contributed to understanding different characteristics of cancer and its treatment from different perspectives. However, despite global research findings in the therapeutics of certain forms of cancer, the disease in general remains a major cause of death. These facts support that cancer modeling is still a current issue of great importance that even the World Health Organization (WHO) encourages to do far more research work in this field.

In this dissertation, our goal is to contribute to such efforts to eradicate cancer as a major cause of death by proposing discrete mathematical models to study the dynamics of an aggressive cancerous tumor with chemotherapy. These models let us describe the cancer evolution and determine suitable chemotherapy schemes for cancer control or its eradication. It is of utmost importance to have discrete models as treatment regimens, the review of trends and data collection take place discretely. We consider that an aggressive cancerous tumor is characterized by its cellular heterogeneity, the high differentiation from the original tissue, its high proliferation rate and its ability to invade healthy host tissue. The most common anticancer treatment is chemotherapy in spite of presenting disadvantages such as drug resistance and drug toxicity that could contribute to the failure or success of the treatment. Therefore, it is essential to include the treatment in the modeling of cancer evolution considering these problems.

Our general methodology to propose the discrete models consist of modeling the cancer growth dynamics in a continuous fashion. Then by using a nonstandard finite difference scheme, we obtain discrete systems that are dynamically consistent with the continuous one. Our next step is to include the application of chemotherapy with instantaneous or gradual effect in the discrete models. Finally, we search for a suitable treatment of chemotherapy, by analyzing different treatment combinations, in order to control cancer or its eradication. Moreover, we analyze and describe the model evolution according to the variation of important characteristics taken into account in our models.

Introduction

Cancer is a serious health public issue due to the fact it is a leading cause of deaths worldwide. According to the World Health Organization (WHO), it was registered 14.1 million new cases of cancer that caused 8.2 million deaths worldwide in 2012. Cancer is a generic name that is used to identify a set of diseases. Cancer consists of a disordered growth of abnormal cells in a certain tissue or organ, that involves complex biological and chemical processes. These cells form a mass which is called a tumor. A cancerous tumor by itself is heterogeneous because it consists of normal tissue, macrophages, lymphocytes and other types of cells growing at the tumor locus. Some of these cells can have the same characteristics as the tissue or can mutate and acquire different characteristics with respect to the original tissue. According to the National Cancer Institute (NCI), an aggressive cancerous tumor is characterized by its acute dissimilarity from the original tissue (poorly differentiated or undifferentiated), its heterogeneity due to its sensitivity to cell mutation, its high proliferation rate and its capacity to invade healthy surrounding tissue. Several types of aggressive cancers include lung, liver, stomach, colorectal and breast cancer, according to International Agency for Research Cancer (IARC) [17]. Early diagnosis and treatment of aggressive tumors are important factors in decreasing the chance of their spreading, after which they are difficult to eradicate. The main anticancer treatments are chemotherapy, radiotherapy, immunotherapy and surgery. The most common anticancer treatment is chemotherapy which consists of the application of cytotoxic drugs in order to kill cancer cells, to reduce the tumor size or to stop its growth. Two fundamental problems that limit the use of chemotherapy are drug resistance and drug toxicity, which reduce treatment success.

Recently cancer modeling has had a significant advance in the development of relevant cancer models. The scientific community has developed such models by using several mathematical and computational tools from different perspectives such as carcinogenesis, the growth dynamic of homogeneous or heterogeneous tumors, avascular or vascular tumors, necrosis, angiogenesis, invasion and metastasis. Moreover, the evolution of cancer with anticancer treatments has been also analyzed. All these models have helped us to understand this serious disease and the effects of different treatments. Cancer modeling have been widely explored predominantly by means of continuous models, two remarkable historical reviews are [3, 4]. On the other hand, there has been a lot of interest and research in their analog counterparts, namely discrete models, see for example [6, 37, 36, 27, 16]. It is of utmost importance to have discrete models because treatment regimens, the review of trends and data collection take place discretely [39].

This dissertation focus on the mathematical modeling of an aggressive cancerous tumor under chemotherapy treatment, using discrete dynamical systems. The main purpose of this work is to describe the cancer evolution and to determine effective treatment schemes for the control or eradication of cancer. The general methodology we use to establish the discrete mathematical models consists of proposing continuous models that describe the evolution of an aggressive cancer tumor with the desired characteristics, based on the vast literature in this area. Our next step is to construct suitable discretization schemes of the continuous models, in such a way that the obtained discrete models satisfy the positiveness and dynamical properties of the continuous models. This is achieved using nonstandard finite difference schemes which emerged in 1989 with Ronald E. Mickens, see [34]. Finally, the application of chemotherapy treatments with instantaneous or gradual effect are included in the discrete models. Once we have the discrete models, we determine effective treatments of chemotherapy to control or to eradicate the tumor.

The relevance of this dissertation is supported by the importance of the topic and the fact that we propose discrete models for aggressive cancerous tumors. This field has been basically unexplored despite the fact that the chemotherapy treatments are given in a discrete way. Another advantage of the discrete models is that we can have accurate numerical simulations with low computational time. In this work, we recognize two modeling stages. In the first stage, we focus on modeling the growth dynamic of an aggressive cancerous tumor (Chapters 1 and 2), analyzing the evolution of a heterogeneous cancerous tumor with high growth rates and the effect of chemotherapy treatment, where the proposed models are systems of two difference equations. The second stage consists in modeling the evolution of an invasive aggressive cancerous tumor (Chapter 3). In this stage, we model the invasion of an heterogeneous tumor to the healthy tissue with an environmental acidification mechanism, as well as, the effect of chemotherapy application. These models are given in terms of systems of four difference equations.

Let us describe briefly the importance of the aspects considered in our models and also to provide some background of such characteristics. In the first stage, the most important aspects taken into account in the modeling are: the cellular heterogeneity, the high proliferation rates of the cancer cells and the chemotherapy application. We begin by discussing the characteristic of cellular heterogeneity. It is well known that aggressive cancerous tumors frequently have cell groups which are different morphologically (different phenotype) that are growing and coexisting within the tumor [2, 9, 15, 32]. In this sense, different authors have oriented their research work, in which it is considered two subpopulations of cancer cells that compete for the oxygen and nutritional resources, for example Michelson in [33]. The consideration of the competition between different types of cancer cells is relevant due to the fact that it could alter cancer composition as shown in the ex-

perimental study [29]. However, cancer heterogeneity may arise due to anticancer therapy application.

Other aspect that we discuss is chemotherapy since it is one of the anticancer treatments most commonly used. Actually, it could be indicated in combination with other anticancer treatments such as radiation or surgery. Chemotherapy usually is administered well before surgery to reduce the tumor size and to eliminate possible metastases in the organism, in order to have a better prognosis. In our case, the chemotherapeutic treatment consists in the application of several cytotoxic drugs in order to cause the death of cancer cells. However, chemotherapy might cause that tumors become more aggressive since cancer cells may become resistant to some of chemotherapeutic drugs. Thus, it is important to include chemotherapy modeling in the cancer evolution with the aim of proposing better chemotherapy schedules to eradicate tumors that present drug resistance. Two types of resistance have been widely analyzed and modeled. The first one is caused by a chemotherapeutic drug which induces genetic changes in cancer cells and it is called induced or acquired resistance. In the second one, the genetic changes are part of the natural development of cancer cells and it is known as intrinsic or natural resistance. In order to avoid resistance, the drugs can be combined in different ways depending on their action mechanism and their toxicity. Pioneer works related with the induced and intrinsic resistance can be attributed to Goldie and Coldman (see [21, 10]). They analyzed how the chemotherapy efficacy is affected when spontaneous mutation is considered. They also developed a probabilistic model of cell mutations that cause drug resistance where such a probability depends on the drug doses. Birkhead in 1987 [7], modeled the development of drug resistance when chemotherapy is applied. They investigated the potential of hypothetical chemotherapy strategies in order to identify general principles for successful treatment. One of their conclusions was that an early detection and therapy application reduce the probability of the emerging resistance subpopulation. Gyori et al. in [23], analyzed a model for the emergence of drug resistant cancer cells in a growing neoplasm, but considering time-dependent mutation rates. They also studied the spontaneous mutation into the resistant cancer cell. Otherwise, in previous works multi-drug chemotherapy treatments with an instantaneous effect have been modeled. For example, Panetta in 1998 [36], modeled a heterogeneous cancerous tumor with induced drug resistance. He considered exponential growth rates but he did not consider the competition for the nutritional resources. In the first stage of this dissertation, we are interested in modeling the cellular heterogeneity that arises due to drug resistance, but considering proliferation rates more adequate to describe the rapid growth of the tumor.

On the other hand, chemotherapy treatments could cause a severe condition to the health of cancer patients. This is because most cytotoxic drugs act on the division process, also causing damage to normal cells. Therefore, an effective

chemotherapeutic treatment consists in the application of the right dose of drug(s) which kill as many tumor cells as possible and cause minimum damage to the organism. Regarding the determination of effective chemotherapy schedules, many authors use optimization techniques to minimize the tumor mass subject to the constraint that preserves a healthy cell mass minimum to avoid a severe condition of the patient (see [35, 28, 12, 13]). For instance, Murray in [35] studied the effects of drug resistance on the determination of treatment schedules of chemotherapy with two drugs to eradicate the tumor. He considered an exponential growth rate and drug effectiveness as linear functions. De Pillis et al. [12] presented a model to describe the growth dynamic of a cancer tumor that is interacting with normal cells and immune system cells. They used optimal control to determine chemotherapy schedules to eradicate the tumor and compared these schemes with pulsed chemotherapy schedules.

The second stage of this work consists in modeling the dynamic of an invasive aggressive cancerous tumor. In this stage, we include the characteristic of invasion in our model. Cancer invasion promotes the traveling of cancer cells through the blood vein towards other organs. These cancer cells create there small tumors which are called metastases. This medical condition generates the most cancer patient deaths. For this reason, cancer invasion is another fundamental characteristic that is worthy of consideration in our model. Moreover, invasive cancers presumably are heterogeneous because variations in the cell phenotype have been found in human tumors [2, 15]. Some current references in this topic are described as follows. Gatenby and Wilinsky in 1996 [18], modeled the cancer invasion to healthy tissue by a reaction-diffusion system on an acidic environment. Meanwhile, Bellomo [5] has modeled the interaction between cancer cells, healthy cells and immune system cells, by also using reaction-diffusion systems. Anderson and Chaplain [1] have also used diffusion models to model the cancer invasion. Anderson et al in 2006 [8] posed and studied a model in which they considered the growth dynamics and the spatial movement of the tumor by quimiotaxis and the interaction between cancer cells, healthy cells and the immune system cells. Nevertheless, these authors have not considered the heterogeneity of cancerous tumors in their models, neither the chemotherapy treatment.

The outline of this dissertation is as follows: In Chapter 1, we propose discrete mathematical models that describe an aggressive cancerous tumor characterized by the cell heterogeneity and high proliferation rates. These models correspond to an exact nonstandard finite difference scheme of a continuous model based on Michelson [33]. However, we consider more suitable intrinsic growth rates to model the rapid tumor growth but at this stage we do not include the cellular competition for the nutritional resources. The models include the simultaneous application of a chemotherapy treatment with instantaneous effect. The treatment considered con-

sists of the application of two cytotoxic drugs. A first drug is applied to eliminate the majority of tumor cells with the possibility of causing induced resistance and a second drug to eliminate resistant cells. Here, we consider dose-effect functions that include the toxicity for the second drug. Afterwards, treatment schemes of two different drugs are analyzed in order to identify a suitable one to eradicate or to control the tumor.

In Chapter 2, we retake the continuous mathematical model that describes the growth dynamic of an aggressive cancerous tumor proposed in the previous chapter. Now we focus on the cellular competition by the oxygen and other nutritional resources. Since an exact discretization of the continuous model does not exist, a nonstandard finite difference scheme dynamically consistent with the continuous model is proposed. After that, we model the application of a chemotherapy treatment with instantaneous and gradual effects over the discrete model. Our central goal is to determine the relevance of the inclusion of the competition of both types of cancer cells for the nutritional resources. An effective treatment index that depends on the toxicity of the cytotoxic drugs is introduced in order to analyze the evolution of the tumor and to compare different treatments.

In Chapter 3, we propose discrete mathematical models of an invasive aggressive cancerous tumor that is characterized by cell heterogeneity, high proliferation rates and by the potential invasion of cancer cells into surrounding healthy tissue. The fact of considering the invasion characteristic leads us to propose a reaction-diffusion system to describe the evolution of a heterogeneous tumor that is interacting with normal cells on an acidified medium. Then, we develop a nonstandard finite difference scheme to obtain a discrete model dynamically consistent with the continuous one. Afterwards a chemotherapy treatment with a gradual effect is added to our model. We also analyze the effects of including important aspects such as different types of resistance and drug toxicity which facilitate the cancer invasion and hence complicate its eradication when chemotherapy is applied. Our goal in this chapter is to analyze how the chemotherapy schedule is modified when the mutation rate of intrinsic resistance is varying. We make comparisons among different chemotherapy schemes to identify effective schemes to eradicate or to reduce the aggressive cancerous tumor.

Chapter 1

An aggressive heterogeneous cancer with chemotherapy [1]

1.1 Introduction

Cancer involves disordered growth of abnormal cells in a certain tissue with a complex process involving biological and chemical interactions. According to the NCI an aggressive cancer is characterized by its acute dissimilarity from the original tissue in its structure, its sensitivity to cell mutation and high growth rates. Early diagnosis and treatment of aggressive tumors is fundamental to decrease the chance of spreading, after which their eradication is difficult. The most common anticancer treatment is chemotherapy which uses cytotoxic drugs to reduce tumor size or to stop its growth. Two main problems that limits the use of chemotherapy are drug toxicity and drug resistance. The first problem, drug toxicity, may result in a severe condition which can cause the death of cancer patients. The best chemotherapeutic treatment consists of the application of the right dose of drug(s) which will kill as many tumor cells as possible and will cause minimum damage to the organism. The second problem is drug resistance that cells may show towards the chemotherapeutic drugs that is a relevant factor to the success of chemotherapy treatments. There are two types of drug resistance: acquired (or induced) and intrinsic. The first one is caused by a drug which induces genetic changes in the cells and, in the second one, the genetic changes are part of the natural development of cells. In order to avoid resistance, the drugs can be combined in different ways depending on their action mechanism and their toxicity.

[1] This chapter is based on F. Solis, S. Delgadillo, Discrete mathematical models of an aggressive heterogeneous tumor growth with chemotherapy treatment, Mathematical and Computer Modeling 50 (2009) 646-652.

Mathematical cancer models have been developed taking into account the heterogeneity that results from drug resistance. Nevertheless, many controversies have appeared regarding cell resistance modeling since their introduction. Pioneer works can be attributed to Coldman and Goldie [10]. They suggest that spontaneous mutations during tumor evolution are responsible for the presence of intrinsically resistant cells before the exposure of a tumor to cytotoxic drugs. The role of drugs is to function as selective agents, killing off sensitive cells in the population, and leaving behind a residual of drug-resistant cells. This suggestion is the one that we will consider in this work. On the other hand, there has been a lot of interest and research in discrete models about heterogeneous tumors treated with chemotherapy, for example [37, 36, 27, 16]. There are several reasons for this interest, mainly because the systems from these models are very manageable, clinical data is discretely collected and periodicity is easy to establish.

In this chapter, we propose discrete models that describe the growth dynamic of an aggressive cancerous tumor treated with chemotherapy. We consider that an aggressive cancerous tumor is characterized by their high proliferation rates and their ability to mutate when the chemotherapy is applied. That means, the aggressive cancerous tumor become a heterogeneous tumor when it is treated with chemotherapy. The models include the application of a chemotherapy treatment with instantaneous effect which leads us to obtain an exact discretization of the cancer growth model. The chemotherapy consists of two cytotoxic drugs denoted by A and B, the first drug is applied to eliminate the majority of tumor cells with the possibility of causing induced resistance and a second drug to eliminate the cells that become resistant to the first one. The models are studied analytically and numerically considering different effectiveness functions which depend on dose and toxicity. Finally, different combinations of drugs are analyzed in order to identify effective schemes to control or to eradicate the tumor.

1.2 Model formulation

A basic model that describes the growth dynamic of a heterogeneous tumor modeled using the classic Lotka-Volterra systems was given by Michelson (see [33]). The following model describes the evolution of a cancerous tumor that becomes a heterogeneous tumor that is the result of drug resistance:

$$\begin{aligned} \frac{dT_1(t)}{dt} &= T_1(t)([g_1(T_1(t)) - d_1] - \beta_1 T_2(t)), \\ \frac{dT_2(t)}{dt} &= T_2(t)([g_2(T_2(t)) - d_2] - \beta_2 T_1(t)) + b_1 d_1 T_1(t), \end{aligned} \tag{1.1}$$

where $T_1(t)$ represents the density of sensitive cancer cells to drug A, $T_2(t)$ represents the density of cancer cells resistant to drug A and sensitive to the drug B, both at time t. $g_1(T_1)$ and $g_2(T_2)$ are the intrinsic proliferation rates of the sensitive and resistant cancer cells at time t, respectively. β_1, β_2 are the death rates caused by the competition between the cells for oxygen and nutrients. d_1, d_2 are the death rates of the cancer cells due the cycle of drug A and B, respectively. b_1 is the coefficient of induction to the resistance and $b_1 d_1 T_1$ represents the amount of sensitive cancer cells that become resistant to drug A. We consider an aggressive growth of the tumor, which is modeled by a proliferation rate of the form $g_1(T_1) = r_1 T_1^{m_1}$ and $g_2(T_2) = r_2 T_2^{m_2}$, where $m_1, m_2 \geq 0$ are integer numbers.

In general, the application of the chemotherapy cycles in patients with cancer takes place discretely. For this reason, it is more convenient to model the chemotherapy treatment in a discrete way. So, this is achieved by considering that the effect of the cytotoxic drugs is instantaneous as in Panetta [36]. Therefore, we have a continuous-discrete model to describe the evolution of cancer treated with chemotherapy. The continuous model that describes the tumor growth arises when we take $d_1 = d_2 = 0$ in the system (1.1), that is,

$$\begin{aligned} \frac{dT_1(t)}{dt} &= T_1(t)(g_1(T_1(t)) - \beta_1 T_2(t)), \\ \frac{dT_2(t)}{dt} &= T_2(t)(g_2(T_2(t)) - \beta_2 T_1(t)). \end{aligned} \tag{1.2}$$

Now, the following discrete system describes the non-linear instantaneous chemical reaction of drugs A and B after the n chemotherapy cycle,

$$\begin{aligned} T_{1_{nT}}^{+} &= h_1(d) T_{1_{nT}}^{-} - h_4(d)(T_{1_{nT}}^{-})^2, \\ T_{2_{nT}}^{+} &= h_2(d) T_{2_{nT}}^{-} - h_5(d)(T_{2_{nT}}^{-})^2 + h_3(d) T_{1_{nT}}^{-}. \end{aligned} \tag{1.3}$$

In this system, $T_{1_{nT}}^{-}, T_{2_{nT}}^{-}$ and $T_{1_{nT}}^{+}, T_{2_{nT}}^{+}$ are the cell densities just before and after the n-cycle of chemotherapy, respectively. $h_j(d)$, $j = 1, 2, 3, 4, 5$, are functions of the dose d. $h_1(d)$ represents the proportion of the density of survival cancer cells for drug A that remains sensitive to this drug. $h_2(d)$ represents the proportion of the density of resistant cancer cells that survive drug B dose and are still sensitive to this drug. $h_3(d)$ represents the density of sensitive cells that become resistant to drug A and survive the n-th application of drug A and B. $h_4(d)$ and $h_5(d)$ represent the specific reaction of the organism that could enhance drug effects.

It is possible to construct a discrete system that describes the tumor evolution using the continuous system (1.2) and the discrete one (1.3). In order to model the effect of a chemotherapy cycle each period of time T, it is necessary to determine the density of the heterogeneous tumor at times nT, $n = 1, 2, ...$ In other words, it

is imperative to discretize the continuous system (1.2). For the sake of simplicity, we assume that $\beta_1 = \beta_2 = 0$, that means, the competition between cancer cells is not considered. Then we get,

$$\begin{aligned} T_{1(n+1)T} &= \frac{T_{1nT}}{\sqrt[m_1]{1 - m_1 r_1 T (T_{1nT})^{m_1}}}, \\ T_{2(n+1)T} &= \frac{T_{2nT}}{\sqrt[m_2]{1 - m_2 r_2 T (T_{2nT})^{m_2}}}, \end{aligned} \tag{1.4}$$

with $T_{inT} = T_i(nT)$, $T_{i(n+1)T} = T_i((n+1)T)$, $i = 1, 2$. The discrete system (1.4) is an exact nonstandard finite differential scheme because it emerges from the analytical solution of the system (1.2) with $\beta_1 = \beta_2 = 0$, which is decoupled. The positivity is provided when $T_{inT} \leq T_{iM}$ where $T_{iM} = \sqrt[m_i]{\frac{1}{m_i r_i T}}$ is the limit of the densities of sensitive or resistant cancer cells for which it is not possible to eradicate the tumor for $i = 1, 2$.

Using (1.3) we obtain the discrete system which describes the growth of the tumor after the n-th chemotherapy dose cycle:

$$\begin{aligned} T_{1n+1} &= \frac{h_1(d) T_{1n} - h_4(d) T_{1n}^2}{\sqrt[m_1]{1 - m_1 r_1 T (h_1(d) T_{1n} - h_4(d) T_{1n}^2)^{m_1}}}, \\ T_{2n+1} &= \frac{h_2(d) T_{2n} - h_5(d) T_{2n}^2 + h_3(d) T_{1n}}{\sqrt[m_2]{1 - m_2 r_2 T (h_2(d) T_{2n} - h_5(d) T_{2n}^2 + h_3(d) T_{1n})^{m_2}}}. \end{aligned} \tag{1.5}$$

Let us remark that the eradication of the tumor given by the point $(0, 0)$ is a stable fixed point of the discrete system whenever $|h_1(d)| < 1$ and $|h_2(d)| < 1$, that is the proportion of cancer cells killed by drugs is less than one. This means that under these conditions the tumor can be eradicated for small densities of sensitive and resistant cancer cells.

1.3 Numerical simulations

In this section, we analyze the numerical solution of the discrete system to understand the effect of drugs on the tumor and the role that the coefficients of drug resistance play. We use a graphical approach to show the changes in the percentage of the reduction of the tumor and also bifurcation diagrams to show the asymptotic behavior of the system as drug effectiveness or induced resistance rate vary. In each graph, the horizontal axis represents drug effectiveness (the proportion of cancer cell density that survive the chemotherapy cycle) or the induced resistance rate, and the vertical axis represents the number of chemotherapy cycles. Each

color in the graphs represents the minimum percentage of the initial tumor density that is eradicated. The relationship of the color and its corresponding percentage range is as follows: blue (R_0) 0% - 50%, purple (R_1) 50% - 90%, green (R_2) 90% - 95%, red (R_3) 95% - 99%, pink (R_4) 99% - 99.99% and yellow (R_5) more than 99.99%. Absence of color means that the treatment is no longer pertinent. We analyze the dynamic of the system considering $h_4(d) = h_1(d)$ and $h_5(d) = h_2(d)$. Following the notation from [36], $h_1(d) = f_A(d)(1 - r(d))$, $h_2(d) = f_B(d)$ and $h_3(d) = f_B^{1-w}(d)f_A^w(d)r(d)$, $w \in (0, 1)$, where $f_A(d)$ and $f_B(d)$ are the proportion of the densities of survival sensitive cancer cells and resistant cancer cells to drug A, respectively. Let us note these functions represent the complement of the effectiveness of drugs A and B. $r(d)$ is the proportion of the density of sensitive cancer cells that become drug A resistant. We consider that $d \in (0, 1)$ is a standardized dose, in such a way $d = 1$ is the maximum dose of chemotherapy. First, we assume that the complement of the effectiveness of drugs are constant such as $f_A(d) = 0.05$, $f_B(d) = 0.8$ and the induced resistance coefficient $r(d) = 0.15$. As clinical treatments should not be too long, we compute the numerical solutions of the discrete system for 24 months where the period of each cycle is one month. We assume that the tumor is eradicated by the chemotherapy treatment when $T_{1n} + T_{2n} < 10^{-4}({T_1}^0 + {T_2}^0)$, and when the nadir is less than 24. The nadir is defined as the number of drug cycles that can be administered before the tumor starts to grow again. This value is obtained numerically and depends on initial conditions and the parameter values. Finally, we consider different initial conditions of the form $({T_1}^0, 0)$ and values of $m_i \in \{0, 1\}$ for $i = 1, 2$. These correspond to a constant and a linear intrinsic rate as a first approximation to modeling cancer with high proliferation rates.

1.3.1 Varying the drug effectiveness and the drug resistance rate

Now, we focus on how the heterogeneous tumor evolution is affected when the effectiveness of drugs and induced resistance rate are varied. Our goal is to determine the range for effectiveness of drugs and for induced resistance rate in such a way there is an effective chemotherapy treatment. First, we vary the proportion of density of sensitive cancer cells that survive after the A drug application, $f_A(d)$, from zero to one, keeping constant the rest of the parameters, $f_B(d) = 0.8$ and $r(d) = 0.15$. Under these considerations it is not possible to eradicate the tumor, even so, when $f_A(d)$ takes values close to 0, that means, drug A has a high effectiveness. In this case, it is only possible to reduce the tumor density for some values of the drug effectiveness. This fact is due to the solution is converging slowly to the attractor, the origin. So the tumor reduction is more significant after 12 applications of drugs. See Figure 1.1.

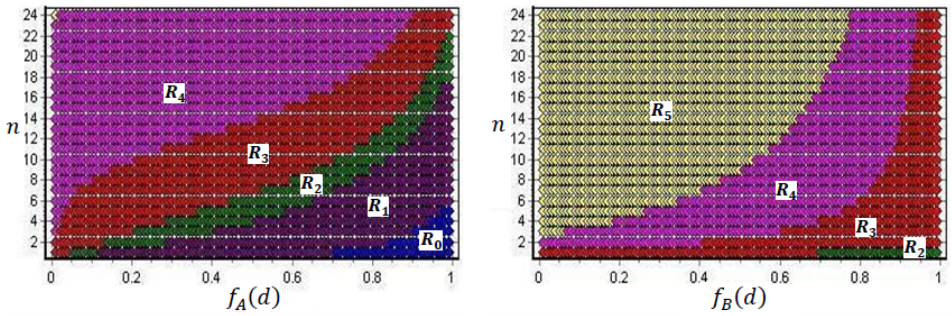

Figure 1.1: Reduction percentage of tumor when $f_A(d)$ and $f_B(d)$ are varied.

Now, we vary the proportion of the density of resistant cells that survive the chemotherapy cycle, $f_B(d)$ from zero to one, keeping constant the rest of the parameters. Also in this case, the sanity level $(0, 0)$ is an attractor for every value of the drug effectiveness which are less than 1, $0 < f_i(d) < 1, i = A, B$. However, we can observe that when $f_A(d)$ varies, it is not possible to eradicate the tumor and the reduction percentage depends on the number of the chemotherapy applications. Nevertheless, it is possible to eradicate the tumor when the drug B effectiveness is greater than 25%, $f_B(d) < 0.75$, $f_A(d) = 0.05$ and $r(d) = 0.15$. That means, when drug B has a high effectiveness it is possible to eradicate the tumor with a relatively short therapy. The required number of chemotherapy applications depend on the drug B effectiveness. As the drug B effectiveness is higher, the number of chemotherapy application decreases, see Figure 1.1. Otherwise, when we vary the induced resistance coefficient to drug B, $r(d)$, similar results as varying $f_A(d)$ are obtained. Therefore, it is important to have a drug B with high effectiveness to achieve the eradication of the cancerous tumor.

1.3.2 Dose-effect function for drug B including toxicity

The application of a cytotoxic drug can cause severe damage to the organism and this is another problem that limits the use of chemotherapy. Therefore, now we address the inclusion of toxicity in the dose functions $h_2(d)$ because of the importace of drug B to eradicate tumors that present drug resistance. Here we study the behavior of the tumor by considering different functions $h_2(d)$, fixing $h_1(d)$ and $h_3(d)$. The goal is to determine the optimal value of the dose as a function of these variables. To show how this is possible, first let us note the physiological meaning of $h_1(d)$ and $h_2(d)$. If $h_1(d)$ or $h_2(d)$ are zero for a fixed dose, then all cancer cells die due to the application of drug A or B, respectively. If $h_1(d)$ or $h_2(d)$ are equal

to one, then all cancer cells survive, meaning that drugs are no longer effective. On the other hand, if $h_1(d) > 1$ or $h_2(d) > 1$, then the application of drugs helps the proliferation of the cells and if $h_1(d) < 0$ or $h_2(d) < 0$ then the treatment eradicates the tumor killing some normal cells. In this way, the toxicity level is included in the dose functions having less effect on the tumor according to the drug toxicity. This criterion is used to define different functions for $h_2(d)$ that describe the proportion of survival resistant cells after a chemotherapy cycle, since this function is of paramount importance in order to eradicate the tumor. So, we propose that $h_2(d)$ could be a linear, quadratic or cubic function due to any function could be approximated by polynomials. These functions were chosen trying to keep the biological meaning. Besides, we assume that drug A is a drug with low toxicity profile and its effectiveness is bigger for stronger doses, then $h_1(d)$ is set as a linear function with a negative slope. Also, we will assume that the proportion of the density of sensitive cells that become resistant is also proportional to the drug dose, but in this case $h_3(d)$ is an increasing linear function.

Linear Function $h_2(d)$

The simplest form of the complement of the effectiveness of drug B is considering it as a linear function, namely, $h_2(d) = a_1 d + a_0$, with $a_1 < 0$ and $a_0 = 1$. The bifurcation diagrams for the discrete systems (1.5) are simple, since the origin is an attracting fixed point whenever $h_1(d) < 1$ and $h_2(d) < 1$, otherwise it becomes a repulsing fixed point. If $a_1 < -1$ that means that the drug toxicity is really high then the bifurcation point appears and it is lower as the slope is steeper. Moreover, the nadir decreases for values of doses close to the maximum dose allowed, which is 0.45. Then, it is possible to reduce the tumor for doses less than 0.45 and to eradicate it using a maximum dose of $d = 0.44$.

Quadratic Function $h_2(d)$

We set $h_2(d) = b_2 d(d - b_1) + b_0$ so that it is a quadratic function, with $b_2 > 0$, $b_1 = b_0 = 1$. The parameter b_2 indicates the maximum effectiveness of drug B. We consider that drug B is a little less effective for higher doses due to toxicity. The origin is an attracting fixed point for $h_2(d) < 1$. We have two cases: for $b_2 < 4$, $h_2(d)$ takes values in $[0, 1]$ and for small values of h_2 it would be possible to eradicate the tumor with less cycles. For $b_2 > 4$, the nadir becomes smaller and the asymptotic behavior does not change except when $|h_2(d)| > 1$ and here we obtain Jeff's phenomenon [12], which is a clinically observed temporal oscillation in tumor size, see Figure 1.2.

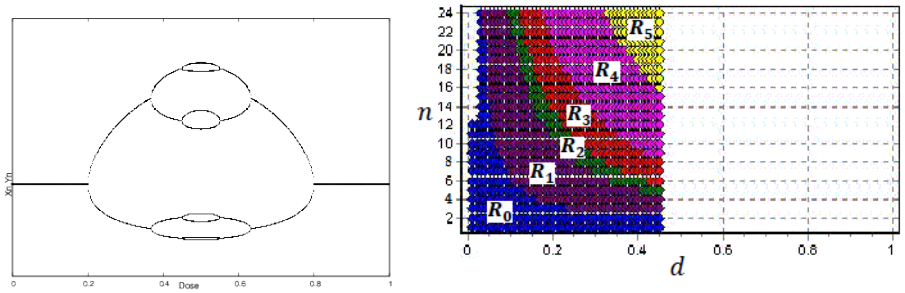

Figure 1.2: Bifurcation diagram and the reduction percentage of tumor.

Cubic Function $h_2(d)$

Now we study the case $h_2(d) = c_3d^3 + c_2d^2 + c_1d + c_0$ with $c_3 < 0$, $c_2 > 0$, $c_1 < 0$ and $c_0 = 1$, to guarantee that $h_2(0) = 1$; with the same dose functions $h_1(d)$ and $h_3(d)$ as before. The origin $(0, 0)$ is a stable equilibrium when $h_2(d) \neq 1$. If $c_3 < 0$ then we have two scenarios, one with $c_3 < -11$, and the other with $c_3 > -11$. In the first scenario, $h_2(d)$ takes the value 1 for three different values of the dose. And these values decrease as c_3 decreases. For the second scenario, the value of d for which $h_2(d) = 1$ is smaller and the nadir decreases, also the tumor density is reduced slower. The treatment does not eradicate the tumor, however the most effective treatment is achieved close to $d = 0.2$.

1.4 Chemotherapy combinations

In this section, we analyze different treatments in order to determine the best one to reduce or to eradicate the cancerous tumor. We consider a treatment as a combination of applications of two drugs A and B, starting with drug A. The discrete system that describes the behavior of the tumor treated with chemotherapy considering $h_1(d) = f_A(d)(1 - r(d))$, $h_2(d) = f_B(d)$ and $h_3(d) = f_B^{1-w}(d)f_A^w(d)r(d)$ is

$$\begin{aligned} T_{1n+1} &= \frac{f_A(d)(1-r(d))T_{1n}(1-T_{1n})}{\sqrt[m_1]{1-m_1r_1T[f_A(d)(1-r(d))T_{1n}(1-T_{1n})]^{m_1}}}, \\ T_{2n+1} &= \frac{f_B(d)T_{2n}(1-T_{2n}) + {f_B}^{1-w}(d)f_A^w(d)r(d)T_{1n}}{\sqrt[m_2]{1-m_2r_2T[f_B(d)T_{2n}(1-T_{2n}) + {f_B}^{1-w}(d)f_A^w(d)r(d)T_{1n}]^{m_2}}}, \end{aligned} \tag{1.6}$$

or in a more compact form $T_{1n+1} = \tilde{g}_1(T_{1n}) \quad T_{2n+1} = \tilde{g}_2(T_{1n}, T_{2n})$. Here the chemotherapy cycle consist in the application of both drugs simultaneously in each period of time. One way to obtain different treatments is by not applying both drugs simultaneously. When drug A is applied we have that $f_B(d) = 1$ and $w = 1$ since all resistant cancer cells survive, in this case the system becomes $T_{1n+1} = \tilde{g}_{1A}(T_{1n}) = \tilde{g}_1(T_{1n})$ and $T_{2n+1} = \tilde{g}_{2A}(T_{1n}, T_{2n})$, where

$$\tilde{g}_{2A}(T_{1n}, T_{2n}) = \frac{T_{2n}(1 - T_{2n}) + f_A(d)r(d)T_{1n}}{\sqrt[m_2]{1 - m_2 r_2 T[T_{2n}(1 - T_{2n}) + f_A(d)r(d)T_{1n}]^{m_2}}}.$$

When we apply drug B we have that $f_A(d) = 1$, $r(d) = 0$ and $w = 0$, meaning that all sensitive cancer cells survive and the system becomes $T_{1n+1} = \tilde{g}_{1B}(T_{1n})$ and $T_{2n+1} = \tilde{g}_{2B}(T_{1n}, T_{2n})$, where

$$\tilde{g}_{1B}(T_{1n}) = \frac{T_{1n}(1 - T_{1n})}{\sqrt[m_1]{1 - m_1 r_1 T[T_{1n}(1 - T_{1n})]^{m_1}}} \quad \text{and}$$

$$\tilde{g}_{2B}(T_{1n}, T_{2n}) = \frac{T_{2n}(1 - T_{2n}) + f_A(d)r(d)T_{1n}}{\sqrt[m_2]{1 - m_2 r_2 T[T_{2n}(1 - T_{2n}) + f_A(d)r(d)T_{1n}]^{m_2}}}.$$

Now we focus on comparing the systems obtained from different treatments which must have the same periodicity. The treatment period is defined as the time necessary to apply a complete combination of drugs. It is of paramount importance to determine the drug effectiveness that has better results in the eradication of the tumor for each treatment. So we vary one of the drug effectiveness functions in the interval $[0, 1]$ while keeping the rest of the parameters constant in order to compare the different treatments.

1.4.1 Two period combinations

We consider the following three combinations with $2T$ period: $(AB)^2$ in which both drugs are applied simultaneously each period $2T$, A^1B^1 where drugs are applied separately each period T and A^1A^1 in which only drug A is applied each period T. Here, the exponent means the periods of time elapsed before applying a drug.

Combination $(AB)^2$

The system that describes this treatment is obtained from the original system by considering the period as the double of the period T of the original system(1.6). In this combination, both drugs A and B are applied simultaneously, we allow two

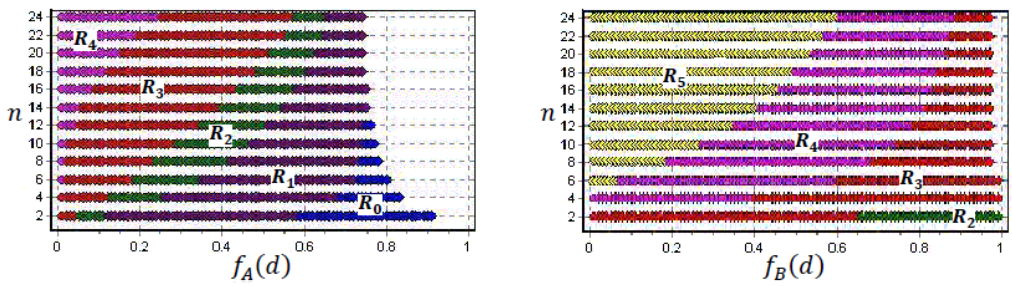

Figure 1.3: Tumor size when $f_A(d)$ and $f_B(d)$ are varied para $(AB)^2$.

periods of time without chemotherapy and then we apply both drugs A and B again. The discrete model for this combination is,

$$T_{1(n+2)} = \tilde{g}_1(T_{1n}) \qquad T_{2(n+2)} = \tilde{g}_2(T_{1n}, T_{2n}). \tag{1.7}$$

In this case, it is not possible to eradicate the tumor, only a reduction is possible whenever the effectiveness of drug A is greater than 9%. When the effectiveness is greater than 9%, the maximum percentage that the tumor can be reduced is 50%. If drug A has a high effectiveness ($\geq 75\%$) then the tumor density can be reduced between 99% and 99.99%. Varying the effectiveness of drug B fixing $f_A(d) = 0.05$, we find that it is possible to eradicate the tumor whenever the drug effectiveness is bigger than 40%. Moreover, it is always possible to reduce the tumor and when the drug effectiveness is low, then a 95% reduction can be achieved for some initial conditions. This is shown in Figure 1.3. Varying $r(d)$ it is not possible to eradicate the tumor but we can reduce it. If $r(d)$ is close to one, the tumor can be reduced up to 90% with the maximum number of cycles allowed.

Combination A^1B^1

In this case, we first apply drug A and after a period of time T, we apply drug B. The discrete system that models this case is

$$T_{1(n+2)} = \tilde{g}_{1B}(\tilde{g}_{1A}(T_{1n})) \qquad T_{2(n+2)} = \tilde{g}_{2B}(\tilde{g}_{1A}(T_{1n}), \tilde{g}_{2A}(T_{1n}, T_{2n})). \tag{1.8}$$

In this case the nadir is always equal to zero, and for this reason this treatment is never recommended. Let us recall that the nadir value depends on the initial conditions and the parameter values.

Table 1.1: Two period chemotherapy combinations

Combinations	**Varying drug A effectiveness**	**Varying drug B effectiveness**
$(AB)^2$	*reduction*$(99\% - 99.99\%)$ with $f_A(d) \leq 0.25$	*eradication* with $f_B(d) \leq 0.60$
A^1A^1	*reduction* $(99\% - 99.99\%)$ with $f_A(d) \leq 0.10$	-

Combination A^1A^1

First, we apply drug A and after a period of time T, we apply it again. Note that the resistant cells survive because drug B is not being applied. The discrete system becomes

$$T_{1(n+2)} = \tilde{g}_{1A}(\tilde{g}_{1A}(T_{1n})) \qquad T_{2(n+2)} = \tilde{g}_{2A}(\tilde{g}_{1A}(T_{1n}), \tilde{g}_{2A}(T_{1n}, T_{2n}). \tag{1.9}$$

The fixed point $(0, 0)$ of the system is not a local attractor which means that it is not possible to eradicate the tumor, the only possibility is to reduce the size of the density of the sensitive cancer cells by applying drug A an equal number of times as the nadir. When the effectiveness of drug A is higher than 90%, the reduction percentage of the tumor varies from 99% to 99.99%. This reduction percentage decreases as the drug effectiveness is lower. The minimum reduction percentage of the tumor that can occur is 50%. The same result that in the combination $(AB)^1$ is obtained when the induced resistance coefficient to drug A is varied.

Comparing the numerical results of each chemotherapy combinations, we can conclude that the best chemotherapy combination is $(AB)^2$ because the required minimum drug effectiveness for drugs A and B, to reduce or to eradicate the tumor are the lowest. In Table 1.1, we summarize the main results of the numerical simulations that correspond to the two period chemotherapy combinations.

1.4.2 Higher periodicity combinations

In this section we define and compare several treatments of 3T and 4T periods. The three period combinations considered are the following: $(AB)^3$, $A^1B^1A^1$, $A^1B^1B^1$, $A^1A^1B^1$. We do not include the description of these models because all of them are derived in a similar way to the $2T$ period models.

Using combination $(AB)^3$ and varying $f_A(d)$, $f_B(d)$ and $r(d)$ from zero to one, we find that it is not possible to eradicate the tumor, only reduce its density. If the

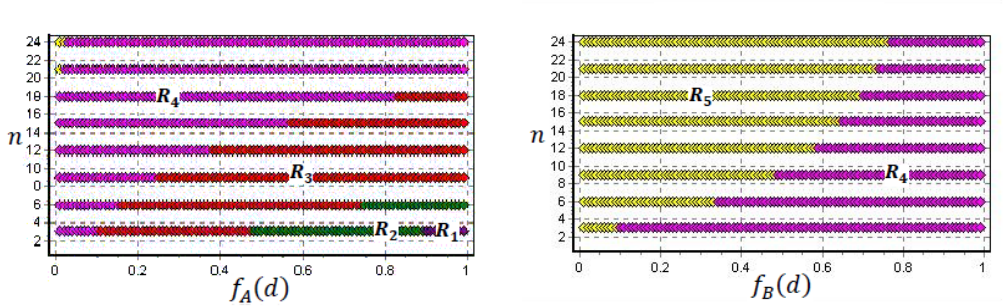

Figure 1.4: Tumor size percentage when $f_A(d)$ and $f_B(d)$ are varied for combination $A^1A^1B^1$

effectiveness of drug A is higher than 28%, then we can reduce the tumor density to half its size. But if the effectiveness of drug B is higher than 45% then we can eradicate the tumor. Conversely, the reduction percentage of the tumor varies from 95% to 99.99%.

The combination $A^1B^1A^1$ can be used to reduce the tumor from 99% to 99.99% when the effectiveness of drug A is higher than 60%. Otherwise, the reduction percentage of the tumor can only be from 95% to 99%. This combination can eradicate the tumor when the effectiveness of drug B is higher 42%. The combination $A^1B^1B^1$ is not recommended since the nadir is equal to zero. For the combination $A^1A^1B^1$, we obtain a discrete system with a unique fixed point given by the sanity level. In order to eradicate the tumor the effectiveness of drug A needs to be higher than 98%, which is very unrealistic. However, for lower effectiveness of drug A, the reduction percentage varies from 99% to 99.99%. When we vary the effectiveness of drug B and it is higher than 25%, it is possible the eradication of the tumor, see Figure 1.4.

Another relevant factor to study is the induced resistance rate which can be varied for each combination. In these cases, it is not possible to eradicate the tumor, only reduce it. The minimum reduction percentage of the tumor is 50% with exception of the combination $A^1B^1B^1$ which is not recommendable to apply. This reduction percentage increases for smaller induced resistance rates. Moreover, we can observe a better prospect for the combination $A^1A^1B^1$. This is reasonable because the effectiveness of drug A is high (95%). Thus, it is better apply drug A two times consecutively in order to reduce as be possible and then apply drug B to reduce the resistant cells density. According with the results showed in Table 1.2, we can conclude that the best $3T$ chemotherapy combination is $A^1A^1B^1$ followed by $A^1B^1A^1$.

Table 1.2: Three period chemotherapy combinations

Combinations	**Varying drug A effectiveness**	**Varying drug B effectiveness**
$(AB)^3$	*reduction* $(0\% - 50\%)$ with $f_A(d) \leq 0.72$	*eradication* with $f_B(d) \leq 0.45$
$A^1B^1A^1$	*reduction* $(99\% - 99.99\%)$ with $f_A(d) \leq 0.35$	*eradication* with $f_B(d) \leq 0.58$
$A^1A^1B^1$	*eradication* with $f_A(d) \leq 0.02$	*eradication* with $f_B(d) \leq 0.75$

The four period combinations analyzed were $A^1B^1B^1A^1$ and $A^1B^1A^1B^1$. Basically, there is no difference between these two combinations since both reduce the tumor. However, if the effectiveness of drug B is higher than 95%, then it is better to apply the second combination since the tumor can be eradicated with only four cycles.

1.5 Conclusions

In this Chapter, discrete mathematical models have been proposed to describe the growth dynamic of an aggressive cancerous tumor treated with chemotherapy. In order to develop this model was necessary to obtain an exact nonstandard finite difference scheme, which provided us a simple way to estimate tumor growth each period of time T with zero discretization error. We modeled a chemotherapy treatment of two drugs with instantaneous effect in this discrete model. We focus mainly on analyzing the heterogeneity of the tumor that arises due to drug resistance. These models have been useful to understand tumor evolution under different two drug chemotherapy combinations that we hope they provide tools and benchmarks for clinicians. So far we can conclude that the most important factors to eradicate an aggressive tumor are the effect of the non-cross resistant drug and the effectiveness of such drugs, mainly the drug B. Moreover, when the effectiveness of such drugs is higher, a smaller number of chemotherapy cycles is needed. We also can conclude that it is possible to model in an implicit way the toxicity of drug B in the effectiveness function and the maximum dose could be determined using the numerical simulations. On the other hand, in order to identify better treatments to eradicate or to reduce the tumor, we established and analyzed different two drugs chemotherapy combinations with the same periodicity. We found that the best $2T$

combination was $(AB)^2$ and the best $3T$ combination was $A^1A^1B^1$. By comparing the results of treatments $(AB)^1$, $(AB)^2$ and $(AB)^3$, we can conclude that treatments with shorter period between applications are more effectives. The disadvantages of these new models are basically based on the assumptions made by ignoring the effect of competition among tumor cells and by assuming an instantaneous effect of chemotherapy.

Chapter 2

Discrete modeling of aggressive tumor growth with gradual effect of chemotherapy [1]

2.1 Introduction

Discrete models have been useful to understand tumor growth and treatments from different perspectives. The main treatment considered is chemotherapy, which consists of the application of several cytotoxic drugs. A first set of drugs is applied to eliminate the majority of tumor cells with the possibility of causing induced resistance and a second group of drugs to eliminate resistant cells. Among these models are those developed in [27, 36, 37] which assume that chemotherapy has an instantaneous effect. In the previous chapter, we presented new features by considering an aggressive cancerous tumor and different drug effectiveness functions which depend on dose and toxicity. Moreover, different combinations of two drugs were considered in order to identify a suitable one to eliminate the tumor. As we concluded in the previous chapter, two disadvantages of those models are that they did not model the cell competition and the assumption of an instantaneous effect of chemotherapy.

In this chapter, we take the model of an aggressive cancerous tumor that we proposed in the previous chapter. Now we consider the competition between the different types of cancer cells for the nutritional resources (competition coefficients β_1 and β_2 non zero). Let us recall that the general methodology that we use to obtain the discrete models consists of proposing a continuous model of cancer growth with the desired characteristics, to apply a Nonstandard Finite Difference

[1] This chapter is based on F. Solis, S. Delgadillo, Discrete modeling of aggressive tumor growth with gradual effect of chemotherapy, Mathematical and Computer Modeling 57 (2013) 1919-1926.

Scheme (NSFDS) to discretize the continuous model and to include the application of chemotherapy with instantaneous effect in the discrete models. Afterward, we enhance our model by incorporating the chemotherapy treatment that has a gradual and instantaneous effect, distributed along the period between chemotherapy applications. A treatment index is introduced in order to analyze the evolution of the tumor and to compare different treatments. The qualitative behavior of the discrete systems is analyzed by establishing different chemotherapy combinations in order to suggest a suitable schedule.

2.2 Discrete competitive model

In this section, we focus on establishing a discrete model of a heterogeneous aggressive tumor with two different types of cancer cells which are competing for nutrients, oxygen, etc. This model is developed by using the general methodology described formerly. Since proliferating cells consume much more oxygen, their consumption rate is much higher than that of normal cells, therefore, we consider competition among tumor cells. The tumor is treated with a chemotherapy treatment which consists of the simultaneous application of two drugs denoted by A and B. The growth dynamics of the tumor are modeled as in the previous chapter:

$$\begin{aligned}\frac{dT_1(t)}{dt} &= T_1(t)([g_1(T_1(t)) - d_1] - \beta_1 T_2(t)),\\ \frac{dT_2(t)}{dt} &= T_2(t)([g_2(T_2(t)) - d_2] - \beta_2 T_1(t)) + b_1 d_1 T_1(t),\end{aligned} \tag{2.1}$$

where $T_1(t)$ represents the density of sensitive cancer cells to drug A (type I), $T_2(t)$ represents the density of resistant cancer cells to drug A and sensitive to drug B (type II). Functions $g_1(T_1(t))$ and $g_2(T_2(t))$ are the intrinsic rates of growth of the sensitive and resistant cancer cells, respectively. Constants β_1 and β_2 are the coefficient rates caused by the competition between cancer cells for oxygen and nutrients. Constants d_1 and d_2 are the coefficient rates of affected cells by drugs A and B, respectively. $b_1 d_1$ is the coefficient rate of resistant cancer cells. Modeling the effect of chemotherapy in a continuous system is not suitable in our case since the application of chemotherapy is done discretely. Another reason to avoid continuous systems is because they can not always account correctly for diverse aspects (microscopic or genetic) of tumor growth. For these reasons and also to make the model more realistic we retain the discrete framework. However, in making this modification to the model, one of the consequences is that we obtain non autonomous discrete systems.

Consider model (2.1) without the application of chemotherapy

$$\begin{aligned}\frac{dT_1(t)}{dt} &= T_1(t)[g_1(T_1(t)) - \beta_1 T_2(t)],\\ \frac{dT_2(t)}{dt} &= T_2(t)[g_2(T_2(t)) - \beta_2 T_1(t)],\end{aligned} \tag{2.2}$$

where $g_1(T_1(t)) = r_1 T_1(t)$ and $g_2(T_2(t)) = r_2 T_2(t)$, since we are modeling an aggressive cancerous tumor with high proliferation rate. This rate corresponds to a higher rate than the constant rate commonly studied in the literature.

The only equilibrium point of the system (2.2) is the origin, provided that

$$r_1 r_2 \neq \beta_1 \beta_2. \tag{2.3}$$

Otherwise, there is an infinite number of equilibrium points that are given by $T_1 = \frac{\beta_1}{r_1} T_2$ and $T_2 \in \mathbb{R}$. From now on, we assume that condition (2.3) holds. The origin is an unstable equilibrium point, which is consistent with the fact that the tumor is aggressive. Thus, an anticancer therapy is indispensable in order to reduce the tumor density. The only solutions of the system (2.2) that are of biological interest are the positive ones, unfortunately such solutions are unbounded, which can be numerically observed in the portrait phase.

2.2.1 Discrete initial model

Unlike the previous chapter, it is not possible to obtain an exact discretization of the model (2.2). Thus, we propose the following discretization for (2.2)

$$\frac{dT_1}{dt}(nh) \cong \frac{T_{1n+1} - T_{1n}}{\phi(h)}, \quad \frac{dT_2}{dt}(nh) \cong \frac{T_{2n+1} - T_{2n}}{\phi(h)}, \tag{2.4}$$

${T_1}^2(nh) \cong T_{1n}T_{1n+1}$ and $T_1(nh)T_2(nh) \cong \alpha T_{1n}T_{2n+1} + (1-\alpha)T_{1n+1}T_{2n}$ in the first equation and ${T_2}^2(nh) \cong T_{2n}T_{2n+1}$ and $T_1(nh)T_2(nh) \cong (1-\alpha)T_{1n}T_{2n+1} + \alpha T_{1n+1}T_{2n}$ in the second equation, where $T_{1nh} = T_1(nh)$ and $T_{2nh} = T_2(nh)$, being h the time step. The nonlinear terms are approximated in this way for mathematical convenience in order to obtain the explicit scheme. Let us note that if we set $\alpha = 0$, we obtain a discretization proposed by Liu and Elaydi for a competition model [31]. If we set $\alpha = \frac{1}{2}$ the resulting discretization is one proposed by Kahan [38].

Substituting (2.4) in (2.2) and choosing $\phi(h) = h$, we obtain our initial discrete dynamical system without chemotherapy.

$$\begin{aligned}T_{1(n+1)h} &= \frac{1}{\Delta}[T_{1nh}(1 - r_2 h T_{2nh} + \beta_2 h(1-\alpha)T_{1nh}) - \beta_1 h\alpha T_{1nh}T_{2nh}],\\ T_{2(n+1)h} &= \frac{1}{\Delta}[-\beta_2 h\alpha T_{1nh}T_{2nh} + T_{2nh}(1 - r_1 h T_{1nh} + \beta_1 h(1-\alpha)T_{2nh})],\end{aligned} \tag{2.5}$$

where Δ is given by

$$(1-r_2hT_{2nh}+\beta_2h(1-\alpha)T_{1nh})(1+\beta_1h(1-\alpha)T_{2nh}-r_1hT_{1nh})-\beta_1\beta_2h^2\alpha^2T_{1nh}T_{2nh}.$$

According with Mickens [34], the discrete system is dynamically consistent if the system and/or their solutions have the same properties as the continuous system. The main properties are positivity, boundedness, monotony, equilibrium points and their stabilities, periodic solutions and limit cycles. In the next result, we show that the discretization used preserve dynamical properties (equilibrium points and their stabilities) that are important from the biological point of view.

Theorem 2.2.1 *If* $\frac{\beta_1K-r_1}{\phi(h)(r_1\beta_2(1-\alpha)+r_2\beta_1(1-\alpha)K^2-r_1r_2K-\beta_1\beta_2(1-2\alpha)K)} < 0$ *and* $r_1r_2 \neq \beta_1\beta_2$*, then the system (2.5) is dynamically consistent with system (2.2).*

Proof. To determine the consistency of both systems we find the equilibrium points of (2.5), which are $(0,0)$, $(0, \frac{-1}{\beta_1\phi(h)(1-\alpha)})$, $(\frac{-1}{\beta_2\phi(h)(1-\alpha)}, 0)$ and $({T_1}^*, K{T_1}^*)$ where ${T_1}^* = \frac{\beta_1K-r_1}{\phi(h)(r_1\beta_2(1-\alpha)+r_2\beta_1(1-\alpha)K^2-r_1r_2K-\beta_1\beta_2(1-2\alpha)K)}$ with $K = \frac{r_1+\beta_2}{r_2+\beta_1}$. The origin is the only one in the positive quadrant if and only if ${T_1}^* < 0$, that is, if $\frac{\beta_1K}{r_1} < 1$ then $r_1\beta_2(1-\alpha)+r_2\beta_1(1-\alpha)K^2 > r_1r_2K+\beta_1\beta_2(1-2\alpha)K$ or if $\frac{\beta_1K}{r_1} > 1$, then we must have that $r_1\beta_2(1-\alpha)+r_2\beta_1(1-\alpha)K^2 < r_1r_2K+\beta_1\beta_2(1-2\alpha)K$. Thus, assuming ${T_1}^* < 0$ and by standard techniques it can be shown that the origin is an unstable equilibrium point for the discrete system (2.5).

Remark If $\beta_1 = \beta_2 = 0$ in the discrete system (2.5), we recover the exact discretization of system 1.2 without competition studied in Chapter 1.

2.2.2 Chemotherapy

As we mentioned before, in our case, chemotherapy consists of the simultaneous application of two drugs A and B each interval of time T (we set $h = T$). We are assuming that a proportion of the density of cancer cells that survive the application of drug A become resistant. Therefore, the application of the second drug B is necessary in order to reduce the tumor density. We consider that the effect of drugs in each cycle is instantaneous as in the previous chapter. So the application of both drugs at time nT is modeled by

$$\begin{aligned} {T_1}_{nT}^{+} &= h_1(d){T_1}_{nT}^{-} - h_4(d)({T_1}_{nT}^{-})^2, \\ {T_2}_{nT}^{+} &= h_2(d){T_2}_{nT}^{-} - h_5(d)({T_2}_{nT}^{-})^2 + h_3(d){T_1}_{nT}^{-}, \end{aligned} \tag{2.6}$$

where ${T_1}_{nT}^{-}, {T_2}_{nT}^{-}$ and ${T_1}_{nT}^{+}, {T_2}_{nT}^{+}$ represent the densities of cancer cells just before and after the n-th application of a chemotherapy cycle, respectively. Functions

$h_j(d), j = 1, 2, 3, 4, 5$ are dose dependent. $h_1(d)$ represents the proportion of density of cancer cells that survive and remain sensitive to drug A. $h_2(d)$ represents the proportion of density of cancer cell that survive drug B. $h_3(d)$ represents the proportion of density of sensitive cancer cells that survive drugs A and B and become resistant to drug A. $h_4(d)$ and $h_5(d)$ represent the reaction of a specific organism that could enhance the drug effects.

After modeling the application of a chemotherapy cycle at time nT in the discrete system (2.5), we get the following system:

$$\begin{aligned} T_{1_{(n+1)T}} &= \frac{1}{\Delta}[T_{1_{nT}}^{+}(1 - r_2 T T_{2_{nT}}^{+} + \beta_2 T(1-\alpha)T_{1_{nT}}^{+}) - \beta_1 T\alpha T_{1_{nT}}^{+} T_{2_{nT}}^{+}], \\ T_{2_{(n+1)T}} &= \frac{1}{\Delta}[-\beta_2 T\alpha T_{1_{nT}}^{+} T_{2_{nT}}^{+} + T_{2_{nT}}^{+}(1 - r_1 T T_{1_{nT}}^{+} + \beta_1 T(1-\alpha)T_{2_{nT}}^{+})], \end{aligned} \tag{2.7}$$

where Δ is equal to

$$(1-r_2 T T_{2_{nT}}^{+}+\beta_2 T(1-\alpha)T_{1_{nT}}^{+})(1+\beta_1 T(1-\alpha)T_{2_{nT}}^{+}-r_1 T T_{1_{nT}}^{+})-\beta_1\beta_2 T^2\alpha^2 T_{1_{nT}}^{+} T_{2_{nT}}^{+}.$$

Let us note that taking $\beta_1 = \beta_2 = 0$ in this system, meaning that there is no competition, we obtain the model analyzed in the preceding chapter.

The dose functions $h_1(d)$, $h_2(d)$ and $h_3(d)$ are defined in terms of the complement of the effectiveness of drugs A and B and the induced resistance as in [36], namely $h_1(d) = f_A(d)(1 - r(d))$, $h_2(d) = f_B(d)$, $h_3(d) = f_A(d)^w f_B(d)^{1-w} r(d)$, $h_4(d) = \kappa h_1(d)$ and $h_5(d) = \kappa h_2(d)$, with $0 < \kappa \ll 1$. Here, $f_A(d)$ represents the proportion of type I cell density that survive one application of drug A, $f_B(d)$ represents the proportion of the density of type II cancer cells that survive and remain sensitive to drug B. Finally, $r(d)$ is the proportion of cells that survive and become resistant to drug A. Our next goal is to determine the relevance of competition among cells of type I and II.

2.2.3 Effect of cellular competitive interaction

Let us analyze the competition effect in system 2.7 by introducing a treatment index over a region of health. Such an index enables us to quantify the different treatments. Let us mention that we consider a health level as the maximum density of cancer cells or pre-cancerous cells present in a healthy organism.

Definition We define a health region, R_{sn}, as the set of ordered pairs (d, n) in $\mathbb{R}_+^2$ such that the total density of tumor cells is less than a given health level, denoted

by s. Here, d is the applied dose and n is the number of chemotherapy applications which are applied every period of time T. Thus,

$$R_{sn} = \left\{(d,n) \in \mathbb{R}^2_+ \mid z_{nT}(d) \leq \mathrm{s} \quad \text{with} \quad z_{nT}(d) = T_{1nT}(d) + T_{2nT}(d)\right\},$$

where $z_{nT}(d)$ is the sum of the densities of both types of cancer cells after the application of a dose d for n chemotherapy cycles of period T.

Note that the anticancer substances in general have no threshold. They begin to cause effects from doses as low as possible, which in practice can not be determined by laboratory analytical techniques but can be estimated by mathematical models.

Definition We define the treatment index as a power average between the proportion of drugs used to eradicate the tumor and the toxicity caused by those drugs every T time. This is given by the following function,

$$I(d,n) = I_1(d,n)^{\gamma} I_2(d)^{1-\gamma}, \gamma \in (0,1),$$

where $I_1(d,n) = \frac{dn}{n_T}$ is the proportion of drugs used to eradicate the tumor and n_T is the number of days that the chemotherapy treatment takes; $I_2(d) = \frac{\sqrt{d}T^4}{0.25+T^4}$ is the toxicity caused by the application of a certain amount of drugs every T period of time.

The expression I_2 was chosen in order to emulate a greater toxicity as drug dose rises. Now we can define a suitable treatment by means of the treatment index.

Definition A suitable treatment is given by the set $\{(d^*, n^*) \in R_{sn}\}$ such that $I(d^*, n^*)$ is the minimum of the function $I(d,n)$ over R_{sn}.

The effectiveness and the induced resistance of a given drug for a particular cancer has been discovered by trial and error on patients enrolled in clinical trials. In our case, we will consider the following scenarios:

1. The effectiveness of drugs and induced resistance as linear functions,

$$f_A(d) = a_1 d + a_0, \quad f_B(d) = b_1 d + b_0, \quad r(d) = c_0 d. \tag{2.8}$$

2. The effectiveness of drug A as an exponential function and the induced resistance and the effectiveness of drug B as sigmoidal functions,

$$f_A(d) = e^{-a_0 d}, \quad f_B(d) = \frac{K_0 d^{c_0}}{f_0^{c_0} + d^{c_0}}, \quad r(d) = \frac{K_1 d^{c_1}}{f_1^{c_1} + d^{c_1}}. \tag{2.9}$$

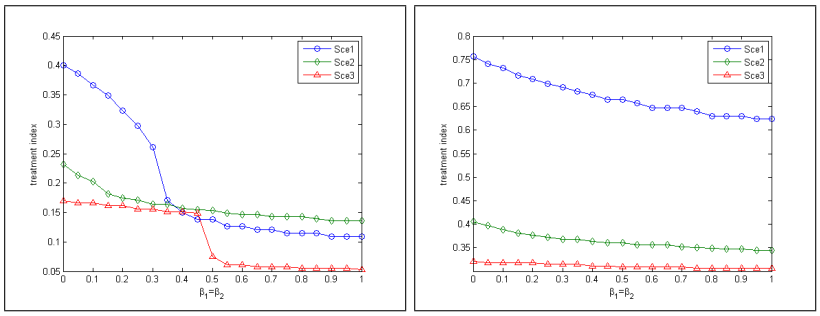

Figure 2.1: Treatment index as competition coefficients $\beta_1 = \beta_2$ are varied, considering three different scenarios for a) a short and b) a long chemotherapy treatment.

3. The effectiveness of A and the induced resistance as exponential functions and the effectiveness of drug B as a sigmoidal function,

$$f_A(d) = e^{-a_0 d}, \quad f_B(d) = \frac{K_0 d^{c_0}}{f_0^{c_0} + d^{c_0}}, \quad r(d) = 1 - e^{-b_0 d}. \tag{2.10}$$

where all the coefficients are real positive constants.

For a short treatment (12-weeks), the competition between cancer cells of type I and II is relevant as the treatment index decreases for an increment of the coefficients of the competition rates. In the first scenario, it is more evident that competition may suggest the use of a less aggressive treatment, in terms of dose, number of applications and toxicity. For the second scenario, the treatment index decreases moderately when the competition coefficients increase. Finally, in the third scenario, changes in the competition coefficients produce a decreasing step behavior for the treatment index. We can also conclude that if drug A is highly effective but with a high induced resistance rate, the drug B must be also highly effective in order to obtain a lower treatment index which means a better chemotherapy treatment, see Figure 2.1 a). For a long treatment (48-weeks) the competition between the cancer cells is less relevant, except in the first scenario. See Figure 2.1 b).

2.3 Gradual effect of chemotherapy

In order to make our model realistic, we relax the assumption of the instantaneous effect of drugs and we consider that such effect is distributed along a period of time

T. The daily effect is defined as,

$$f_d(n) = \begin{cases} 0, & n = 0, \\ \frac{1}{A}e^{-\xi[n]_T+1}[(e^{\xi}-1)([n]_T+\frac{1}{\xi})-e^{\xi}], & [n]_T \neq 0, \\ \frac{1}{A}e^{-\xi T+1}[(e^{\xi}-1)(T+\frac{1}{\xi})-e^{\xi}], & [n]_T = 0, \end{cases} \tag{2.11}$$

where $[n]_T$ denotes $n\, mod\, T$, $n \in \mathbb{N}^+$. The parameter ξ is chosen according to the specific pharmacodynamics of the applied drugs.

The function (2.11) has the property that

$$\sum_{n=n_0}^{n_0+T-1} f_d(n) = 1, n_0 \in \mathbb{N}.$$

Therefore, we redefine the functions h_i, as follows:

$$\begin{aligned} &h_1(d,n) = (1-f_d(n)\sigma_A(d))(1-r(d)), \quad h_2(d,n) = (1-f_d(n)\sigma_B(d)), \\ &h_3(d,n) = (1-f_d(n)\sigma_A(d))^w(1-f_d(n)\sigma_B(d))^{1-w}r(d), w \in (0,1), \\ &h_4(d,n) = \kappa h_1(d,n), \quad h_5(d,n) = \kappa h_2(d,n), 0 < \kappa \ll 1. \end{aligned} \tag{2.12}$$

where $\sigma_A(d) = 1 - f_A(d)$ and $\sigma_B(d) = 1 - f_B(d)$ represent the effectiveness of drugs A and B, that means, the proportions of density of sensitive and resistant cancer cells that die after a chemotherapy cycle. Therefore, the non-autonomous system that we obtain considering $\alpha = 0$ is,

$$\begin{aligned} T_{1_{n+1}} &= \frac{h_1(d,n)T_{1_n}(1-\kappa T_{1_n})}{(1+\beta_1 h_2(d,n)T_{2_n}(1-\kappa T_{2_n})+h_3(d,n)T_{1_n}-r_1 h_1(d,n)T_{1_n}(1-\kappa T_{1_n}))}, \\ T_{2_{n+1}} &= \frac{h_2(d,n)T_{2_n}(1-\kappa T_{2_n})+h_3(d,n)T_{1_n}}{(1-r_2 h_2(d,n)T_{2_n}(1-\kappa T_{2_n})+h_3(d,n)T_{1_n}+\beta_2 h_1(d,n)T_{1_n}(1-\kappa T_{1_n}))}, \end{aligned} \tag{2.13}$$

$$n = 0, 1, 2, \ldots$$

The competition between both types of cancer cells is no longer relevant when the gradual effect of chemotherapy is applied for a long treatment. However, the competition is relevant for different ranges of competition coefficients for short treatments. See Figure 2.2.

2.4 Chemotherapy combinations

In this section, we consider different chemotherapy treatments with two drugs in order to analyze whether there is a better treatment to eradicate the tumor. The

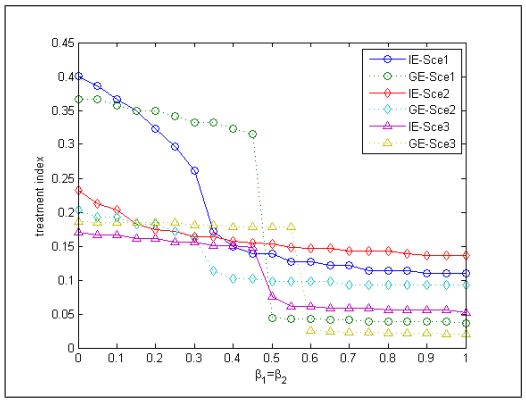

Figure 2.2: Treatment index as competition coefficients $\beta_1 = \beta_2$ are varied, considering three scenarios with instantaneous (IE) and gradual effects (GE).

system that describes the dynamics of tumor growth under chemotherapy treatment is given by system (2.13), that for simplicity we write as:

$$T_{1n+1} = \tilde{g}_1(T_{1n}, T_{2n}, n), \quad T_{2n+1} = \tilde{g}_2(T_{1n}, T_{2n}, n), \quad n = 0, 1, 2, ...$$

Let us remember that in the previous sections, we considered the application of the chemotherapeutic drugs A and B simultaneously. However, new treatments arise from the consideration that the drugs can be applied separately.

When only drug A is applied, we have that $f_B(d) = 1$ and $w = 1$, that means, the whole density of resistant cancer cells survive because drug B is not applied. In this case the functions h_i are as follows: $h_1(d, n) = (1 - f_d(n)\sigma_A(d))(1 - r(d))$, $h_2(d, n) = 1$ and $h_3(d, n) = (1 - f_d(n)\sigma_A(d))r(d)$ where $\sigma_A(d) = 1 - f_A(d)$. If drug A is applied at time nT, then the densities of type I and II cancer cells are given by

$$T_{1n+1} = \tilde{g}_{1A}(T_{1n}, T_{2n}, n), \quad T_{2n+1} = \tilde{g}_{2A}(T_{1n}, T_{2n}, n), \quad n = 0, 1, 2, \ldots$$

where $\tilde{g}_{1A}(T_{1n}, T_{2n}, n)$ is given by

$$\frac{(1 - f_d(n)\sigma_A(d))(1 - r(d))T_{1n}(1 - \kappa T_{1n})}{(1 + \beta_1 T_{2n}(1 - \kappa T_{2n}) + (1 - f_d(n)\sigma_A(d))r(d)T_{1n} - r_1(1 - f_d(n)\sigma_A(d))(1 - r(d))T_{1n}(1 - \kappa T_{1n}))},$$

and $\tilde{g}_{2A}(T_{1n}, T_{2n}, n)$ by

$$\frac{T_{2n}(1 - \kappa T_{2n}) + (1 - f_d(n)\sigma_A(d))r(d)T_{1n}}{(1 - r_2 T_{2n}(1 - \kappa T_{2n}) + (1 - f_d(n)\sigma_A(d))r(d)T_{1n} + \beta_2(1 - f_d(n)\sigma_A(d))(1 - r(d))T_{1n}(1 - \kappa T_{1n}))}.$$

However, when drug B is applied, we have that $f_A(d) = 1$, because the whole density of sensitive cancer cells to drug A survive, also $w = 0$ and $r(d) = 0$ since

there are no resistant cells. In this case, the dose functions h_i turn out to be the following: $h_1(d,n) = 1$, $h_2(d,n) = (1 - f_d(n)\sigma_B(d))$ and $h_3(d,n) = 0$, where $\sigma_B(d) = 1 - f_B(d)$. The system in this case is:

$$\begin{aligned} T_{1n+1} &= \tilde{g}_{1B}(T_{1n}, T_{2n}, n) = \frac{T_{1n}(1-\kappa T_{1n})}{1+\beta_1(1-f_d(n)\sigma_B(d))T_{2n}(1-\kappa T_{2n}) - r_1 T_{1n}(1-\kappa T_{1n})}, \\ T_{2n+1} &= \tilde{g}_{2B}(T_{1n}, T_{2n}, n) = \frac{(1-f_d(n)\sigma_B(d))T_{2n}(1-\kappa T_{2n})}{1-r_2(1-f_d(n)\sigma_B(d))T_{2n}(1-\kappa T_{2n}) + \beta_2 T_{1n}(1-\kappa T_{1n})}. \end{aligned} \tag{2.14}$$

In order to compare different chemotherapy combinations, they should have the same time period. We consider combinations of period $2T$ or $3T$.

2.4.1 Chemotherapy combination 2T

In this subsection, we compare three chemotherapy combinations.

1. The first combination is the original scheme, where drugs A and B are applied simultaneously each period of time T. This scheme is tagged by $(AB)^1$, where the exponent denotes the periods of time elapsed before the application of a drug. This combination is modeled by the discrete system given by

$$\begin{aligned} T_{1n+2} &= \tilde{g}_1(\tilde{g}_1(T_{1n}, T_{2n}, n), \tilde{g}_2(T_{1n}, T_{2n}, n), n+1), \\ T_{2n+2} &= \tilde{g}_2(\tilde{g}_1(T_{1n}, T_{2n}, n), \tilde{g}_2(T_{1n}, T_{2n}, n), n+1), \quad n = 0, 1, 2, \ldots \end{aligned} \tag{2.15}$$

   Let us recall that the gradual effect of chemotherapy is modeled by

$$f_d(n) = \begin{cases} 0, & n = 0, \\ \frac{1}{A} e^{-\xi[n]_T + 1}[(e^{\xi} - 1)([n]_T + \frac{1}{\xi}) - e^{\xi}], & [n]_T \neq 0, \\ \frac{1}{A} e^{-\xi T + 1}[(e^{\xi} - 1)(T + \frac{1}{\xi}) - e^{\xi}], & [n]_T = 0. \end{cases}$$

2. The second combination is the original scheme with an application each period of time $2T$, tagged by $(AB)^2$. System (2.13) with period $2T$ models this combination with a modified $f_d(n)$ given as in the previous model but with period $2T$.

$$f_d(n) = \begin{cases} 0, & n = 0, \\ \frac{1}{A} e^{-\xi[n]_{2T} + 1}[(e^{\xi} - 1)([n]_{2T} + \frac{1}{\xi}) - e^{\xi}], & [n]_{2T} \neq 0, \\ \frac{1}{A} e^{-\xi 2T + 1}[(e^{\xi} - 1)(2T + \frac{1}{\xi}) - e^{\xi}], & [n]_{2T} = 0. \end{cases}$$

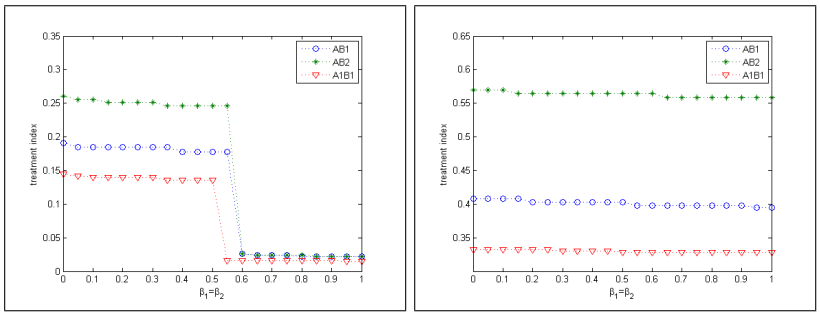

Figure 2.3: Comparison of combinations 2T for the third scenario: a) short treatment b) long treatment.

3. The third combination consists of the application of A and after a period of time T, the application of drug B, denoted by A^1B^1. Here, the associated system is,

$$T_{1n+2} = \tilde{g}_{1B}(\tilde{g}_{1A}(T_{1n}, T_{2n}, n), \tilde{g}_{2A}(T_{1n}, T_{2n}, n), n+1),$$
$$T_{2n+2} = \tilde{g}_{2B}(\tilde{g}_{1A}(T_{1n}, T_{2n}, n), \tilde{g}_{2A}(T_{1n}, T_{2n}, n), n+1) \quad n = 0, 1, 2, \ldots$$

where the gradual effect of chemotherapy is modeled as in the first combination.

By comparing all proposed $2T$ combinations we conclude that for the case of a long treatment, the best combination suggested to eradicate the tumor is $(AB)^1$, regardless of the competition between tumor cells. However, when drugs A and B are highly effective, the suggested treatment is A^1B^1. For a short treatment, the scheme A^1B^1 is suggested, but if the competition coefficients are high ($\beta_1 = \beta_2 \geq 0.6$), then the proposed scheme can be any of the three analyzed treatments. See Figure 2.3.

2.4.2 Chemotherapy schemes 3T

In this subsection we compare the following chemotherapy combinations of period 3T: $(AB)^1$, $(AB)^3$, $A^1B^1B^1$, $A^1A^1B^1$ and $A^1B^1A^1$. For a long treatment, it is suggested to apply $A^1B^1B^1$ regardless of the competition level and the scenario. A second option is given by $(AB)^1$. For a short treatment, the application suggested is the scheme $A^1B^1B^1$, but for a set of doses when competition coefficients are greater than or equal to 0.5, then it is better to use a treatment such as $A^1A^1B^1$ or $A^1B^1A^1$. See Figure 2.4.

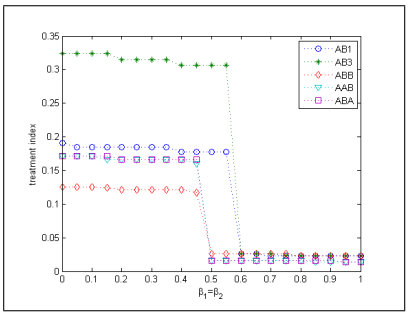

Figure 2.4: Comparison of combinations 3T for the third scenario with a short treatment.

2.5 Conclusions

In this Chapter, we have presented discrete mathematical models for an aggressive heterogeneous tumor. We focused mainly on analyzing the effect of the consideration of competitive interaction between both types of cancer cells in our models. These discrete models were developed using nonstandard finite difference schemes that preserve important properties of a nonlinear competitive system. Moreover, we included the application of two drug chemotherapy treatments with instantaneous and gradual effects in the discrete models. These models have provided useful information regarding the dynamics of tumor growth under chemotherapy treatment and how the success of treatments depend tightly on the effectiveness of drugs. We find that it is really important to consider the competitive interaction between cancer cells due this characteristic is fundamental to avoid treatments more aggressive. This behavior is more notable for short treatments (neoadjuvant treatments). The treatment index presented was a useful quantitative tool to analyze the relevance of considering the competition between cancer cells in our models. Moreover, it lets us compare and evaluate different two drug chemotherapy treatments in order to select a suitable treatment according to the specific effectiveness of drugs. Then, in the case that both drugs A and B are highly effective, the best treatment of period $2T$ was A^1B^1 and of period $3T$ was $A^1B^1B^1$ for long treatments. We also observed that in the case of short treatment, the best treatments were the same provided that $\beta_1, \beta_2 \leq 0$. In the next chapter, we address other important characteristics of aggressive cancerous tumors that we have still not considered such as the invasion and environmental acidification.

Chapter 3

A discrete model of an aggressive-invasive cancer under chemotherapy [1]

3.1 Introduction

In this chapter, our goal is to contribute to the understanding of an aggressive cancerous tumor by enhancing the discrete mathematical models proposed in the previous chapters. These models described the dynamic of a cancerous tumor characterized mainly by their heterogeneity due to the high mutation capacity of the cancer cells and their high proliferation rates. Nevertheless, one important characteristic of an aggressive cancer that has not been considered in our work is cancer invasion. This peculiarity of cancer is the cause of traveling cancer cells through blood veins and create small tumors in other parts of the organism. These small tumors are called metastases. This medical condition generates most deaths of cancer patients. For this reason, it is worthy to incorporate in our models the cancer cells ability to invade surrounding healthy tissue. On the other hand, invasive cancers presumably are heterogeneous because it has been found relevant differences in the cell phenotype in human tumors [2]. Such groups compete for nutritional resources, and their interaction will be modeled assuming two subpopulations of cancer cells with logistic growth rates; analogous works have been done in [29, 33, 22]. However, heterogeneity may also arise due to anticancer therapy application. Different authors have modeled cancer invasion of healthy tissue by reaction-diffusion systems (see [18, 2]) but none of these works have considered invasion and heterogeneity in the way that we do. Our base model follows ideas from [18] where the invasion

[1] This chapter is based on the submitted paper F. Solis, S. Delgadillo, Discrete modeling of aggressive tumor growth with gradual effect of chemotherapy.

of healthy tissue was modeled by reaction-diffusion equations in an acidic environment. The consideration of cancer invasion in our model has advantages over the non-invasion models because it allows us to analyze the spatial evolution of the densities of the different types of cells on an acidic medium and by providing information about the invasion radius. Moreover, we compute the evolution of the discrete model and analyze the effects on cancer invasion by varying important factors such as the normal death rate due to the environmental acidification, the competition coefficients and the mutation rate.

From our point of view it is essential to include a treatment in the modeling of cancer evolution. In our case, the treatment consist in the application of several cytotoxic drugs in order to eradicate the cancer cells. Moreover, we consider factors such as drug resistance and drug toxicity which could contribute to the success or failure of the therapy. Normally, a first set of drugs is applied to eliminate the majority of cancer cells with the possibility of causing induced resistance and a second group of drugs to eliminate possible resistant cells. As a first step in this direction we developed simplified models in the previous chapter, where we presented new features by considering aggressive tumors and including the application of a two drug chemotherapy with gradual effect. There has been development of many mathematical cancer models that take into account the heterogeneity that results of drug resistance but they have ignored the spontaneous changes in the cell genetics even the environmental factors [9]. Therefore, we address the situation of having different types of resistance and evaluate their effects on the anticancer treatments.

Let us recall that the general methodology of our work is first to model the growth dynamics in a continuous fashion to take advantage of our work in the previous chapters. Then to obtain a discrete version by using a Nonstandard Finite Difference Scheme. Our aim is to construct basic discrete schemes that reproduce important properties of the proposed continuous system without numerical instabilities. More specifically to obtain discrete systems that are dynamically consistent for large step sizes. Our next step will be to include the modeling of the application of a chemotherapy treatment that includes a realistic gradual effect in discrete models. Finally, we search for a suitable treatment of chemotherapy by analyzing different treatment combinations in order to eradicate or to reduce the tumor.

3.2 Construction of a discrete model

Mathematical models for the evolution of cancer cells based on population dynamics has been a new trend by considering tumor cells as invading populations [11, 18, 20, 19]. Such populations normally modify the surrounding environment in order to increase its density and at the same time affecting the local populations.

We will start our modeling process by considering a heterogeneous tumor consisting in two types of interacting cancer cells that behave as the invading populations and the normal cell behaving as the local population. We hypothesize that production and the diffusion of that acid into surrounding healthy tissue, creates an environment in which tumor cells survive and proliferate. Our starting point is the differential model with two interacting population cells obtained from [40]. To this model we have added the competition terms among normal and cancer cells, and the intrinsic mutation term, getting:

$$\begin{aligned} \frac{dT_1(t)}{dt} &= g_1(T_1) - \beta_1 T_1 T_2 - \rho T_1 - \gamma_1 N T_1, \\ \frac{dT_2(t)}{dt} &= g_2(T_2) - \beta_2 T_1 T_2 + \rho T_1 - \delta_1 N T_2, \end{aligned} \tag{3.1}$$

where $T_1(t)$ represents the sensitive cell density to drug A (type I cancer cells) at time t, $T_2(t)$ represents the cancer cell density that became resistant to drug A, but are sensitive to drug B (type II cancer cells), at time t and $N(t)$ represents the density of normal cells. Functions $g_1(T_1)$ and $g_2(T_2)$ are the intrinsic proliferation rates. β_1 and β_2 are the coefficients of the interaction terms between both types of cancer cells. We assume that the competition between cancer and normal cells has the same functional Lotka-Volterra competition form, so that, γ_1 and δ_1 measure how both types of cancer cells are affected by their interactions with normal cells. ρ is the intrinsic mutation rate of cancer cells from type I to type II.

3.2.1 Continuous models

Recent studies have shown that each invading tumor has a unique way of colonize the surrounding environment [25, 26], although most cancers have a common growth that exhibits a progressive invasion with a result of the elimination of normal tissue. Our hypothesis is that the similarity in the invasion characteristics is due to a mechanism related to phenotypic features exhibited by most tumors. Such mechanism may be described as follows: Tumor metabolism is transformed since cancer cells convert glucose to Adenosine triphosphate (ATP) by an anaerobic procedure. The production of ATP is maintained by a significant increment in the glucose flux compared with those of the normal tissue. The intracellular pH of tumors and normal cells is basically the same since tumor cells excrete protons through up-regulation of the NA^+/H^+ antiport, by intracellular buffer systems and other membrane bound proton transporters [14]. A consequence of this transformation is the alteration of environment due to increased glycolysis and acid excretion,

which reduces intratumoral extracellular pH, H^+ produced by the tumor is carried by some buffering species along concentration gradients into adjacent normal tissues. The new models that we propose consist of four dimensionless systems of partial differential equations. The first two equations model the growth dynamics of the heterogeneous tumor and they have their genesis in system (3.1) where the spatial dependence is included with the addition of diffusion terms, in order to incorporate the cancer invasion of healthy tissue. They are given by:

$$\frac{\partial T_1(x,t)}{\partial t} = g_1(T_1) - \beta_1 T_1 T_2 - \rho T_1 - \gamma_1 N T_1 + D_1 \nabla^2 T_1, \tag{3.2}$$

$$\frac{\partial T_2(x,t)}{\partial t} = g_2(T_2) - \beta_2 T_1 T_2 + \rho T_1 - \delta_1 N T_2 + D_2 \nabla^2 T_2, \tag{3.3}$$

where D_1 and D_2 are constant diffusion coefficients and x represents the spatial variable. The third equation models the environmental acidification caused by the presence of the tumor. The presence of cancer cells affects the surrounding medium by the excess of ions H^+ that are produced in a proportional rate to the density of cancer cells. We assume that its natural reabsorption is proportional to the excess of ions H^+. Finally, we model the diffusivity property assuming that the Fick law holds. Then, the equation that models the excess of concentration of ions H^+ can be written as:

$$\frac{\partial L(x,t)}{\partial t} = \xi(T_1 + T_2) - r_4 L + D_4 \nabla^2 L. \tag{3.4}$$

where $L(x,t)$ represents the excess of ions H^+ at position x and time t. ξ is the production rate of the ions H^+, r_4 is the coefficient of the reabsorption rate and D_4 is the constant diffusion coefficient of the excess of ions H^+. Notice that we are assuming a linear contribution of both cancer cells. Finally, in order to model the drug toxicity we incorporate a fourth equation in our model. Such equation describes the growth dynamic of normal cells of the host organ which are affected by the cancerous tumor growth. So for future chemotherapeutic application modeling, we will use this equation to assess the damage produced on normal cells. Thus we will be considering chemotherapy toxicity, at least locally. The correspondent equation is:

$$\frac{\partial N(x,t)}{\partial t} = g_3(N) - \gamma_2 N T_1 - \delta_2 N T_2 - \sigma L N, \tag{3.5}$$

where $N(x,t)$ represents the density of normal cells at position x and time t. $g_3(N)$ represents the intrinsic growth rate of normal cells. Finally, γ_2 and δ_2 measures the interaction between both cancer cells with normal cells, respectively. Summarizing,

the models are given by this system of partial differential equations:

$$\begin{aligned}
\frac{\partial T_1(x,t)}{\partial t} &= g_1(T_1) - \beta_1 T_1 T_2 - \rho T_1 - \gamma_1 N T_1 + D_1 \nabla^2 T_1, \\
\frac{\partial T_2(x,t)}{\partial t} &= g_2(T_2) - \beta_2 T_1 T_2 + \rho T_1 - \delta_1 N T_2 + D_2 \nabla^2 T_2, \\
\frac{\partial N(x,t)}{\partial t} &= g_3(N) - \gamma_2 N T_1 - \delta_2 N T_2 - \sigma L N, \\
\frac{\partial L(x,t)}{\partial t} &= \xi(T_1 + T_2) - r_4 L + D_4 \nabla^2 L.
\end{aligned} \tag{3.6}$$

For simplicity, we assume that the tumor has a symmetric geometry, thus we consider only a one dimensional spatial variable and also we assume that cancer and normal cells have logistic proliferation rates of the form $g_j(X) = r_j X(1 - X)$ for $j = 1, 2, 3$. Also, the diffusion coefficients are assumed to be constant. Then (3.6) is reduced to the following system,

$$\begin{aligned}
\frac{\partial T_1(x,t)}{\partial t} &= r_1 T_1(1 - T_1) - \beta_1 T_1 T_2 - \rho T_1 - \gamma_1 N T_1 + D_1 \frac{\partial^2 T_1}{\partial x^2}, \\
\frac{\partial T_2(x,t)}{\partial t} &= r_2 T_2(1 - T_2) - \beta_2 T_1 T_2 + \rho T_1 - \delta_1 N T_2 + D_2 \frac{\partial^2 T_2}{\partial x^2}, \\
\frac{\partial N(x,t)}{\partial t} &= r_3 N(1 - N) - \gamma_2 N T_1 - \delta_2 N T_2 - \sigma L N, \\
\frac{\partial L(x,t)}{\partial t} &= \xi(T_1 + T_2) - r_4 L + D_4 \frac{\partial^2 L}{\partial x^2}.
\end{aligned} \tag{3.7}$$

3.2.2 Discrete model

Our next step consists in obtaining a discrete version of models (3.7) by using an appropriate discretization. A discretization is recommended since data are mostly available in a discrete basis and also because treatments are administered in the same fashion. It is important to remark the difficulty to discretize these systems because of their complex behavior and as larger step sizes are required. We will use the discretization methodology from [41] which has been successfully applied. Thus, we will use a nonstandard discretization via the finite difference divided method. This new methodology is based in the creation of new methods for constructing finite difference schemes such that numerical instabilities do not occur or are minimized. So far the research in this area is starting to set the mathematical foundation and so far the effort has been in constructing nonstandard schemes that incorporate the important dynamical properties of the original differential equations such as positivity or conservation requirements. So far for partial differential equations

having nonlinear advection or diffusion terms very little work has been done on constructing nonstandard schemes. This work is one of the few contributions in the subject and here we will show that a explicit scheme in the dependent variables can be constructed.

Let us start the discretization process by subdividing the domain into a rectangular mesh of equal rectangles of sides Δt and Δx. Let us denote $T_{1_m}^k = T_1(x_m, t_k)$, $T_{2_m}^k = T_2(x_m, t_k)$, $N_m^k = N(x_m, t_k)$, $L_m^k = L(x_m, t_k)$ where $x_m = m\Delta x$ and $t_k = k\Delta t$ for $m, k \in \mathbb{N}$. We have the following approximation of the first temporal derivative,

$$\partial_t^{(1)} T_{im}^k \approx \frac{T_{im}^{k+1} - T_{im}^k}{\varphi_i(\Delta t)},\ \partial_t^{(1)} N_m^k \approx \frac{N_m^{k+1} - N_m^k}{\varphi_3(\Delta t)},\ \partial_t^{(1)} L_m^k \approx \frac{L_m^{k+1} - L_m^k}{\varphi_4(\Delta t)}, i = 1, 2,$$

with $\varphi_i(\Delta t) = \frac{e^{r_i \Delta t} - 1}{r_i}, \quad i = 1, 2, 3, 4$. The diffusion terms are approximated as

$$\partial_x^{(2)} T_{im}^k \approx \frac{T_{im-1}^k - 2T_{im}^k + T_{im+1}^k}{\psi_i(\Delta t)}, \quad \partial_x^{(2)} L_m^k \approx \frac{L_{m-1}^k - 2L_m^k + L_{m+1}^k}{\psi_4(\Delta t)},$$

where $\psi_i(\Delta t) = \frac{4}{\rho_i^2} \sin^2(\rho_i \frac{\Delta x}{2})$, and $\psi_4(\Delta t) = \frac{4}{\rho_4^2} \sinh^2(\rho_4 \frac{\Delta x}{2})$, with $\rho_i = \sqrt{\frac{r_i}{D_i}}$, $i = 1, 2, 4$. Such approximations have appropriate numerical properties for several equations [24]. The nonlinear terms are approximated by nonlocal terms as,

$$r_i T_i (1 - T_i)_m^k \approx r_i T_{im}^k (1 - T_{im}^k), \quad (\beta_1 T_2 + \gamma_1 N) T_{1_m}^k \approx (\beta_1 T_{2_m}^k + \gamma_1 N_m^k) T_{1_m}^{k+1},$$

$$r_3 N (1 - N)_m^k \approx r_3 N_m^k (1 - N_m^k), \quad (\beta_2 T_1 + \delta_1 N) T_{2_m}^k \approx (\beta_2 T_{1_m}^k + \delta_1 N_m^k) T_{2_m}^{k+1},$$

$$(\gamma_2 T_1 + \delta_2 T_2 + \sigma L) N_m^k \approx (\gamma_2 T_{1_m}^k + \delta_2 T_{2_m}^k + \sigma L_m^k) N_m^{k+1}.$$

The linear terms are approximated as:

$$\rho T_{1_m}^k \approx \rho T_{1_m}^k, \quad r_4 L_m^k \approx r_4 L_m^{k+1}, \quad \xi (T_1 + T_2)_m^k \approx \xi (T_{1_m}^k + T_{2_m}^k).$$

Based on the deduction of nonstandard finite difference schemes obtained for each equation, and by solving for $T_{1_m}^{k+1}$, $T_{2_m}^{k+1}$, N_m^{k+1} and L_m^{k+1}, we get the following discrete system, where $R_i = \frac{\varphi_i(\Delta t)}{\psi_i(\Delta x)}, \quad i = 1, 2, 4,$

$$
\begin{aligned}
T_{1_m}^{k+1} &= \frac{(1+(r_1-\rho)\varphi_1(\Delta t)-2D_1R_1)T_{1_m}^k + D_1R_1(T_{1_{m-1}}^k + T_{1_{m+1}}^k)}{1+\varphi_1(\Delta t)(r_1T_{1_m}^k + \beta_1 T_{2_m}^k + \gamma_1 N_m^k)},\\
T_{2_m}^{k+1} &= \frac{(1+r_2\varphi_2(\Delta t)-2D_2R_2)T_{2_m}^k + \rho\varphi_1(\Delta t)T_{1_m}^k + D_2R_2(T_{2_{m-1}}^k + T_{2_{m+1}}^k)}{1+\varphi_2(\Delta t)(r_2T_{2_m}^k + \beta_2 T_{1_m}^k + \delta_1 N_m^k)},\\
N_m^{k+1} &= \frac{(1+\varphi_3(\Delta t)r_3)N_m^k}{1+\varphi_3(\Delta t)(r_3N_m^k + \gamma_2 T_{1_m}^k + \delta_2 T_{2_m}^k + \sigma L_m^k)},\\
L_m^{k+1} &= \frac{(1-2D_4R_4)L_m^k + \xi\varphi_4(\Delta t)(T_{1_m}^k + T_{2_m}^k) + D_4R_4(L_{m-1}^k + L_{m+1}^k)}{1+r_4\varphi_4(\Delta t)}.
\end{aligned}
\tag{3.8}
$$

For further details about the discretization construction, see appendix A.

3.2.3 Dynamical consistency

In this section, we will validate system (3.8) by verifying that it has the same dynamical properties as the continuous system (3.7). It is important to recall that our purpose in the previous section was to obtain a discrete model and not to provide a numerical scheme to solve the continous system. Two essential features that we require are that the solutions of both systems are positive and that both systems are dynamically consistent in the sense that they both have the same equilibria with the same stability properties for the space independent case.

Positivity of solutions

Here we give conditions such that the model (3.8) has positive solutions. Since the denominators in such a system are already positive we only have to show that their respective numerators are also positive. To achieve this property we have the following theorem.

Theorem 3.2.1 *The discrete system (3.8) has positive solutions if Δt is given by*

$$
\min\left\{\frac{1}{r_1}\ln(\vartheta_1), \frac{1}{r_2}\ln\left(\frac{r_2\psi_2(\Delta x)}{(2+\mu_2)D_2 - r_2\psi_2(\Delta x)}+1\right), \frac{1}{r_4}\ln\left(\frac{r_4\psi_4(\Delta x)}{(2+\mu_4)D_4}+1\right)\right\},
$$

where $\vartheta_1 = \frac{r_1\psi_1(\Delta x)}{(2+\mu_1)D_1-(r_1-\rho)\psi_1(\Delta x)}+1$ and μ_i, $i=1,2,4$ are given positive constants satisfying $\mu_1 > \frac{(r_1-\rho)\Delta x^2}{D_1} - 2$ and $\mu_2 > \frac{r_2\Delta x^2}{D_2} - 2$.

Proof Let us show that $(1+(r_1-\rho)\varphi_1(\Delta t)-2D_1R_1)$, $(1+r_2\varphi_2(\Delta t)-2D_2R_2)$ and $(1-2D_4R_4)$ are positive. We notice that system (3.8) preserves the positivity if,

$$\begin{aligned} 1+(r_1-\rho)\varphi_1(\Delta t)-2D_1R_1 &= \mu_1 D_1 R_1, \\ 1+r_2\varphi_2(\Delta t)-2D_2R_2 &= \mu_2 D_2 R_2, \\ 1-2D_4R_4 &= \mu_4 D_4 R_4, \end{aligned}$$

where μ_1, μ_2 and μ_4 are positive constants or equivalently, that the functional relations between $\varphi_i(\Delta t)$ and $\psi_i(\Delta t)$ is given by:

$$\varphi_1(\Delta t)=\frac{\psi_1(\Delta x)}{(2+\mu_1)D_1-(r_1-\rho)\psi_1(\Delta x)}, \quad \mu_1>\frac{(r_1-\rho)\psi_1(\Delta x)}{D_1}-2$$

$$\varphi_2(\Delta t)=\frac{\psi_2(\Delta x)}{(2+\mu_2)D_2-r_2\psi_2(\Delta x)}, \quad \mu_2>\frac{r_2\psi_2(\Delta x)}{D_2}-2$$

$$\varphi_4(\Delta t)=\frac{\psi_4(\Delta x)}{(2+\mu_4)D_4}, \quad \mu_4>0.$$

Now, since $\varphi_i(\Delta t)=\frac{e^{r_i\Delta t}-1}{r_i}, i=1,2,4$ and solving for Δt and taking the minimum, we obtain:

$$\Delta t=\min\left\{\frac{1}{r_1}\ln(r_1\varphi_1(\Delta t)+1), \frac{1}{r_2}\ln(r_2\varphi_2(\Delta t)+1), \frac{1}{r_4}\ln(r_4\varphi_4(\Delta t)+1)\right\}.$$

Therefore, substituting the values of φ_i for $i=1,2,4$ the positivity conditions becomes:

$$\Delta t=\min\left\{\frac{1}{r_1}\ln(\vartheta_1), \frac{1}{r_2}\ln\left(\frac{r_2\psi_2(\Delta x)}{(2+\mu_2)D_2-r_2\psi_2(\Delta x)}+1\right), \frac{1}{r_4}\ln\left(\frac{r_4\psi_4(\Delta x)}{(2+\mu_4)D_4}+1\right)\right\},$$

where $\mu_1>\frac{(r_1-\rho)\psi_1(\Delta x)}{D_1}-2$, $\mu_2>\frac{r_2\psi_2(\Delta x)}{D_2}-2$, and $\mu_4>0$.

Remark If we choose the standard derivative, that is, choosing $\varphi_i(\Delta t)=\Delta t$ and $\psi_i(\Delta x)=\Delta x^2$, $i=1,2,4$, then the functional relation between Δt and Δx becomes

$$\Delta t=min\left\{\frac{\Delta x^2}{(2+\mu_1)D_1-(r_1-\rho)\Delta x^2}, \frac{\Delta x^2}{(2+\mu_2)D_2-r_2\Delta x^2}, \frac{\Delta x^2}{(2+\mu_4)D_4}\right\}.$$

where $\mu_1>\frac{(r_1-\rho)\Delta x^2}{D_1}-2$, $\mu_2>\frac{r_2\Delta x^2}{D_2}-2$, and $\mu_4>0$.

Space independent system

Let us now show that the space independent continuous system has the same properties as its discrete counterpart. In this case, the system (3.7) becomes an ordinary differential equation system given by:

$$\begin{aligned}
\frac{dT_1}{dt} &= r_1 T_1(1-T_1) - \beta_1 T_1 T_2 - \rho T_1 - \gamma_1 N T_1, \\
\frac{dT_2}{dt} &= r_2 T_2(1-T_2) - \beta_2 T_1 T_2 + \rho T_1 - \delta_1 N T_2, \\
\frac{dN}{dt} &= r_3 N(1-N) - \gamma_2 N T_1 - \delta_2 N T_2 - \sigma L N, \\
\frac{dL}{dt} &= \xi(T_1+T_2) - r_4 L.
\end{aligned} \tag{3.9}$$

The equilibria of the previous continuous system are the roots of the equations given by the right hand sides of (3.9) equal to zero, which are exactly the same equations for the corresponding discrete system when $\varphi_1(\Delta t) = \varphi_2(\Delta t)$. Such equilibrium points are: the unstable trivial point $(0,0,0,0)$, the point $(0,1,0,\frac{\xi}{r_4})$ which represents the total invasion by type II cancer cells and is stable when $r_1 < \beta_1 + \rho$ and $r_3 < \delta_2 + \sigma$. The healthy point $(0,0,1,0)$ is stable when $r_1 < \rho + \gamma_1$ and $r_2 < \delta_1$. There are in general five more equilibrium points consisting in chronic states in an acidic environment: one equilibrium point of the form $(0, T_2^*, N^*, L^*)$, representing the coexistence between type II cancer and normal cells. Two equilibria of the form $(T_1^*, T_2^*, 0, L^*)$, which represents the total invasion by a heterogeneous cancer, and finally two of the form (T_1^*, T_2^*, N^*, L^*) representing the coexistence among cancer and normal cells in an acidic environment. The functional dependence on the parameters of those equilibria is different from point to point and it is cumbersome to write it explicitly. Their stabilities are parametric dependent but they coincide, verified numerically, for both the continuous and the discrete cases. For more details see appendix B.

3.3 Discrete system evolution

In this section, we analyze the evolution of model (3.8), first by showing the general behavior of its solutions with parameter values already reported in the literature. Then, we focus on the heterogeneity of the tumor by considering the variation of the intrinsic mutation rate ρ for different diffusion coefficients, which will help to describe scenarios where the tumor tends to be dominated by a specific type of cancer cells, which is also reflected in the radius of invasion. Later, we analyze the effect of acidification on tumor surroundings, which also contributes

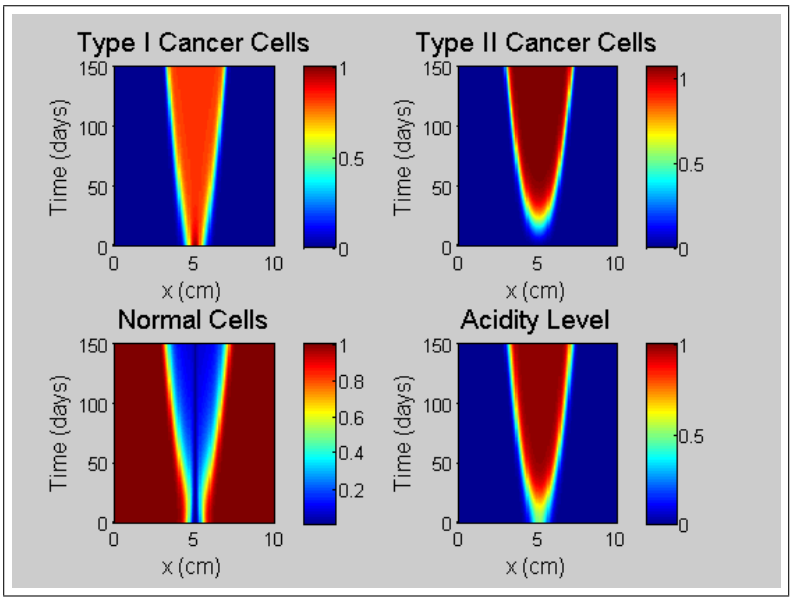

Figure 3.1: Evolution of the densities of cancer and normal cells and the acidity level in space and time with a mutation rate $\rho = 0.15$, after 150 days.

to the cancer invasion. We require values of the parameters that are suitable for the specific cancer under consideration. From [18], we take the following dimensionless parameters values: $r_1 = r_3 = 1$, $r_4 = \xi = 109$, $0 \leq \sigma \leq 12.5$, and $D_4 = 1$. We consider $D_1 = D_2 = 3.5 \times 10^{-4}$ which are in the coefficient range given by [8]. According to [13], the competition coefficients could have values in a range between 0 and 1. Then we fix these coefficients in the simulations as $\beta_1 = 0.15, \beta_2 = 0.15, \gamma_1 = 0.15, \gamma_2 = 0.3, \delta_1 = 0.25$ and $\delta_2 = 0.35$. We assume that type II cancer cells have more aggressive growth, that is, $r_1 < r_2 = 1.2$ and the intrinsic mutation rate is $\rho = 0.15$. We consider an initial homogeneous tumor (with radius of 1.45 cm) in the same way as in [8], but centered on a domain with a length of $l = 10$ cm. The initial conditions are given by:

$$\begin{aligned} &T_1(0,x) = Ke^{-\frac{1}{\epsilon_0}(x-5)^2}, \quad T_2(0,x) = 0, \\ &N(0,x) = 1 - Ne^{-\frac{1}{\epsilon_1}(x-5)^2}, \quad L(0,x) = Ke^{-\frac{1}{\epsilon_2}(x-5)^2}, \end{aligned} \tag{3.10}$$

with $K = 1.01, N = 0.99, \epsilon_0 = \epsilon_1 = 0.005$, and $\epsilon_2 = 0.075$. The boundary conditions are: $T_i(t,x) = L(t,x) = 0$, with $i = 1, 2$ and $N(t,x) = 1$ at $x = 0, l$.

The evolution of the model (3.8) has the following qualitative behavior after a period of time (we choose 150 days): the density of type I cancer cells invades the surrounding normal tissue, but such density decreases with time due to the diffusion

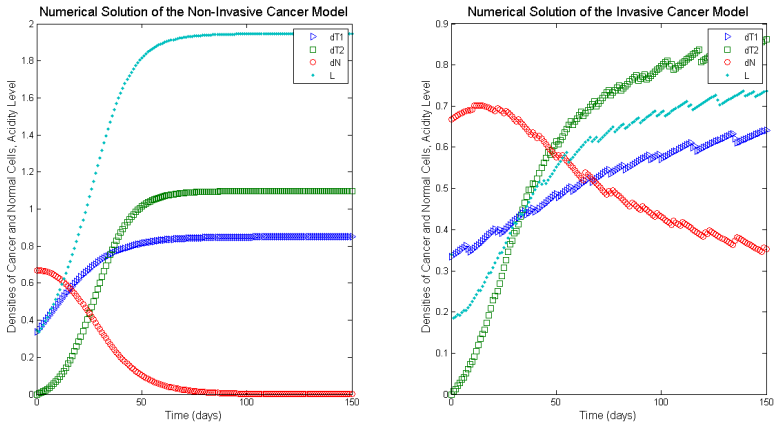

Figure 3.2: Densities of the variables of the discrete model of a) non-invasive and b) invasive cancerous tumor with a mutation rate of $\rho = 0.15$.

effect. Meanwhile, the density of type II cancer cells increases due to the intrinsic mutation rate and continues increasing over time. The density of normal cells decreases as a result of the invasion from both types of cancer cells and because the environmental acidification. This last variable keeps constant levels when the system starts to evolve, but after around twenty days it starts to increase rapidly. It is important to remark that under these previous considerations, the density of type II cancer cells tends to outweigh the density of type I cancer cells, see Figure 3.1 for qualitative details.

Now, our goal is to analyze how the dynamics of the tumor growth is affected when the mutation rate and the diffusion coefficients vary for 150 days. We divide the invasion level in three different types of invasion: a low invasion level by considering small values of the diffusion coefficients, for example $D_1 = D_2 = 1\times10^{-8}$ and $D_4 = 1$, a second invasion level given by medium diffusion coefficients, for example $D_1 = D_2 = 3.5 \times 10^{-4}$ and $D_4 = 1$, and a high level of invasion given by high diffusion values like $D_1 = D_2 = 1 \times 10^{-3}$ and $D_4 = 1$. For the second level of invasion, the cell densities show a slow growth but in the absence of diffusivity the cancer cells have a logistic behavior, meaning that they increase exponentially for a short period of time and then become almost constant, see Figure 3.2. The densities of cancer cells for all diffusion levels increase abruptly for small ρ-values and then decrease when ρ increases. Such densities have an inverse proportional behavior to the diffusion coefficients. With respect to the density of normal cells, it decreases drastically for small ρ-values and then it approaches to a fixed value. Normal cells density is more affected for lower diffusivity. The radius of invasion

shows a growing trend and is stabilized rapidly as ρ varies which is the same behavior for all different invasion levels. However, the stabilization is faster for the lower levels of invasion. So, the tumor size will be bigger when the diffusion coefficients are higher. Therefore, we conclude that the tumor, as expected, is more invasive for higher diffusion levels but its density decreases more than those for medium or low diffusion levels. Notice that the homogeneous cancer ($\rho = 0$) is less invasive than the heterogeneous one ($\rho > 0$). In Figure 3.3 a) we show three curves which correspond to the three invasion diffusion levels mentioned above. On the horizontal axis we vary the mutation rate, ρ, and on the vertical axis the total density of cancer cells. Note that all three densities increase linearly for small values of ρ, each one increases up to a respective maximum value that correspond to a critical value of the mutation rate, that is, a value where the density of type II cancer cells have a significant volume to compete for nutritional resources causing an reduction effect on the tumor mass. This effect is graphically translate on a singularity on each curve. In Figure 3.3 b) we show a case for which the invasion radius increases in a stepwise fashion for a high diffusion level, whereas for lower diffusion levels it grows linearly for small values of ρ and after that it becomes constant. This case shows the sensitivity of the invasion radius on the diffusion level.

The final important aspect that must be analyzed is the normal death rate due the environmental acidification under different levels of competition since it catalyzes the invasion of normal tissue. Cancer cell density has a steep exponential growth for small values of the parameter σ and it stabilizes for larger values of such a parameter, whereas this density keeps constant without competition. It is worthy to mention that independently of the values of σ, cancer cell density is a decreasing function of competition level. The density of normal cells decreases drastically for small σ-values and then stabilizes for larger values of σ. This qualitative behavior is independent of cell competition. However, in the case of low acidification levels, normal cells benefit the most when there is no competition between cells. For $\sigma > 1.5$, the damage of normal cells is less if the competition level between cancer cells is higher. Which reaffirms the fact the acidification benefits more the invasion of the healthy tissue, but it is also important the consideration of the competition for nutritional resources. In Figure 3.4, we show the densities of type I cancer cells and normal cells for 150 days varying σ for different levels of the competition coefficients. We use the labels: *comp 0* in the absence of competition, *comp 1* for parameter values $b1 = 0.15, b2 = 0.15, g1 = 0.2, g2 = 0.3, d1 = 0.15, d2 = 0.35$, and *comp 2* for parameter values $b1 = 0.25, b2 = 0.15, g1 = 0.3, g2 = 0.5, d1 = 0.25, d2 = 0.55$. Notice the logistic behavior mentioned above for the curves in figure 3.4 a) when competition is present whereas an almost constant behavior for a non competition case. In figure 3.4 b) we show how the the density of normal cells decay in an interlaced fashion depending on competition and on the values of σ.

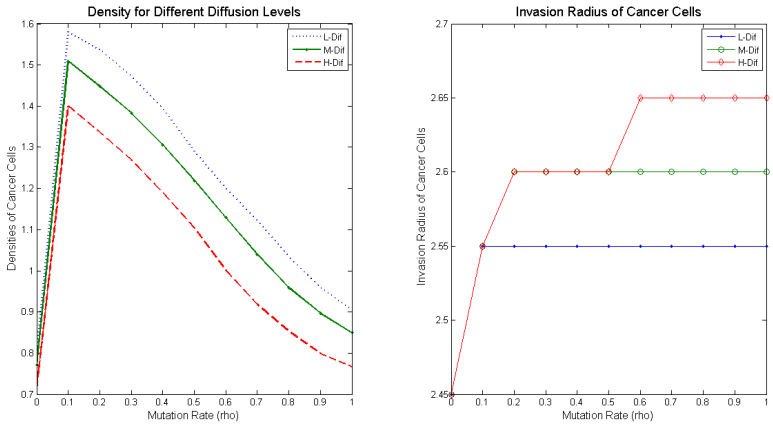

Figure 3.3: a) Density and b) the invasion radius of cancer cells when the mutation rate ρ varies, for different invasion levels.

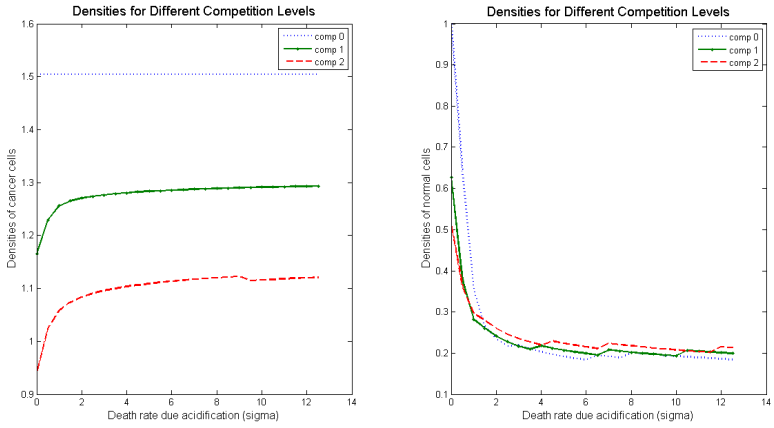

Figure 3.4: Densities of a) cancer and b) normal cells as σ varies, for different sets of competition coefficients.

3.4 Chemotherapy Modeling

The chemotherapeutic treatment consists of the simultaneous application of two drugs, labeled as drug A and drug B, at each period of time T. The application of drugs A and B reduces the densities of type I and type II cancer cells, respectively. We consider a gradual effect of both drugs, which means that their effects are distributed through the time period T between each application. So, after including the application of a chemotherapy cycle in the kT period of time, where $k \in \mathbb{N}$, we get the following system:

$$\begin{aligned}
T_{1_m}^{(k+1)} &= \frac{(1+(r_1-\rho)\varphi_1(\Delta t)-2D_1R_1)T_{1_m}^{k+}+D_1R_1(T_{1_{m-1}}^{k+}+T_{1_{m+1}}^{k+})}{1+\varphi_1(\Delta t)(r_1T_{1_m}^{k+}+\beta_1T_{2_m}^{k+}+\gamma_1N_m^{k+})},\\
T_{2_m}^{(k+1)} &= \frac{(1+r_2\varphi_2(\Delta t)-2D_2R_2)T_{2_m}^{k+}+\rho\varphi_1(\Delta t)T_{1_m}^{k+}+D_2R_2(T_{2_{m-1}}^{k+}+T_{2_{m+1}}^{k+})}{1+\varphi_2(\Delta t)(r_2T_{2_m}^{k+}+\beta_2T_{1_m}^{k+}+\delta_1N_m^{k+})},\\
N_m^{(k+1)} &= \frac{(1+\varphi_3(\Delta t)r_3)N_m^{k+}}{1+\varphi_3(\Delta t)(r_3N_m^{k+}+\gamma_2T_{1_m}^{k+}+\delta_2T_{2_m}^{k+}+\sigma L_m^{k+})},\\
L_m^{(k+1)} &= \frac{(1-2D_4R_4)L_m^{k+}+\xi\varphi_4(\Delta t)(T_{1_m}^{k+}+T_{2_m}^{k+})+D_4R_4(L_{m-1}^{k+}+L_{m+1}^{k+})}{1+r_4\varphi_4(\Delta t)},
\end{aligned} \tag{3.11}$$

where $T_{1_m}^{k+}, T_{2_m}^{k+}, N_m^{k+}, L_m^{k+}$ represent the densities of cancer, normal cells and acidity just after the application of k-th cycle of chemotherapy. Particularly, we include an instantaneous reaction of the application during chemotherapy cycles as follows:

$$\begin{aligned}
T_{1_m}^{k+} &= \phi_1(T_{1_m}^k, f_\delta(k), d), \quad T_{2_m}^{k+} = \phi_2(T_{1_m}^k, T_{2_m}^k, f_\delta(k), d),\\
N_m^{k+} &= \phi_3(N_m^k, f_\delta(k), d), \quad L_m^{k+} = \phi_4(L_m^k, f_\delta(k), d),
\end{aligned}$$

$f_\delta(k)$ represents the gradual effect of drugs at $k \in \mathbb{N}$ and d represents the applied dose of each drug. We consider

$$\phi_1(T_{1_m}^k, f_\delta(k), d) = \tilde{f}_A(k,d)(1-r(d))T_{1_m}^k, \text{ and}$$

$$\phi_2(T_{1_m}^k, T_{2_m}^k, f_\delta(k), d) = \tilde{f_B}(k,d)T_{2_m}^k + \tilde{f_A}^{\,w}(k,d)\tilde{f_B}(k,d)^{1-w}r(d)T_{1_m}^k,$$

where $w \in (0,1)$. The last term of ϕ_2 represent an induced resistance given by a weighted average as defined in [36]. The toxicity is model by $\phi_3(N_m^k, f_\delta(k), d) = \tilde{f}_{AB}(k,d)N_m^k$ and the acidification is considered by $\phi_4(L_m^k, f_\delta(k), d) = (1+\chi_0\tilde{f}_{AB}(k,d))L_m^k$ where $\tilde{f}_A, \tilde{f}_B, \tilde{f}_{AB}$ are the proportions of cell densities that survive the drug application. The functions are of the form:

$$\tilde{f}_J(k,d) = 1 - f_\delta(k)\sigma_J(d) \text{ with } J = A, B, AB,$$

where $\sigma_A(d)$, $\sigma_B(d)$, $\sigma_{AB}(d)$ are the proportions of cells dying due to drug effects. The effectiveness and induced resistance of each drug depend on the specific cancer and vary also with each patient. However, for simplicity, we consider the following scenario: the effectiveness of drug A can be expressed as an exponential function, the effectiveness of drug B and the induced resistance are both considered as sigmoid functions, and the normal death rate due to toxicity is considered as a linear combination of the death rates of drugs (A and B). These functions are of the form:

$$\sigma_A(d) = 1-e^{-a_0 d}, \quad \sigma_B(d) = \frac{f^{c_0} + (1-K_0)d^{c_0}}{f_0^{c_0} + d^{c_0}} = r(d), \quad \sigma_{AB}(d) = \alpha\sigma_A(d)+\beta\sigma_B(d).$$

The effect of drugs is distributed through time period T with a daily effect defined by,

$$f_\delta(k) = \begin{cases} \frac{1}{A}e^{-\varsigma[k]_T+1}[(e^\varsigma-1)([k]_T+\frac{1}{\varsigma})-e^\varsigma], & [k]_\delta = 0, [k]_T \neq 0, \\ \frac{1}{A}e^{-\varsigma T+1}[(e^\varsigma-1)(T+\frac{1}{\varsigma})-e^\varsigma], & [k]_\delta = 0, [k]_T = 0, \\ 0, & [k]_\delta \neq 0, \end{cases} \tag{3.12}$$

where $[k]_T$ denotes $k\,mod\,T$, $[k]_\delta$ denotes $k\,mod\,\delta$, δ is a fixed value that corresponds to a day in the dimensionless model. The parameter ς is chosen according to the specific pharmacodynamics of the applied drugs. Function (3.12) satisfies $\sum_{k=k_0}^{k_0+n_\delta(T-1)} f_\delta(k) = 1,$ for all $k_0 \in \mathbb{N}, n_\delta = \frac{\delta}{\Delta t}$. The inclusion of all these factors give rise to the following explicit non autonomous system:

$$\begin{aligned}
T_1{}_m^{(k+1)} &= \frac{(1+(r_1-\rho)\varphi_1 - 2D_1R_1)\phi_1(T_1{}_m^k,k,d) + D_1R_1(\phi_1(T_1{}_{m-1}^k,k,d)+\phi_1(T_1{}_{m+1}^k,k,d))}{1+\varphi_1(r_1\phi_1(T_1{}_m^k,k,d)+\beta_1\phi_2(T_1{}_m^k,T_2{}_m^k,k,d)+\gamma_1\phi_3(N_m^k,k,d))}, \\
T_2{}_m^{(k+1)} &= \frac{(1+r_2\varphi_2 - 2D_2R_2)\phi_2(T_1{}_m^k,T_2{}_m^k,k,d) + \rho\varphi_1\phi_1(T_1{}_m^k,k,d)+}{1+\varphi_2(r_2\phi_2(T_1{}_m^k,T_2{}_m^k,k,d)+\beta_2\phi_1(T_1{}_m^k,k,d)+\delta_1\phi_3(N_m^k,k,d))}, \\
&\quad \frac{D_2R_2(\phi_2(T_1{}_{m-1}^k,T_2{}_{m-1}^k,k,d)+\phi_2(T_1{}_{m+1}^k,T_2{}_{m+1}^k,k,d))}{1+\varphi_2(r_2\phi_2(T_1{}_m^k,T_2{}_m^k,k,d)+\beta_2\phi_1(T_1{}_m^k,k,d)+\delta_1\phi_3(N_m^k,k,d))}, \\
N_m^{(k+1)} &= \frac{(1+r_3\varphi_3)\phi_3(N_m^k,k,d)}{1+\varphi_3(r_3\phi_3(N_m^k,k,d)+\gamma_2\phi_1(T_1{}_m^k,k,d)+\delta_2\phi_2(T_1{}_m^k,T_2{}_m^k,k,d)+\sigma\phi_4(L_m^k,k,d))}, \\
L_m^{(k+1)} &= (1+r_4\varphi_4)^{-1}\Big[(1-2D_4R_4)\phi_4(L_m^k,k,d)+\xi\varphi_4(\phi_1(T_1{}_m^k,k,d)+\phi_2(T_1{}_m^k,T_2{}_m^k,k,d)) \\
&\qquad +D_4R_4(\phi_4(L_{m-1}^k,k,d)+\phi_4(L_{m+1}^k,k,d))\Big].
\end{aligned} \tag{3.13}$$

As a first step, we assume that the application of a chemotherapy cycle does not modify the acidification level, that means, $\chi_0 = 0$.

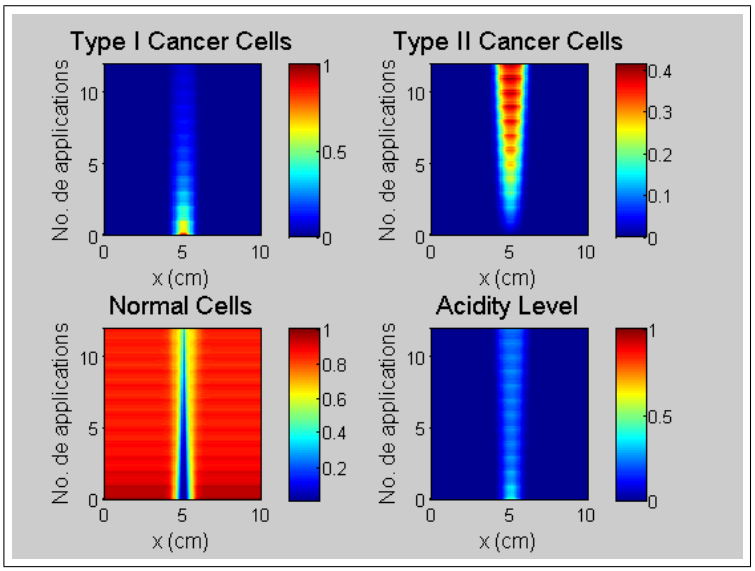

Figure 3.5: Densities of type I and II cancer cells and normal cells, the acidification for the discrete model with chemotherapy. Intrinsic resistance and medium drug effectiveness are considered.

3.4.1 Evolution of the discrete system with chemotherapy

Let us describe the evolution of the discrete model (3.13) that includes chemotherapy by presenting the evolutions of the densities of the tumor, the normal cells, and the surrounding acidification for the cases of intrinsic and induced resistances for a short treatment (12 chemotherapy cycles). Here we consider an average drug effectiveness to illustrate the model behavior. For the case of intrinsic resistance, the density of type I cancer cells decreases and the density of type II cancer cells increases over time and only the invasion radius of the second type of cancer cells increases. On the other hand, the density of normal cells decreases and the invasion radius increases as expected. This behavior is shown in Figure 3.5. For the induced resistance, there is an eradication of type I cancer cells whereas type II cancer cells increase affecting only temporarily the density of normal cells, see Figure 3.6 for details. Therefore, the treatment is more effective in this case even if the drug effectiveness is increased.

Now, let us analyze the variation in the densities of tumor and normal cells when the mutation rate varies. In this case, due to the treatment, the density of the tumor decreases drastically and the healthy tissue does not have severe damage when the mutation rate increases. It is important to remark that the aggressiveness of the tumor is higher for a range of values of the mutation rate similar to the case without

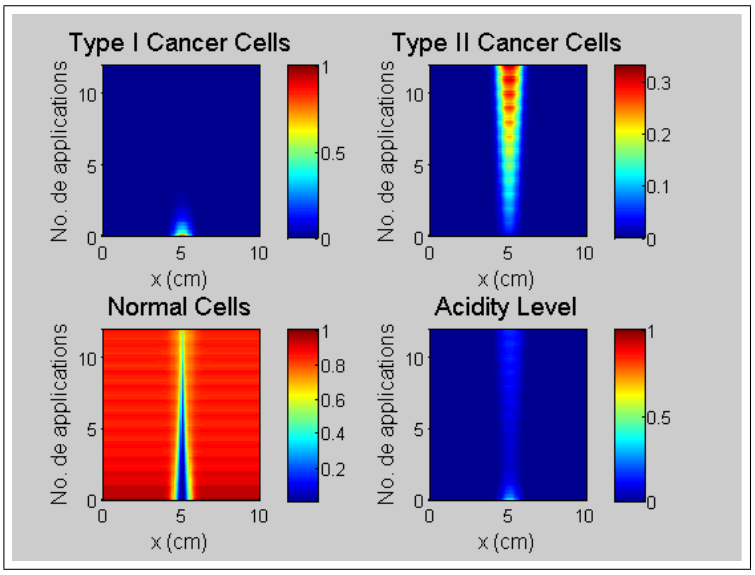

Figure 3.6: Densities of type I and II cancer cells and normal cells, the acidification for the discrete model with chemotherapy. Induced resistance and medium drug effectiveness are considered.

treatment for low drug effectiveness. The invasion radius of types I and II cancer cells decreases gradually and increases drastically and stabilizes as the mutation rate increases, respectively, see Figure 3.7. Actually, for $\rho > 0.7$, the density of type I cancer cells becomes zero. So the cancerous tumor become a homogeneous tumor consisting of only type II cancer cells. However, we can observe that the tumor can only be reduced to a certain size for both cases of resistance (intrinsic and induced). We show in Figure 3.8 a) how the average densities of cancer and normal cells and the acidification, in the case of intrinsic resistance, change temporarily by the effect of the chemotherapy. Notice that in this figure and in the next one the oscillations presented are due to the gradual effect of the chemotherapy. In Figure 3.8 b) we compare the evolution of densities of the cancer cells for different instances of resistance. In the non resistance case, the density of cancer cells decreases gradually until the tumor is eradicated. In the case of intrinsic resistance, the density of cancer cells decreases slightly and tends to stabilize. For the case of induced resistance or when both types of resistance are present, the density of cancer cells decreases rapidly but after 3 or 4 chemotherapy applications they begin to increase despite the chemotherapy application. Therefore short treatments are suggested for these two cases.

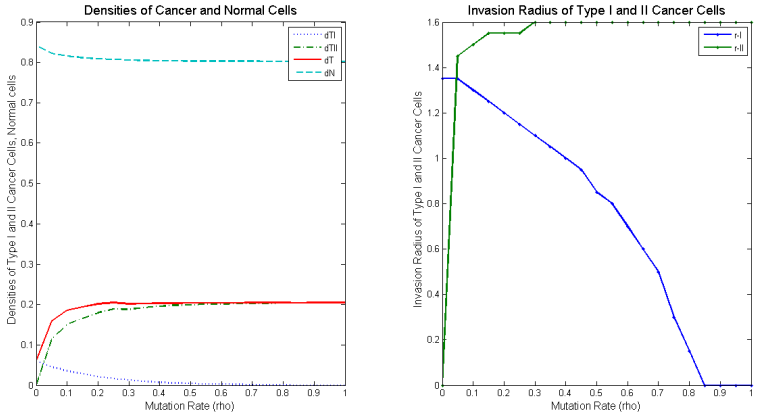

Figure 3.7: a) Densities and b) invasion radius of type I and II cancer cells when chemotherapy is applied with an average drug effectiveness.

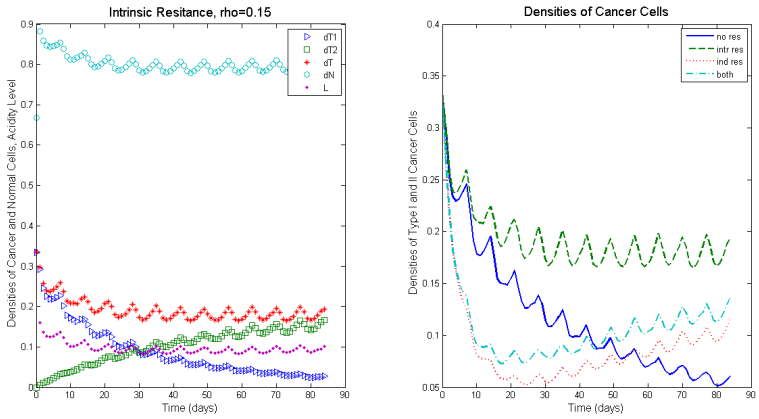

Figure 3.8: a) Densities of each variables of the discrete system for the case of intrinsic resistance and b) the comparison between four scenarios of resistance for $\sigma = 1$ and with medium drug effectiveness.

3.4.2 Chemotherapy combinations

In this section we consider different treatment combinations in order to determine whether there exists a better chemotherapy combination that reduces or eradicates the tumor. Let us recall that in the previous sections, we only considered the application of both drugs simultaneously. New treatments arise from the consideration that drugs can be applied separately. When drug A is applied, we have that $\tilde{f}_B(k,d) = 1$ and $w = 1$ because all resistant cells survive. In this case, the instantaneous reaction of an application of a chemotherapy cycle is as follows:

$$\begin{aligned} T_{1_m}^{k+} &= \tilde{f}_A(k,d)(1-r(d))T_{1_m}^k, \quad T_{2_m}^{k+} = T_{2_m}^k + \tilde{f}_A(k,d)r(d)T_{1_m}^k, \\ N_m^{k+} &= \tilde{f}_{AB}(k,d)N_m^k, \quad L_m^{k+} = 1 + \chi_0 \tilde{f_{AB}}(k,d)L_m^k. \end{aligned} \tag{3.14}$$

Thus, the discrete system (3.13) becomes:

$$\begin{aligned} T_{1_m}^{(k+1)} &= \frac{\tilde{f_A}(k,d)(1-r(d))[(1+(r_1-\rho)\varphi_1 - 2D_1R_1)T_{1_m}^k + D_1R_1(T_{1_{m-1}}^k + T_{1_{m+1}}^k)]}{1+\varphi_1(r_1\tilde{f_A}(k,d)(1-r(d))T_{1_m}^k + \beta_1(T_{2_m}^k + \tilde{f}_A(k,d)r(d)T_{1_m}^k) + \gamma_1\tilde{f}_{AB}(k,d)N_m^k)}, \\ T_{2_m}^{(k+1)} &= \frac{(1+r_2\varphi_2 - 2D_2R_2)(T_{2_m}^k + \tilde{f}_A(k,d)r(d)T_{1_m}^k) + \rho\varphi_1\tilde{f_A}(k,d)(1-r(d))T_{1_m}^k}{1+\varphi_2(r_2(T_{2_m}^k + \tilde{f}_A(k,d)r(d)T_{1_m}^k) + \beta_2\tilde{f_A}(k,d)(1-r(d))T_{1_m}^k + \delta_1\tilde{f}_{AB}(k,d)N_m^k)} + \\ &\quad \frac{D_2R_2((T_{2_{m-1}}^k + T_{2_{m+1}}^k) + \tilde{f}_A(k,d)r(d)(T_{1_{m-1}}^k + T_{1_{m+1}}^k))}{1+\varphi_2(r_2(T_{2_m}^k + \tilde{f}_A(k,d)r(d)T_{1_m}^k) + \beta_2\tilde{f_A}(k,d)(1-r(d))T_{1_m}^k + \delta_1\tilde{f}_{AB}(k,d)N_m^k)}, \\ N_m^{(k+1)} &= \frac{(1+\varphi_3 r_3)\tilde{f}_{AB}(k,d)N_m^k}{1+\varphi_3(r_3\tilde{f}_{AB}(k,d)N_m^k + (\gamma_2(1-r(d)) + \delta_2 r(d))\tilde{f_A}(k,d)T_{1_m}^k + \delta_2 T_{2_m}^k + \sigma v)}, \\ L_m^{(k+1)} &= (1+r_4\varphi_4)^{-1}\Big[(1-2D_4R_4)(1+k_0\tilde{f_{AB}}(k,d)L_m^k) + \xi\varphi_4(\tilde{f_A}(k,d)T_{1_m}^k + T_{2_m}^k) \\ &\quad + D_4R_4(2+k_0\tilde{f_{AB}}(k,d)(L_{m-1}^k + L_{m+1}^k))\Big], \end{aligned} \tag{3.15}$$

with $v = 1 + k_0\tilde{f}_{AB}(k,d)L_m^k$. When drug B is applied, $\tilde{f}_A(k,d) = 1, r(d,k) = 0$ and $w = 0$ since all resistant cells survive. In this case, the instantaneous reaction of the application of a chemotherapy cycle is as follows: $T_{1_m}^{k+} = \phi_1(T_{1_m}^k, f_\delta(k), d)$, $T_{2_m}^{k+} = \phi_2(T_{1_m}^k, T_{2_m}^k, f_\delta(k), d)$, and $N_m^{k+} = \phi_3(N_m^k, f_\delta(k), d)$. The new system in this case has a similar form as (3.15). In order to compare the different chemotherapy combinations, they should have the same application period and we only consider some combinations of period $2T$ or $3T$.

3.4.3 Chemotherapy combinations 2T and 3T

In this subsection we will first compare three chemotherapy combinations with period $2T$.

1. The first combination is the original scheme with an application period of $2T$, tagged by $(AB)^2$. System (3.13) with period $2T$ models this combination with $f_\delta(k)$ given by (3.12) but with period $2T$.

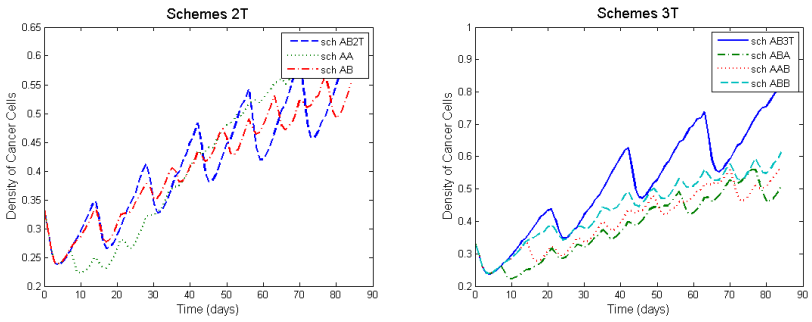

Figure 3.9: Comparison of the densities of cancer cells for a) schemes 2T and b) schemes 3T with intrinsic resistance $\rho = 0.15$.

2. The second combination consists of the application of drug A in each period of time T, denoted by A^1A^1. The discrete system that describes this combination is given by (3.15).

3. The third combination consists of the application of drug A and after a period of time T follows the application of drug B, denoted by A^1B^1. The discrete system that describes this combination is the composition of systems (3.15) and the resulting system of the application of drug B.

Let us compare all proposed chemotherapy schemes of period $2T$ for a short treatment (12 weeks) taking into account the evolution of the densities of cancer and normal cells in order to select an optimal combination. Other variables can be taken in consideration in order to select the scheme but that is an optional choice for the clinicians. When the intrinsic resistance and medium drug effectiveness are considered, the better combination is A^1A^1 with only few applications, see Figure 3.9. Now, if we consider an induced resistance and medium drug effectiveness, the best treatment is given by A^1B^1 since this combination causes less severe damage to the healthy tissue.

Finally, let us compare the following chemotherapy combinations of period 3T for few applications of chemotherapy: $(AB)^3$, $A^1B^1A^1$, $A^1A^1B^1$ and $A^1B^1B^1$. The evolution of the average densities of the cancer and normal cells when the intrinsic resistance is considered, suggest that, according to our numerical simulations, the combination ABA is more suitable. Whereas for the case of induced resistance, the scheme ABB is the best combination due to its low toxicity levels.

3.5 Conclusions

In this Chapter, we have presented discrete mathematical models of an aggressive-invasive cancer characterized by its heterogeneity, high proliferation and capacity to invade healthy tissue. These models are dynamically consistent with the continuous versions and their solutions can be computed with accuracy and with a low computational time. For small values of the mutation rate, cancer becomes more aggressive by modifying the evolution of the densities of cancer and normal cells. We corroborate that by considering the environmental acidification the tumor becomes more invasive. The model keeps the same qualitative behavior when cellular competitions are introduced. However, the combination of higher levels of competition with larger values of the coefficient of normal cell-acidification interaction affects negatively the tumor invasion. The application of chemotherapy is modeled by including important aspects such as induced resistance and drug toxicity. We analyze different types of resistance in order to evaluate their consequences on potential treatments. In the case when the induced resistance is presented then it is better to use treatments with few chemotherapy applications and the same occur when both types of resistance are presented. The worst case is when the cancer cells show intrinsic drug resistance. Finally, we establish different combinations of chemotherapy to identify a suitable scheme to eradicate or to reduce the growth of the tumor. As a consequence of our analysis we conclude that there are some feasible combinations of two drugs applied in different cycles but in general those treatments depend on the knowledge of several factors such as drug effectiveness, the type of resistance presented and the initial medical conditions of the patient.

Chapter 4

Conclusions and Future Research

In this dissertation, discrete mathematical models have been proposed to describe the growth dynamic of an aggressive cancerous tumor which have taken in consideration different characteristics of these types of cancers. This was achieved using the general methodology that consists of discretizing continuous models which describe the evolution of an aggressive cancerous tumor. In each modeling stage, it was necessary to develop a suitable, exact or nonexact nonstandard finite difference schemes dynamically consistent with the continuous model. This allowed us to obtain numerical solutions of our models with low computational time, showing an advantage compared with classic methods. Moreover, chemotherapy treatment with instantaneous and gradual effect was included in our discrete models. The challenge was to model important aspects such as drug resistance and toxicity that limits the use of this anticancer treatment.

In the first Chapter of this thesis, we focus mainly on modeling the characteristics of cell heterogeneity and high proliferation rates. The proposed models were systems of two difference equations which were obtained using an exact nonstandard finite difference scheme. Chemotherapy with instantaneous effect was included in the discrete models and also the drug resistance. According with our numerical simulations, the most relevant factor to eradicate the tumor was the drug B effectiveness. Moreover, the number of chemotherapy applications is lesser as the drug B effectiveness is greater. On the other side, the importance of the drug B effectiveness to eradicate the tumor led us to study the inclusion of the drug B toxicity in the effectiveness function. This was carried out implicitly and let us to determine the maximum allowed doses. Also, it was possible to determine the best chemotherapy scheme which was given by combinations of drugs A and B. In the case of $2T$ period, the best chemotherapy combination was $(AB)^2$ and in the case of $3T$ period was the chemotherapy combination $A^1A^1B^1$. Moreover, we could conclude that treatments with shorter periods between applications are more effectives.

In Chapter 2, we continued the study of our first model, but we focused on the cellular competition by the oxygen and other nutritional resources. This aspect was not taken in consideration in previous models. As a consequence of the inclusion of the new modeling terms, it was necessary to use a nonstandard finite difference scheme in order to obtain a discrete model. It was proven that the scheme is dynamically consistent with the continuous model. Another important modeling characteristic included in the models was the gradual effect of the chemotherapeutic treatment. We constructed a function which distribute the drug effect along a period between two drugs applications. This new feature made possible to have a more realistic model for the chemotherapy application in our discrete model. In order to determine the role of the competition in our model, we defined a treatment index depending on the toxicity and the used amount of the cytotoxic drugs. Our results points out that role of the competition in our model was relevant because this characteristic is fundamental to avoid treatments more aggressive especially for short treatments (neoadjuvant treatments). These models have provided useful information regarding the dynamics of tumor growth under chemotherapy treatment and how the success of treatments depend tightly on the effectiveness of drugs. Moreover, it let us compare and evaluate different two drug chemotherapy treatments in order to select a suitable treatment according to the specific effectiveness of drugs.

In Chapter 3, we dealt with discrete mathematical models of an invasive aggressive cancerous tumor that is characterized by cellular heterogeneity. As can be observed a major feature was introduced in this model, the ability of cancer cell to spread and invade to surrounding healthy tissue. It was achieved using a system difference equations of diffusion-reaction type. Other important modeling aspects incorporated in the system were an equation for the healthy cells, and other equation, for the environmental acidification. Following the general methodology to develop the discrete model, it was necessary to construct a nonstandard finite difference scheme and conditions were given for the dynamical consistency. Let us remark that nonstandard finite difference schemes for system of partial differential equations are scarce in the literature. Our results of the numerical simulations pointed out that the environmental acidification contributes to a faster invasion of the cancer. It also showed that the model keeps the qualitative behavior when the competition is introduced. However, the combination of higher levels of competition with larger values of the coefficient of normal cell-acidification interaction affects negatively the tumor invasion. A chemotherapy treatment with gradual effect was modeled by including important aspects such as drug resistance and toxicity. We evaluated the consequences on potential chemotherapy treatments by considering different types of resistance. Finally, we establish different combinations of chemotherapy to identify a suitable scheme to eradicate or to reduce the growth of the tumor.

Summarizing, our numerical simulations of discrete models reproduced different scenarios of the dynamical evolution of cancerous tumors depending on drug effectiveness functions and drug toxicity. These simulations have provided information about the importance of considering heterogeneity and cellular competition for nutritional resources. This suggests that deeper research on these features of aggressive cancers must be done because ignoring them could result in the prescription of more aggressive chemotherapy treatments for cancer patients.

Regarding future research after this work, there are some interesting projects that we may address and we briefly describe them as follows:

- After this theoretical study of aggressive cancerous tumors, one natural research direction is to model a specific type of cancer such as breast cancer as there is evidence of existence of intrinsic resistance to chemotherapy on breast cancer cells [30]. So we can address this type of cancer using the tools already developed.

- The study of a mathematical model that includes the immune system response is the most natural subsequent model. The immune response is the basic defense mechanism that cancer has to ”defeat” and it continues affecting the tumor growth. The main goal in this model will be to analyze how the immune response affects the cancer invasion, as well as, the selection of suitable treatment.

- As an extension of the previous project, we would like to address deeply the medical condition cause by drug toxicity, called neutropenia. It is defined as a decrement of neutrophils in the blood and a severe condition of this alters the response of the patient's immune system. It could result in aggressive infections which may be fatal for the patient. Our main interest is analyzing the dynamical evolution of the system, as well as, to determine effective chemotherapy schedules with lower risk for the patient, by taking in account the hematological toxicity (neutrophils amounts in the blood).

Appendix A

Construction of nonstandard finite difference equations

A.1 Discretization of ordinary differential equations of 1st and 2nd order

Nonstandard finite difference schemes emerged in 1987 with Ronald E. Mickens, since then these have been amply developed and successfully applied. We start by stating the definition for an exact discretization scheme. The following definition was given by Mickens and formalized by Lubuma [34]:

Definition A scheme is called a nonstandard finite difference scheme if at least one of the following conditions is satisfied,

- The classical denominator Δt or Δx of the discrete derivatives $\partial_{\Delta t} u_m^k$ or $\partial_{\Delta x} u_m^k$ is replaced by the nonstandard function $\phi(\Delta t)$ or $\phi(\Delta x)$ where

$$\phi(z) = z + O(z^2) \quad \textbf{when} \quad 0 < z \to 0.$$

- The nonlinear terms $r_{\Delta t, \Delta x}(u_m^k)$ are approximated by non-local suitable functions ($u^2(k\Delta t, m\Delta x) \approx u_{m-1}^k u_m^k$).

Remark When a scheme has a truncation error zero, it is called an exact scheme or exact nonstandard finite difference scheme.

In the following, we develop exact discretization schemes for basic equations which we will use to discretize our system.

Discretization of the exponential equation

We consider the simplest differential equation, the exponential equation,

$$\frac{du}{dt} = \lambda u; \quad u(t_0) = u_0, \tag{A.1.1}$$

where λ is a number not equal to 0. The solution of this equation is given by,

$$u(t) = u_0 e^{\lambda(t-t_0)}.$$

We assume that the initial condition is $u(t_k) = u_k$ and evaluating the solution in $k+1$, $u(t_{k+1}) = u_{k+1}$, we get that the equation (A.1.1) is equivalent to the following difference equation:

$$u_{k+1} = u(t_{k+1}) = u_k e^{\lambda(\Delta t)}, \tag{A.1.2}$$

where $\Delta t = t_{k+1} - t_k$. Subtracting u_k on both sides of the equation (A.1.2), multiplying by λ, and doing some algebraic manipulations, we get,

$$\frac{u_{k+1} - u_k}{(e^{\lambda \Delta t} - 1)/\lambda} = \lambda u_k. \tag{A.1.3}$$

With an analogous process, we obtain this equivalent equation,

$$\frac{u_{k+1} - u_k}{(1 - e^{-\lambda \Delta t})/\lambda} = \lambda u_{k+1}. \tag{A.1.4}$$

So, equations (A.1.3) and (A.1.4) correspond to two exact nonstandard finite difference schemes.

For these schemes the discrete representation for the first order derivative is,

$$\frac{du}{dt} \approx \frac{u_{k+1} - u_k}{\varphi(\Delta t)},$$

where

$$\varphi(\Delta t) = \frac{e^{\lambda \Delta t} - 1}{\lambda} \quad o \quad \varphi(\Delta t) = \frac{1 - e^{-\lambda \Delta t}}{\lambda}$$

and u can be replaced by u_k in the scheme (A.1.3) or by u_{k+1} in the scheme (A.1.4).

Discretization of the logistic equation

Consider the logistic growth equation,

$$\frac{du}{dt} = \lambda u(1-u), \quad \lambda > 0. \tag{A.1.5}$$

We deduce the exact nonstandard finite difference scheme solving the differential equation in the interval (t_k, t_{k+1}). To do this, we establish boundary conditions, $u(t_k) = u_k$ and $u(t_{k+1}) = u_{k+1}$. The differential equation (A.1.5) is equivalent to,

$$\frac{1}{u(1-u)}\frac{du}{dt} = \lambda,$$

and integrating from t_k to t_{k+1},

$$\int_{t_k}^{t_{k+1}} \frac{1}{u(1-u)}\frac{du}{d\eta}d\eta = \int_{t_k}^{t_{k+1}} \lambda d\eta,$$

we get,

$$\ln\frac{u(t_{k+1})}{1-u(t_{k+1})} - \ln\frac{u(t_k)}{1-u(t_k)} = \lambda(t_{k+1}-t_k),$$

given that $u(t_k) = u_k$, $u(t_{k+1}) = u_{k+1}$, and $\Delta t = t_{k+1} - t_k$, we rewrite the equation as,

$$\ln\frac{u_{k+1}}{1-u_{k+1}} - \ln\frac{u_k}{1-u_k} = \lambda(\Delta t),$$

which is equivalent to,

$$\frac{u_{k+1}(1-u_k)}{(1-u_{k+1})u_k} = e^{\lambda(\Delta t)},$$

that is,

$$u_{k+1}(1-u_k) = e^{\lambda(\Delta t)}u_k(1-u_{k+1}).$$

Subtracting u_k from both sides of the equation and doing some algebraic manipulations, the equation could be written as,

$$\frac{u_{k+1}-u_k}{\frac{e^{\lambda\Delta t}-1}{\lambda}} = \lambda u_k(1-u_{k+1}), \tag{A.1.6}$$

this corresponds to an exact nonstandard finite difference scheme for the logistical equation (A.1.5).

This scheme can be written in the following way, in which $u_k = u(t_k)$, with $t_k = k\Delta t$, for $k \in N_0$. Given $\varphi(\Delta t) = \frac{e^{\lambda \Delta t}-1}{\lambda}$, we propose an approximation of the first order derivative given by

$$\frac{du}{dt} \approx \frac{u_{k+1} - u_k}{\varphi(\Delta t)},$$

and we approximate the right hand side of the equation using nonlocal terms, u by u_k and $1 - u$ by $1 - u_{k+1}$.

Now, solving for u_{k+1}, we get the following difference equation,

$$u_{k+1} = \frac{(1 + \lambda\varphi(\Delta t))u_k}{1 + \lambda\varphi(\Delta t)u_k},$$

which preserves the positivity property, inasmuch as $\varphi(\Delta t) \geq 0$ for all Δt, and if $0 \leq u_m^k \leq 1$, we have $u_m^{k+1} \geq 0$ for all k. Now, it is easy to prove that given that $0 \leq u_m^k \leq 1$, then $u_m^{k+1} \leq 1$; thus it also preserves the bounding property. Moreover, this discretization has the same equilibrium solutions, then it can be concluded that the nonstandard finite difference scheme is dynamically consistent with the differential equation (A.1.5).

Discretization of a 2nd order differential equation

We consider the following homogeneous linear differential equation of 2nd order,

$$au_{xx} + bu_x + cu = 0, \tag{A.1.7}$$

we assume that its solution is of the form $u(x) = e^{\lambda x}$, then λ has to satisfy the following characteristic equation,

$$a\lambda^2 + b\lambda + c = 0.$$

We identify three cases that depend on the discriminant:

1. If $b^2 - 4ac > 0$, then the general solution of the differential equation $(A.1.7)$ has the form,
$$u(x) = K_1 e^{\lambda_1 x} + K_2 e^{\lambda_2 x}.$$

2. If $b^2 - 4ac = 0$, then the general solution is given by,
$$u(x) = K_1 e^{\lambda_1 x} + K_2 t e^{\lambda_1 x}.$$

3. If $b^2 - 4ac < 0$, then $\lambda_{1,2} = \alpha \pm i\beta$ the general solution is given by,

$$u(x) = K_1 e^{\alpha x} cos(\beta x) + K_2 e^{\alpha x} sin(\beta x).$$

We focus on the particular case of equation $(A.1.7)$ where $a > 0, b = 0, c \neq 0$. Thus, we only study the following two cases,

1. If $c < 0$, then $\lambda_1, \lambda_2 = \pm\rho$ and the solution is given by,

$$u(x) = K_1 e^{\rho x} + K_2 e^{-\rho x}, \quad \rho = \sqrt{\frac{c}{a}}.$$

2. If $c > 0$, then $\lambda_1, \lambda_2 = \pm i\sqrt{\frac{c}{a}}$ and the solution has the form,

$$u(x) = K_1 \cos(\rho x) + K_2 \sin(\rho x), \quad \rho = \sqrt{\frac{c}{a}}.$$

Now, in order to obtain the exact difference finite scheme, we propose to approximate the second derivative by means of $u_{xx} \approx \frac{u_{m+1} - 2u_m + u_{m-1}}{\psi(h)}$, and we determine $\psi(h)$, in a such way,

$$lim_{h\to 0} \frac{u_{m+1} - 2u_m + u_{m-1}}{\psi(x)} = u_{xx}. \tag{A.1.8}$$

In the first case, we define $u_m = u(x_m) = u(mh)$, then the solution could be written as,

$$\begin{aligned} u_{m+1} &= K_1 e^{\rho(m+1)h} + K_2 e^{-\rho(m+1)h}, \\ u_m &= K_1 e^{\rho mh} + K_2 e^{-\rho mh}, \\ u_{m-1} &= K_1 e^{\rho(m-1)h} + K_2 e^{-\rho(m-1)h}. \end{aligned} \tag{A.1.9}$$

From the solution, we have that

$$u_{xx} = \rho^2 K_1 e^{\rho x} + \rho^2 K_2 e^{-\rho x}.$$

Substituting $(A.1.9)$ in $(A.1.8)$ and solving for $\psi(h)$ we obtain that,

$$\psi(h) = \frac{4}{\rho^2} \sinh^2(\frac{\rho h}{2}). \tag{A.1.10}$$

In the second case, we define $u_m = u(x_m) = u(mh)$, whereby the solution could be written as,

$$\begin{aligned} u_{m+1} &= K_1 \cos(\rho(m+1)h) + K_2 \sin(\rho(m+1)h), \\ u_m &= K_1 \cos(\rho mh) + K_2 \sin(\rho mh), \\ u_{m-1} &= K_1 \cos(\rho(m-1)h) + K_2 \sin(\rho(m-1)h). \end{aligned} \tag{A.1.11}$$

From the solution, we have that

$$u_{xx} = \rho^2 K_1 \cos^2(\rho x) + \rho^2 K_2 \sin^2(\rho x).$$

Substituting $(A.1.11)$ in $(A.1.8)$ and solving for $\psi(h)$ we get,

$$\psi(h) = \frac{4}{\rho^2} \sin^2(\frac{\rho h}{2}). \tag{A.1.12}$$

These former schemes are built using analytical solutions of the differential equations. As the most of the models that arise in practice do not exist an exact scheme. However, exact schemes are used to build new schemes for more complex differential equation or differential equation systems.

A.2 Discretization of Partial Differential Equations

Discretization of Diffusion Equation

We consider the diffusion equation,

$$u_t = bu_{xx}, \quad b > 0.$$

The simplest scheme noted is the Euler explicit standard scheme which is given by the expression,

$$\frac{u_m^{k+1} - u_m^k}{\Delta t} = b[\frac{u_{m+1}^k - 2u_m^k + u_{m-1}^k}{(\Delta x)^2}], \quad m, n \in N_0.$$

This equation is equivalent to,

$$u_m^{k+1} = u_m^k(1 - 2bR) + bR(u_{m+1}^k + u_{m-1}^k)$$

where $R = \frac{\Delta t}{\Delta x^2}$ is known as the relation of parabolic mesh. The approach values of the function over the mesh points is given by $u_m^k = u(x_m, t_k)$ with $x_m = m\Delta x$ and $t_k = k\Delta t \quad m, n \in N_0$. This equation required for positivity $1 - 2bR \geq 0$, that is, $\Delta t \leq \frac{(\Delta x^2)}{2b}$, which is also a smoothness and stability condition.

Discretization of Logistic Equation

We consider the logistic equation,

$$u_t = f(u) = r_1 u(1-u), \quad r_1 > 0.$$

If $u_x = 0$, then there exists an exact scheme for this equation, which is given by,

$$\frac{u^{k+1} - u^k}{\varphi(\Delta t)} = r_1 u^k (1 - u^{k+1}), \quad \varphi(\Delta t) = \frac{e^{r_1 \Delta t} - 1}{r_1},$$

where $u_m^k = u(t_k)$ with $t_k = k\Delta t \quad k \in N_0$. Then, it based on this scheme we propose the following nonstandard discretization scheme for the general case with $u = u(x,t)$. Given $\varphi(\Delta t) = \frac{e^{r_1 \Delta t} - 1}{r_1} = \Delta t + O(\Delta t)$, we replace u_t by $\frac{u_m^{k+1} - u_m^k}{\varphi(\Delta t)}$, N by N_m^k and $1 - N$ by $1 - N_m^{k+1}$, that is, we use a nonlocal approach for nonlinear for nonlinear terms that is found in the right side of equation. Then, the discretized equation obtained is,

$$\frac{u_m^{k+1} - u_m^k}{\varphi(\Delta t)} = r_1 u_m^k (1 - u_m^{k+1}), \quad \varphi(\Delta t) = \frac{e^{r_1 \Delta t} - 1}{r_1}$$

where $u_m^k = u(x_m, t_k)$ with $x_m = m\Delta x$ and $t_k = k\Delta t \quad m, n \in N_0$. This equation is equivalent to,

$$u_m^{k+1} = \frac{(1 + r_1 \varphi(\Delta t)) u_m^k}{1 + r_1 \varphi(\Delta t) u_m^k},$$

that equation preserves the positivity property, given that $\varphi(\Delta t) \geq 0$ for all Δt and if $0 \leq u_m^k \leq 1$, $u_m^{k+1} \geq 0$ for all k. Now, it is easy to prove that given that $0 \leq u_m^k \leq 1$, then $u_m^{k+1} \leq 1$ so that it preserves also the bounded property. Further as it preserves the equilibrium solutions for the stationary case, then it could conclude that nonstandard finite difference scheme is dynamically consistent with partial differential equation.

A.3 Discretization of Partial Differential Equations Systems

We are interested in developing a nonstandard finite difference scheme for the partial differential equation system (3.6) which is given by,

$$\begin{aligned}
\frac{\partial T_1(x,t)}{\partial t} &= g_1(T_1) - \beta_1 T_1 T_2 - \rho T_1 - \gamma_1 N T_1 + D_1 \nabla^2 T_1, \\
\frac{\partial T_2(x,t)}{\partial t} &= g_2(T_2) - \beta_2 T_1 T_2 + \rho T_1 - \delta_1 N T_2 + D_2 \nabla^2 T_2, \\
\frac{\partial N(x,t)}{\partial t} &= g_3(N) - \gamma_2 N T - \delta_2 N T_2 - \sigma L N, \\
\frac{\partial L(x,t)}{\partial t} &= \xi(T_1 + T_2) - r_4 L + D_4 \nabla^2 L,
\end{aligned}$$

where $g_j(X) = r_j X(1 - X)$ for $j = 1, 2, 3$. For more details about the description of this model see Chapter 3.

Let us remark that there barely exist nonstandard schemes for partial differential equation systems. However, we construct a scheme that preserves the following two properties. First, the discrete system preserves the same fixed points and the dynamic stability of the associated space independent system. Second, the solutions of the discrete system keep positivity properties.

Algorithm for the construction of the NSFD scheme

The algorithm that we use to develop a nonstandard finite difference scheme of the partial differential equation system consists of:

1. Firstly, we propose a nonstandard finite difference scheme for the system of partial differential equations that correspond to the invasive heterogeneous cancerous tumor.

2. Secondly, we propose a nonstandard finite difference equation for normal cells and the acidification equation using the subequations method.

3. After that, we propose a nonstandard finite difference scheme for the original system using the previous schemes and approximating the nonlinear terms by means of non local terms.

Discretization of an invasive heterogeneous cancer model

Now, we focus on the discretization of the model that describes the growth dynamic of an invasive heterogeneous cancerous tumor,

$$\frac{\partial T_1}{\partial t} = r_1 T_1(1-T_1) - \beta_1 T_1 T_2 - \rho T_1 + D_1 \frac{\partial^2 T_1}{\partial x^2},$$
$$\frac{\partial T_2}{\partial t} = r_2 T_2(1-T_2) - \beta_2 T_1 T_2 + \rho T_1 + D_2 \frac{\partial^2 T_2}{\partial x^2}.$$

In the case $\rho = 0$, the former system consists of two Fisher equations coupled by means of the competition terms of Lotka-Volterra type. A scheme of the Fisher equation was given in the previous section and we use it to propose the following discretization scheme. We approximate the first derivative by means of

$$\frac{\partial T_i}{\partial t} \approx \frac{T_{im}^{k+1} - T_{im}^{k}}{\phi_i(\Delta t)} \quad and \quad \frac{\partial^2 T_i}{\partial t^2} \approx \frac{T_{im-1}^{k} - 2T_{im}^{k} + T_{im+1}^{k}}{\psi_i(\Delta x)}, \quad i = 1, 2, ...$$

where $\varphi_i(\Delta t) = \frac{e^{r_i \Delta t} - 1}{r_i}$ and $\psi_i(\Delta x) = \frac{4D_i}{r_i} \sin^2(\frac{\sqrt{\frac{r_i}{D_i}}\Delta x}{2})$, with $i = 1, 2$. Moreover, $\rho T_1 \approx \rho {T_1}_m^k$ and the nonlinear competition terms are approximated using nonlocal terms as follow, $\beta_1 T_1 T_2 \approx \beta_1 {T_1}_m^{k+1} {T_2}_m^k$ and $\beta_2 T_1 T_2 \approx \beta_2 {T_1}_m^k {T_2}_m^{k+1}$.

Using the nonstandard finite difference schemes stated, we get,

$$\frac{{T_1}_m^{k+1} - {T_1}_m^k}{\varphi_1(\Delta t)} = r_1 {T_1}_m^k (1 - {T_1}_m^{k+1}) - \beta_1 {T_1}_m^{k+1} {T_2}_m^k - \rho {T_1}_m^k + D_1 \frac{{T_1}_{m-1}^k - 2{T_1}_m^k + {T_1}_{m+1}^k}{\psi_1(\Delta x)},$$
$$\frac{{T_2}_m^{k+1} - {T_2}_m^k}{\varphi_2(\Delta t)} = r_1 {T_2}_m^k (1 - {T_2}_m^{k+1}) - \beta_2 {T_1}_m^k {T_2}_m^{k+1} + \rho {T_1}_m^k + D_2 \frac{{T_2}_{m-1}^k - 2{T_2}_m^k + {T_2}_{m+1}^k}{\psi_2(\Delta x)},$$

from which we can get ${T_1}_m^{k+1}$ and ${T_2}_m^{k+1}$, where $R_1 = \frac{\varphi_1(\Delta t)}{\psi_1(\Delta x)}$ y $R_2 = \frac{\varphi_2(\Delta t)}{\psi_2(\Delta x)}$,

$$\begin{aligned} {T_1}_m^{k+1} &= \frac{{T_1}_m^k (1 + r_1\varphi_1(\Delta t) - \rho\varphi_1(\Delta t) - 2D_1R_1) + D_1R_2({T_1}_{m-1}^k + {T_1}_{m+1}^k)}{1 + \varphi_1(\Delta t)(\beta_1 {T_2}_m^k + r_1 {T_1}_m^k)}, \\ {T_2}_m^{k+1} &= \frac{{T_2}_m^k (1 + r_2\varphi_2(\Delta t) - 2D_2R_2) + \rho\varphi_2(\Delta t){T_1}_m^k + D_2R_2({T_2}_{m-1}^k + {T_2}_{m+1}^k)}{1 + \varphi_2(\Delta t)(\beta_2 {T_1}_m^k + r_2 {T_2}_m^k)}. \end{aligned} \tag{A.3.1}$$

This discrete system has positive solutions if Δt is given by

$$\min\left\{\frac{1}{r_1}\ln\left(\frac{r_1\psi_1(\Delta x)}{(2+\mu_1)D_1-(r_1-\rho)\psi_1(\Delta x)}+1\right),\frac{1}{r_2}\ln\left(\frac{r_2\psi_2(\Delta x)}{(2+\mu_2)D_2-r_2\psi_2(\Delta x)}+1\right)\right\},$$

where μ_i, $i=1,2$ are given positive constants satisfying $\mu_1 > \frac{(r_1-\rho)\Delta x^2}{D_1}-2$ and $\mu_2 > \frac{r_2\Delta x^2}{D_2}-2$.

On the other hand, the space independent system is given by

$$T_{1_m}^{k+1}=\frac{T_{1_m}^{k}(1+r_1\varphi_1(\Delta t)-\rho\varphi_1(\Delta t))}{1+\varphi_1(\Delta t)(\beta_1 T_{2_m}^{k}+r_1 T_{1_m}^{k})},$$
$$T_{2_m}^{k+1}=\frac{T_{2_m}^{k}(1+r_2\varphi_2(\Delta t)+\rho\varphi_2(\Delta t))}{1+\varphi_2(\Delta t)(\beta_2 T_{1_m}^{k}+r_2 T_{2_m}^{k})}.$$

In the case $\rho=0$, the proposed scheme becomes in the Liu and Elaydi scheme for the the Lotka-Volterra competence system. Then, continuous and discrete systems have the same fixed points and their dynamic stability have already been proved in [34].

Discretization of the healthy cells

We consider that healthy cells grow with a logistic growth rate,

$$\frac{\partial N}{\partial t}=r_1 N(1-N).$$

According to discretization of the logistic equation described in the above section, this equation is discretized as,

$$\frac{N_m^{k+1}-N_m^k}{\varphi(\Delta t)}=r_3 N_m^k(1-N_m^{k+1}),\quad \varphi(\Delta t)=\frac{e^{r_3\Delta t}-1}{r_3},$$

where $N_m^k = N(x_m,t_k)$ with $x_m = m\Delta x$ and $t_k = k\Delta t \quad m,k \in N_0$. Such equation is equivalent to,

$$N_m^{k+1}=\frac{(1+r_3\varphi(\Delta t))N_m^k}{1+r_3\varphi(\Delta t)N_m^k},$$

this equation preserves the positivity property, given that $\varphi(\Delta t)\geq 0$ for all Δt and if $0\leq N_m^0\leq 1$, then, we have $0\leq N_m^{k+1}\geq 1$ for all k.

Discretization of the medium acidification equation

The following equation models medium acidification,

$$\frac{\partial L}{\partial t}=-\xi L+D_4\frac{\partial^2 L}{\partial x^2}. \tag{A.3.2}$$

Two subequations of this partial differential equation arise when $\frac{\partial L}{\partial t} = 0$ and $\frac{\partial^2 L}{\partial x^2} = 0$. This is,

$$\frac{\partial L}{\partial t} = -\xi L,$$

and

$$0 = -\xi L + D_4 \frac{\partial^2 L}{\partial x^2}.$$

Both equations have exact finite difference schemes which we developed in the first section of this appendix. These are:

$$\frac{L^{k+1} - L^k}{\varphi_4(\Delta t)} = -\xi L^{k+1}, \varphi_2(\Delta t) = \frac{e^{\xi \Delta t} - 1}{\xi},$$

$$D_4 \frac{L_{m+1} - 2L_m + L_{m-1}}{\psi_4(\Delta x)} - \xi L_m = 0, \psi_4(\Delta x) = \frac{4D_4}{\xi} \sinh^2(\frac{\sqrt{\frac{\xi}{D_4}}\Delta x}{2}).$$

By combining both equations, we have

$$\frac{L_m^{k+1} - L_m^k}{\varphi_4(\Delta t)} = D_4 \frac{L_{m+1}^k - 2L_m^k + L_{m-1}^k}{\psi_4(\Delta x)} - \xi L_m^{k+1},$$

where $R_4 = \frac{\varphi_4(\Delta t)}{\psi_4(\Delta x)}$. Now, solving for L_m^{k+1} we obtain an explicit discrete equation,

$$L_m^{k+1} = \frac{(1 - 2D_4 R_4) L_m^k + D_4 R_4 (L_{m+1}^k + L_{m-1}^k)}{1 + \xi \varphi_4(\Delta t)}.$$

In order that the solutions of the discrete equation preserve the positivity it is necessary that

$$\Delta t = \frac{1}{\xi} ln(\xi \varphi_4(\Delta t) + 1).$$

Summarizing, we start the discretization process by subdividing the domain into a rectangular mesh of equal rectangles of sides Δt and Δx. Let us denote $T_{1m}^k = T_1(x_m, t_k)$, $T_{2m}^k = T_2(x_m, t_k)$, $N_m^k = N(x_m, t_k)$, $L_m^k = L(x_m, t_k)$ where $x_m = m\Delta x$ and $t_k = k\Delta t$ for $m, k \in \mathbb{N}$. We have the following approximation of the first temporal derivative,

$$\partial_t^{(1)} T_{im}^k \approx \frac{T_{im}^{k+1} - T_{im}^k}{\varphi_i(\Delta t)},\ \partial_t^{(1)} N_m^k \approx \frac{N_m^{k+1} - N_m^k}{\varphi_3(\Delta t)},\ \partial_t^{(1)} L_m^k \approx \frac{L_m^{k+1} - L_m^k}{\varphi_4(\Delta t)}, i = 1, 2,$$

with $\varphi_i(\Delta t) = \frac{e^{r_i \Delta t} - 1}{r_i}, \quad i = 1, 2, 3, 4$. The diffusion terms are approximated as

$$\partial_x^{(2)} T_{im}^k \approx \frac{T_{im-1}^k - 2T_{im}^k + T_{im+1}^k}{\psi_i(\Delta t)}, \quad \partial_x^{(2)} L_m^k \approx \frac{L_{m-1}^k - 2L_m^k + L_{m+1}^k}{\psi_4(\Delta t)},$$

where $\psi_i(\Delta t) = \frac{4}{\rho_i^2}\sin^2(\rho_i \frac{\Delta x}{2})$, and $\psi_4(\Delta t) = \frac{4}{\rho_4^2}\sinh^2(\rho_4 \frac{\Delta x}{2})$, with $\rho_i = \sqrt{\frac{r_i}{D_i}}$, $i = 1, 2, 4$. Such approximations have appropriate numerical properties for several equations [24]. The nonlinear terms are approximated by nonlocal terms as,

$$r_i T_i(1 - T_i)_m^k \approx r_i T_{im}^k (1 - T_{im}^k), \quad (\beta_1 T_2 + \gamma_1 N) T_{1m}^k \approx (\beta_1 T_{2m}^k + \gamma_1 N_m^k) T_{1m}^{k+1},$$

$$r_3 N(1 - N)_m^k \approx r_3 N_m^k (1 - N_m^k), \quad (\beta_2 T_1 + \delta_1 N) T_{2m}^k \approx (\beta_2 T_{1m}^k + \delta_1 N_m^k) T_{2m}^{k+1},$$

$$(\gamma_2 T_1 + \delta_2 T_2 + \sigma L) N_m^k \approx (\gamma_2 T_{1m}^k + \delta_2 T_{2m}^k + \sigma L_m^k) N_m^{k+1}.$$

The linear terms are approximated as:

$$\rho T_{1m}^k \approx \rho T_{1m}^k, \quad r_4 L_m^k \approx r_4 L_m^{k+1}, \quad \xi(T_1 + T_2)_m^k \approx \xi(T_{1m}^k + T_{2m}^k).$$

Based on the deduction of nonstandard finite difference schemes obtained for each equation, and by solving for T_{1m}^{k+1}, T_{2m}^{k+1}, N_m^{k+1} and L_m^{k+1}, we get the following discrete system, where $R_i = \frac{\varphi_i(\Delta t)}{\psi_i(\Delta x)}, \quad i = 1, 2, 4,$

$$\begin{aligned}
T_{1m}^{k+1} &= \frac{(1 + (r_1 - \rho)\varphi_1(\Delta t) - 2D_1 R_1) T_{1m}^k + D_1 R_1 (T_{1m-1}^k + T_{1m+1}^k)}{1 + \varphi_1(\Delta t)(r_1 T_{1m}^k + \beta_1 T_{2m}^k + \gamma_1 N_m^k)}, \\
T_{2m}^{k+1} &= \frac{(1 + r_2\varphi_2(\Delta t) - 2D_2 R_2) T_{2m}^k + \rho\varphi_1(\Delta t) T_{1m}^k + D_2 R_2 (T_{2m-1}^k + T_{2m+1}^k)}{1 + \varphi_2(\Delta t)(r_2 T_{2m}^k + \beta_2 T_{1m}^k + \delta_1 N_m^k)}, \\
N_m^{k+1} &= \frac{(1 + \varphi_3(\Delta t) r_3) N_m^k}{1 + \varphi_3(\Delta t)(r_3 N_m^k + \gamma_2 T_{1m}^k + \delta_2 T_{2m}^k + \sigma L_m^k)}, \\
L_m^{k+1} &= \frac{(1 - 2D_4 R_4) L_m^k + \xi\varphi_4(\Delta t)(T_{1m}^k + T_{2m}^k) + D_4 R_4 (L_{m-1}^k + L_{m+1}^k)}{1 + r_4\varphi_4(\Delta t)}.
\end{aligned} \tag{A.3.3}$$

Appendix B

Equilibria and their stabilities for the space independent system

Let us now show that the space independent continuous system associated with the system (3.6) has the same properties as its counterpart discrete system. The continuous model that describes the growth dynamic of an invasive cancerous tumor is given by

$$\begin{aligned}
\frac{\partial T_1(x,t)}{\partial t} &= g_1(T_1) - \beta_1 T_1 T_2 - \rho T_1 - \gamma_1 N T_1 + D_1 \nabla^2 T_1, \\
\frac{\partial T_2(x,t)}{\partial t} &= g_2(T_2) - \beta_2 T_1 T_2 + \rho T_1 - \delta_1 N T_2 + D_2 \nabla^2 T_2, \\
\frac{\partial N(x,t)}{\partial t} &= g_3(N) - \gamma_2 N T - \delta_2 N T_2 - \sigma L N, \\
\frac{\partial L(x,t)}{\partial t} &= \xi(T_1 + T_2) - r_4 L + D_4 \nabla^2 L,
\end{aligned} \tag{B.0.1}$$

where $g_j(X) = r_j X(1-X)$ for $j = 1, 2, 3$. For more details about the description of this model see Chapter 3. The space independent system associated with the system $(B.0.1)$ consists of four ordinary differential equations,

$$\begin{aligned}
\frac{dT_1}{\partial t} &= r_1 T_1(1 - T_1) - \beta_1 T_1 T_2 - \rho T_1 - \gamma_1 N T_1, \\
\frac{dT_2}{\partial t} &= r_2 T_2(1 - T_2) - \beta_2 T_1 T_2 + \rho T_1 - \delta_1 N T_2, \\
\frac{dN}{\partial t} &= r_3 N(1 - N) - \gamma_2 N T_1 - \delta_2 N T_2 - \sigma L N, \\
\frac{dL}{\partial t} &= \xi(T_1 + T_2) - r_4 L.
\end{aligned} \tag{B.0.2}$$

The equilibria of the previous continuous system are the roots of the equations given by the right hand sides of (3.9) equal to zero, which are exactly the same equations for the discrete system when $\varphi_1(\Delta t) = \varphi_2(\Delta t)$. The equilibrium points of this system are: $P_1 = (0, 0, 0, 0)$ that represents one case of death so it is easy to verify that this equilibrium point is unstable. The equilibrium point $P_2 = (0, 1, 0, \frac{\xi}{r_4})$, represents an invasive type II tumor, that is stable when $r_1 < \beta_1 + \rho$ and $r_3 < \delta_2 + \sigma\frac{\xi}{r_4}$. The following equilibrium point $P_3 = (0, 0, 1, 0)$ represents a health condition and this is stable when $r_1 < \rho + \gamma_1$ and $r_2 < \delta_1$. Another equilibrium point has the form $P_4 = (0, a, f(a), \frac{\xi}{r_4}a)$, and represents the coexistence between type II cancer cells and normal cells, where $a = (r_3(\delta_1 - r_2))(\delta_1(\delta_2 + \sigma\frac{\xi}{r_4}) - r_2r_3)^{-1}$, $f(a) = \frac{r_2}{\delta_1}(1-a)$. There are two equilibrium points that have a form $P_{5,6} = (g(b), b, 0, h(b))$, which represents an invasive heterogeneous tumor that produces environmental acidification. b is such as $(a_1\beta_2 - r_2)b^2 + (r_2 - \beta_2 a_0 + \rho a_1)b + a_0 = 0$ is satisfied and $g(b) = a_1b + a_0$, $h(b) = \frac{\xi}{r_4}(g(b) + b)$, with $a_1 = -\beta_1 r_1^{-1}$, $a_0 = (r_1 - \rho)r_1^{-1}$. There are two more equilibrium points of form $P_{7,8} = (j(c), c, k(c), l(c))$ that represent coexistence equilibrium points between the heterogeneous tumor and normal cell in an acidified environment. Here, c is such as $(\beta_2 b_1 - r_2 - \delta_1 a_1 r_3^{-1} + \delta_1 a_2 r_3^{-1})c^2 + (r_2 - \beta_2 b_0 - \rho b_1 - \delta_1 + \delta_1 a_1 r_3^{-1} b_0)c + \rho b_0 = 0$, $j(c) = b_0 - b_1 c$, $k = 1 - a_1 r_3^{-1} f(c) - a_2 r_3^{-1} c$, $l(b) = \frac{\xi}{r_4}(j(c) + c)$ are satisfied. Where $a_1 = \gamma_2 + \sigma\frac{\xi}{r_4}$, $a_2 = \delta_2 + \sigma\frac{\xi}{r_4}$, $b_0 = r_3(r_2 - \rho - \gamma)(r_1r_3 - a_1\gamma_1)^{-1}$, $b_1 = (\beta_1 r_3 - a_2\gamma_1)(r_1r_3 - a_1\gamma_1)^{-1}$.

In the following, we describe in more detail the analysis of the stability of the equilibrium points. First, we determine the Jacobian Matrix,

$$J = \begin{pmatrix} r_1 - 2r_1T_1 - \beta_1T_2 - \rho - \gamma_1 N & -\beta T_1 & -\gamma_1 T_1 & 0 \\ -\beta_2 T_2 + \rho & r_2 - 2r_2T_2 - \beta_2 T_1 - \delta_1 N & -\delta_1 T_2 & 0 \\ -\gamma_2 N & -\delta_2 N & r_3 - 2r_3 N - \gamma_2 T_1 - \delta_2 T_2 - \sigma L & -\sigma N \\ \xi & \xi & 0 & -r_4 \end{pmatrix}$$

.

Now, for the equilibrium point $P_1 = (0, 0, 0, 0)$,

$$J|_{P_1} = \begin{pmatrix} r_1 - \rho & 0 & 0 & 0 \\ \rho & r_2 & 0 & 0 \\ 0 & 0 & r_3 & 0 \\ \xi & \xi & 0 & -r_4 \end{pmatrix}$$

. The eigenvalues are $\lambda_1 = r_1 - \rho$, $\lambda_2 = r_2 > 0$, $\lambda_3 = r_3 > 0$, and $\lambda_4 = -r_4 < 0$. Then the equilibrium point P_1 is unstable.

For the equilibrium point $P_2 = (0, 1, 0, \xi/r_4)$,

$$J|_{P_2} = \begin{pmatrix} r_1 - \beta_1 - \rho & 0 & 0 & 0 \\ -\beta_2 + \rho & -r_2 & -\delta_1 & 0 \\ 0 & 0 & r_3 - \delta_2 - \sigma\frac{\xi}{r_4} & 0 \\ \xi & \xi & 0 & -r_4 \end{pmatrix}$$

. To get the characteristic polynomial,

$$p(\lambda) = \begin{vmatrix} r_1 - \beta_1 - \rho - \lambda & 0 & 0 & 0 \\ -\beta_2 + \rho & -r_2 - \lambda & -\delta_1 & 0 \\ 0 & 0 & r_3 - \delta_2 - \sigma\frac{\xi}{r_4} - \lambda & 0 \\ \xi & \xi & 0 & -r_4 - \lambda \end{vmatrix}$$

, the characteristic polynomial is,

$$p(\lambda) = (r_1 - \beta_1 - \rho - \lambda)(-r_2 - \lambda)(r_3 - \delta_2 - \sigma\frac{\xi}{r_4} - \lambda)(-r_4 - \lambda)$$

. The eigenvalues are $\lambda_1 = r_1 - \beta_1 - \rho$, $\lambda_2 = -r_2 < 0$, $\lambda_3 = r_3 - \delta_2 - \sigma\frac{\xi}{r_4}$ and $\lambda_4 = -r_4 < 0$. Then, the equilibrium point $(0, 1, 0, \xi/r_4)$ is stable when $0 < r_1 - \rho < \beta_1$ and $r_3 < \delta_2 + \sigma\frac{\xi}{r_4}$. The type II cancer total invasion is possible when the difference between the proliferation rate of type I cancer cells and the mutation rate is less than the competition coefficient against the other type of cancer cells, and also the affectation rate of normal cells due to acidification.

For the equilibrium point $P_3 = (0, 0, 1, 0)$,

$$J|_{P_3} = \begin{pmatrix} r_1 - \rho - \gamma_1 & 0 & 0 & 0 \\ \rho & r_2 - \delta_1 & 0 & 0 \\ -\gamma_2 & -\delta_2 & -r_3 & -\sigma \\ \xi & \xi & 0 & -r_4 \end{pmatrix}.$$

In this case, the characteristic polynomial is $p(\lambda) = (r_1 - \rho - \gamma_1 - \lambda)(r_2 - \delta_1 - \lambda)(-r_3 - \lambda)(-\xi - \lambda)$. The eigenvalues are $\lambda_1 = r_1 - \rho - \gamma_1$, $\lambda_2 = r_2 - \delta_1$, $\lambda_3 = -r_3 < 0$ and $\lambda_4 = -\xi < 0$. Then, the equilibrium point P_3 is stable when $0 < r_1 - \rho < \gamma_1$ and $r_2 < \delta_1$. That means, it is possible to achieve a healthy condition if the difference between the proliferation rate of type I cancer cells and the mutation rate is less than the affectation rate due the competition with normal cells. Moreover, the proliferation rate of type II cancer cells is less than the competition affectation.

Another equilibrium point has the form $P_4 = (0, a, f(a), \frac{\xi}{r_4}a)$ that represents the coexistence between type II cancer cells and normal cells, where $a = \frac{r_3(\delta_1 - r_2)}{\delta_1(\delta_2 + \sigma\frac{\xi}{r_4}) - r_2 r_3}$, $f(a) = \frac{r_2}{\delta_1}(1-a)$. Depending on the parameter values, this point could have all non-negative entries (equilibrium point that make biological sense).If $a > 1$ (conditions: $r2 > \delta_1$, $r_2 r_3 - \delta_1(\delta_2 + \sigma\frac{\xi}{r_4}) > 0$, $r_3 > \delta_2 + \sigma\frac{\xi}{r_4}$, particular case that we are studying) then $T_2^* > 1$ and $N^* < 0$. Also, if $a < 0$ then $N > 0$ (Both beyond our interest). If $0 < a \leq 1$, $N \geq 0$, (conditions: $r2 > \delta_1$, $r_2 r_3 - \delta_1(\delta_2 + \sigma\frac{\xi}{r_4}) > 0$, $r_3 < \delta_2 + \sigma\frac{\xi}{r_4}$, for big σ).

For the equilibrium point with the form $P_4 = (0, T_2^*, N^*, L^*)$,

$$J|_{P_5} = \begin{pmatrix} r_1 - \rho - \beta_1 T_2^* - \gamma_1 N^* & 0 & 0 & 0 \\ -\beta_2 T_2^* + \rho & r_2 - 2r_2 T_2^* - \delta_1 N^* & -\delta_1 T_2^* & 0 \\ -\gamma_2 N^* & -\delta_2 N^* & r_3 - 2r_3 N^* - \delta_2 T_2^* - \sigma L^* & -\sigma N^* \\ \xi & \xi & 0 & -r_4 \end{pmatrix}$$

, the characteristic polynomial is,

$$p(\lambda) = (r_1 - \rho - \beta_1 T_2^* - \gamma_1 N^* - \lambda) q(\lambda)$$

, where

$$q(\lambda) = \xi\delta_1\sigma T_2^* N^* + (-r_4 - \lambda)[(r_2 - 2r_2 T_2^* - \delta_1 N^* - \lambda)(r_3 - 2r_3 N^* - \delta_2 T_2^* - \sigma L^* - \lambda) - \delta_1\delta_2 T_2^* N^*]$$

. One eigenvalue of $p(\lambda)$ is $\lambda_1 = r_1 - \rho - \beta_1 T_2^* - \gamma_1 \frac{r_2}{\delta_1}(1 - T_2^*)$. According to the Routh-Hurwitz Criterion, the polynomial $q(\lambda)$ has three negative roots when

$$\alpha + \beta - \delta > 0, \quad \alpha\beta - \gamma + \alpha\delta + \beta\delta > 0, \quad \epsilon + \alpha\beta - \gamma > 0$$

and

$$(\alpha + \beta - \delta)(\alpha\beta - \gamma + \alpha\delta + \beta\delta) > \epsilon + \alpha\beta - \gamma$$

where $\alpha = -\beta_2 T_2^* + \rho$, $\beta = r_3 - 2r_3 N^* - \delta_2 T_2^* - \sigma L^*$, $\gamma = \delta_1\delta_2 T_2^* N^*$, $\delta = -r_4$ and $\epsilon = \xi\delta_1\sigma T_2^*, N^*$.

There are two equilibrium points that have a form $P_{5,6} = (g(b_{1,2}), b_{1,2}, 0, h(b_{1,2}))$, which represent an invasive heterogeneous tumor that produce environmental acidification. $b_{1,2}$ satisfy the quadratic equation $(a_1\beta_2 - r_2)b^2 + (r_2 - \beta_2 a_0 + \rho a_1)b + a_0 = 0$ ($g(b) = a_1 b + a_0$, $h(b) = \frac{\xi}{r_4}(g(b) + b)$, with $a_1 = -\beta_1 r_1^{-1}$, $a_0 = (r_1 - \rho)r_1^{-1}$). $b_{1,2} = -(r_2 - \beta_2 a_0 + \rho a_1) \pm \sqrt{(r_2 - \beta_2 a_0 + \rho a_1)^2 - 4(a_1\beta_2 - r_2)(a_0)}$

For the equilibrium point with the form $P_6 = (T_1^*, T_2^*, 0, L^*)$,

$$J|_{P_6} = \begin{pmatrix} r_1 - \rho - 2r_1 T_1^* - \beta_1 T_2^* & -\beta_1 T_1^* & -\gamma_1 T_1^* & 0 \\ -\beta_2 T_2^* + \rho & r_2 - 2r_2 T_2^* - \beta_2 T_1^* & -\delta_1 T_2^* & 0 \\ 0 & 0 & r_3 - \gamma_2 T_1^* - \delta_2 T_2^* - \sigma L^* & 0 \\ \xi & \xi & 0 & -r_4 \end{pmatrix}$$

, the characteristic polynomial is,

$$p(\lambda) = (-r_4 - \lambda)(r_3 - \gamma_2 T_1^* - \delta_2 T_2^* - \sigma L^* - \lambda)q(\lambda),$$

where

$$q(\lambda) = ((r_1 - \rho) - 2r_1 T_1^* - \beta_1 T_2^* - \lambda)(r_2 - 2r_2 T_2^* - \beta_2 T_1^* - \lambda) + \beta_1 T_1^*(-\beta_2 T_2^* + \rho)$$

.

Two eigenvalues are $\lambda_1 = -r_4 < 0$, $\lambda_2 = r_3 - \gamma_2 T_1^* - \delta_2 T_2^* - \sigma L^*$. Moreover, the polynomial $q(\lambda)$ has two negative roots when $(r_1 - \rho) + r_2 - (2r_1 + \beta_2)T_1^* - (\beta_1 - 2r_2)T_2^* < 0$ and $((r_1 - \rho) - 2r_1 T_1^* - \beta_1 T_2^*)(r_2 - 2r_2 T_2^* - \beta_2 T_1^*) - \beta_1 T_1^*(-\beta_2 T_2^* + \rho) > 0$. Then the equilibrium point is stable when the following conditions are provided: $r_3 < \gamma_2 T_1^* + \delta_2 T_2^* + \sigma L^*$,$(r_1 - \rho) + r_2 < (2r_1 + \beta_2)T_1^* + (\beta_1 - 2r_2)T_2^*$ and $((r_1 - \rho) - 2r_1 T_1^* - \beta_1 T_2^*)(r_2 - 2r_2 T_2^* - \beta_2 T_1^*) - \beta_1 T_1^*(-\beta_2 T_2^* + \rho) > 0$.

For the equilibrium point with the form $P_7 = (T_1^*, T_2^*, N^*, L^*)$,

$$J|_{P_7} = \begin{pmatrix} r_1 - 2r_1 T_1 - \beta_1 T_2 - \rho - \gamma_1 N & -\beta T_1 & -\gamma_1 T_1 & 0 \\ -\beta_2 T_2 + \rho & r_2 - 2r_2 T_2 - \beta_2 T_1 - \delta_1 N & -\delta_1 T_2 & 0 \\ -\gamma_2 N & -\delta_2 N & r_3 - 2r_3 N - \gamma_2 T_1 - \delta_2 T_2 - \sigma L & -\sigma N \\ \xi & \xi & 0 & -r_4 \end{pmatrix}$$

Unfortunately, it is not possible to determine the stability condition for some of the equilibrium points that we obtained analytically. However, these equilibrium points represent distinct interesting scenarios about how the cancerous tumor continues growing in the organism, whereby it is important to analyze the stability of these equilibrium points. Therefore, we focus on analyzing their stability numerically for the parameter values that we consider.

Its discrete counterpart is,

$$\begin{aligned} {T_1}^{k+1} &= \frac{{T_1}^k(1 + r_1\varphi_1(\Delta t) - \rho\varphi_1(\Delta t))}{1 + \varphi_1(\Delta t)(r_1 {T_1}^k + \beta_1 {T_2}^k + \gamma_1 N^k)}, \\ {T_2}^{k+1} &= \frac{{T_2}^k(1 + r_2\varphi_2(\Delta t)) + \rho\varphi_1(\Delta t){T_1}^k}{1 + \varphi_2(\Delta t)(r_2 {T_2}^k + \beta_2 {T_1}^k + \delta_1 N^k)}, \\ N^{k+1} &= \frac{N^k(1 + \varphi_3(\Delta t)r_3)}{1 + \varphi_3(\Delta t)(r_3 N^k + \gamma_2 {T_1}^k + \delta_2 {T_2}^k + \sigma L^k)}, \\ L^{k+1} &= \frac{L^k + r_4\varphi_4(\Delta t)({T_1}^k + {T_2}^k)}{1 + \xi\varphi_4(\Delta t)}. \end{aligned} \tag{B.0.3}$$

Now, to determine the equilibrium points of the discrete system, we have to solve the following system,

$$\begin{aligned}
\frac{T_1(1+r_1\varphi_1(\Delta t)-\rho\varphi_1(\Delta t))}{1+\varphi_1(\Delta t)(r_1T_1+\beta_1T_2+\gamma_1N)} &= T_1,\\
\frac{T_2(1+r_2\varphi_2(\Delta t))+\rho\varphi_1(\Delta t)T_1}{1+\varphi_2(\Delta t)(r_2T_2+\beta_2T_1+\delta_1N)} &= T_2,\\
\frac{N(1+\varphi_3(\Delta t)r_3)}{1+\varphi_3(\Delta t)(r_3N+\gamma_2T_1+\delta_2T_2+\sigma L)} &= N,\\
\frac{L+r_4\varphi_4(\Delta t)(T_1+T_2)}{1+\xi\varphi_4(\Delta t)} &= L,
\end{aligned} \tag{B.0.4}$$

that is equivalent to,

$$\begin{aligned}
T_1(1+r_1\varphi_1(\Delta t)-\rho\varphi_1(\Delta t)) &= T_1(1+\varphi_1(\Delta t)(r_1T_1+\beta_1T_2+\gamma_1N)),\\
T_2(1+r_2\varphi_2(\Delta t))+\rho\varphi_1(\Delta t)T_1 &= T_2(1+\varphi_2(\Delta t)(r_2T_2+\beta_2T_1+\delta_1N)),\\
N(1+\varphi_3(\Delta t)r_3) &= N(1+\varphi_3(\Delta t)(r_3N+\gamma_2T_1+\delta_2T_2+\sigma L)),\\
L+r_4\varphi_4(\Delta t)(T_1+T_2) &= L(1+\xi\varphi_4(\Delta t)),
\end{aligned} \tag{B.0.5}$$

i.e.

$$\begin{aligned}
T_1(\varphi_1(\Delta t)((r_1(1-T_1)-\beta_1T_2-\gamma_1N)-\rho)) &= 0,\\
T_2(\varphi_2(\Delta t)(\beta_2T_1+\delta_1N-r_2(1-T_2))) &= \rho\varphi_1(\Delta t)T_1,\\
N(\varphi_3(\Delta t)(r3(1-N)-\gamma_2T_1-\delta_2T_2-\sigma L)) &= 0,\\
r_4\varphi_4(\Delta t)(T_1+T_2) &= L(\xi\varphi_4(\Delta t)),
\end{aligned} \tag{B.0.6}$$

as $\varphi_i(\Delta t)>0$ for $i=1,2,3,4$. If we suppose $\varphi_1(\Delta t)=\varphi_2(\Delta t)$. We get,

$$\begin{aligned}
T_1(r_1(1-T_1)-\beta_1T_2-\gamma_1N-\rho) &= 0,\\
T_2(\beta_2T_1+\delta_1N-r_2(1-T_2)) &= \rho T_1,\\
N(r3(1-N)-\gamma_2T_1-\delta_2T_2-\sigma L) &= 0,\\
r_4(T_1+T_2) &= \xi L.
\end{aligned} \tag{B.0.7}$$

This system is equivalent to the set of null-surfaces of the continuous system ($B.0.2$). Therefore, the discrete system has the same equilibrium points as the continuous system if $\varphi_1(\Delta t)=\varphi_2(\Delta t)$ is satisfied.

Now, in order to analyze the stability of the equilibrium points of the discrete system, we obtain the Jacobian matrix of the system ($B.0.3$),

$$J=\begin{pmatrix}
j_{11} & j_{12} & j_{13} & 0\\
j_{21} & j_{22} & j_{23} & 0\\
j_{31} & j_{32} & j_{33} & j_{34}\\
\frac{\xi\varphi_4(\Delta t)}{1+r_4\varphi_4(\Delta t)} & \frac{\xi\varphi_4(\Delta t)}{1+r_4\varphi_4(\Delta t)} & 0 & \frac{1}{1+r_4\varphi_4(\Delta t)}
\end{pmatrix},$$

where

$$j_{11} = \frac{(1+(r_1-\rho)\varphi_1(\Delta t))[(1+\varphi_1(\Delta t)(r_1T_1+\beta_1T_2+\gamma_1N))-r_1\varphi_1(\Delta t)T_1]}{[1+\varphi_1(\Delta t)(r_1T_1+\beta_1T_2+\gamma_1N)]^2},$$
$$j_{12} = -\frac{\beta_1\varphi_1(\Delta t)T_1(1+(r_1-\rho)\varphi_1(\Delta t))}{[1+\varphi_1(\Delta t)(r_1T_1+\beta_1T_2+\gamma_1N)]^2},$$
$$j_{13} = -\frac{\gamma_1\varphi_1(\Delta t)T_1(1+(r_1-\rho)\varphi_1(\Delta t))}{[1+\varphi_1(\Delta t)(r_1T_1+\beta_1T_2+\gamma_1N)]^2},$$
$$j_{21} = \frac{\rho\varphi_1(\Delta t)(1+\varphi_2(\Delta t)(r_1T_2+\beta_1T_1+\delta_1N))-\beta_1\varphi_2(\Delta t)(\rho\varphi_1(\Delta t)T_1+(1+r_2\varphi_2(\Delta t))T_2)}{[1+\varphi_1(\Delta t)(r_1T_1+\beta_1T_2+\gamma_1N)]^2},$$
$$j_{22} = \frac{(1+r_2\varphi_2(\Delta t))[1+\varphi_2(\Delta t)(r_1T_2+\beta_1T_1+\delta_1N)-(\rho\varphi_1(\Delta t)T_1+(1+r_2\varphi_2(\Delta t))T_2)]}{[1+\varphi_1(\Delta t)(r_1T_1+\beta_1T_2+\gamma_1N)]^2},$$
$$j_{23} = -\frac{\delta_1\varphi_2(\Delta t)(\rho\varphi_1(\Delta t)T_1+(1+r_2\varphi_2(\Delta t))T_2)}{[1+\varphi_1(\Delta t)(r_1T_1+\beta_1T_2+\gamma_1N)]^2},$$
$$j_{31} = \frac{\gamma_2\varphi_3(\Delta t)N(1+r_3\varphi_3(\Delta t))}{[1+\varphi_3(\Delta t)(\gamma_2T_1+\delta_2T_2+r_3N+\sigma L)]^2},$$
$$j_{32} = -\frac{\delta_2\varphi_3(\Delta t)N(1+r_3\varphi_3(\Delta t))}{[1+\varphi_3(\Delta t)(\gamma_2T_1+\delta_2T_2+r_3N+\sigma L)]^2},$$
$$j_{33} = \frac{(1+r_3\varphi_3(\Delta t))[1+\varphi_3(\Delta t)(\gamma_2T_1+\delta_2T_2+r_3N+\sigma L)-r_3\varphi_3(\Delta t)N]}{[1+\varphi_3(\Delta t)(\gamma_2T_1+\delta_2T_2+r_3N+\sigma L)]^2},$$
$$j_{34} = -\frac{\sigma\varphi_3(\Delta t)N(1+r_3\varphi_3(\Delta t))}{[1+\varphi_3(\Delta t)(\gamma_2T_1+\delta_2T_2+r_3N+\sigma L)]^2}.$$

The Jacobian matrix for $P_1 = (0, 0, 0, 0)$ is,

$$J|_{P_1} = \begin{pmatrix} 1+(r_1-\rho)\varphi_1(\Delta t) & 0 & 0 & 0 \\ \rho\varphi_1(\Delta t) & 1+r_2\varphi_2(\Delta t) & 0 & 0 \\ 0 & 0 & 1+r_3\varphi_3(\Delta t) & 0 \\ \frac{\xi\varphi_4(\Delta t)}{1+r_4\varphi_4(\Delta t)} & \frac{\xi\varphi_4(\Delta t)}{1+r_4\varphi_4(\Delta t)} & 0 & \frac{1}{1+r_4\varphi_4(\Delta t)} \end{pmatrix},$$

then the eigenvalues are $\lambda_1 = 1 + (r_1 - \rho)\varphi_1(\Delta t)$, $\lambda_2 = 1 + r_2\varphi_2(\Delta t)$, $\lambda_3 = 1 + r_3\varphi_3(\Delta t)$ and $\lambda_4 = \frac{1}{1+r_4\varphi_4(\Delta t)}$. The fixed point $P_1 = (0, 0, 0, 0)$ of the discrete system $(B.0.3)$ is unstable since $|1 + (r_1 - \rho)\varphi_1(\Delta t)| > 1, |1 + r_2\varphi_2(\Delta t)| > 1, |1 + r_3\varphi_3(\Delta t)| > 1$ because of the parameters $r_1 - \rho, r_2, r_3$ are positive and also the functions $\varphi_i(\Delta t), \quad i = 1, ..4$.

The Jacobian matrix in $P_2 = (0, 1, 0, \frac{\xi}{r_4})$ is,

$$J|_{P_2} = \begin{pmatrix} \frac{1+(r_1-\rho)\varphi_1(\Delta t)}{1+\beta_1\varphi_1(\Delta t)} & 0 & 0 & 0 \\ \frac{(\rho-\beta_2)\varphi_1(\Delta t)}{1+r_2\varphi_1(\Delta t)} & 1-\frac{r_2\varphi_1(\Delta t)}{1+r_2\varphi_1(\Delta t)} & -\frac{\delta_1\varphi_1(\Delta t)}{1+r_2\varphi_1(\Delta t)} & 0 \\ 0 & 0 & \frac{1+r_3\varphi_3(\Delta t)}{1+\varphi_3(\Delta t)(\delta_2+\sigma\frac{\xi}{r_4})} & 0 \\ \frac{\xi\varphi_4(\Delta t)}{1+r_4\varphi_4(\Delta t)} & \frac{\xi\varphi_4(\Delta t)}{1+r_4\varphi_4(\Delta t)} & 0 & \frac{1}{1+r_4\varphi_4(\Delta t)} \end{pmatrix},$$

then the eigenvalues are $\lambda_1 = \frac{1+(r_1-\rho)\varphi_1(\Delta t)}{1+\beta_1\varphi_1(\Delta t)}$, $\lambda_2 = 1-\frac{r_2\varphi_1(\Delta t)}{1+r_2\varphi_1(\Delta t)}$, $\lambda_3 = \frac{1+r_3\varphi_3(\Delta t)}{1+\varphi_3(\Delta t)(\delta_2+\sigma\frac{\xi}{r_4})}$, $\lambda_4 = \frac{1}{1+r_4\varphi_4(\Delta t)}$. This fixed point $P_2 = (0, 1, 0, \frac{\xi}{r_4})$ of the discrete system $(B.0.3)$ is stable when $0 < r_1 - \rho < \beta_1, r_3 < \delta_2 + \sigma\frac{\xi}{r_4}$.

The Jacobian matrix in $P_3 = (0, 0, 1, 0)$ is,

$$J|_{P_3} = \begin{pmatrix} \frac{1+(r_1-\rho)\varphi_1(\Delta t)}{1+\gamma_1\varphi_1(\Delta t)} & 0 & 0 & 0 \\ \frac{\rho\varphi_1(\Delta t)}{1+\delta_1\varphi_1(\Delta t)} & \frac{1+r_2\varphi_1(\Delta t)}{1+\delta_1\varphi_1(\Delta t)} & 0 & 0 \\ -\frac{\gamma_2\varphi_3(\Delta t)}{1+r_3\varphi_3(\Delta t)} & -\frac{\delta_2\varphi_3(\Delta t)}{1+r_3\varphi_3(\Delta t)} & 1-\frac{r_3\varphi_3(\Delta t)}{1+r_3\varphi_3(\Delta t)} & -\frac{\sigma\varphi_3(\Delta t)}{1+r_3\varphi_3(\Delta t)} \\ \frac{\xi\varphi_4(\Delta t)}{1+r_4\varphi_4(\Delta t)} & \frac{\xi\varphi_4(\Delta t)}{1+r_4\varphi_4(\Delta t)} & 0 & \frac{1}{1+r_4\varphi_4(\Delta t)} \end{pmatrix},$$

then the eigenvalues are $\lambda_1 = \frac{1+(r_1-\rho)\varphi_1(\Delta t)}{1+\beta_1\varphi_1(\Delta t)}$, $\lambda_2 = \frac{1+r_2\varphi_1(\Delta t)}{1+\delta_1\varphi_1(\Delta t)}$, $\lambda_3 = \frac{1}{1+r_3\varphi_3(\Delta t)}$, $\lambda_4 = \frac{1}{1+r_4\varphi_4(\Delta t)}$. This fixed point $P_3 = (0, 0, 1, 0)$ of the discrete system $(B.0.3)$ is stable when $0 < r_1 - \rho < \gamma_1$ and $r_2 < \delta_1$.

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