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Mathematical Model of Gastric Cancer with Immunotherapy: Global Dynamics and Tumor Clearance Conditions

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Abstract. Gastric cancer has positioned itself among the leading causes of cancer death worldwide. Most of these tumors are gastric adenocarcinomas, which originate in the gastric mucosa from a chronic infection linked to H. Pylori bacterium. Traditional treatments are not entirely effective, however, there are high expectations of using the immunotherapies for gastric cancer treatment. Nevertheless, knowledge of the mechanisms of tumor evolution and their interactions with the immune system is limited. For this reason, we present a qualitative mathematical model of first-order Ordinary Differential Equations (ODEs), which describes some survival mechanisms of intestinal-type gastric adenocarcinoma and its interaction with the immune system, assuming that H. Pylori and cellular cannibalism influence the tumor growth. We study the local and global dynamics of the model and propose sufficient conditions in an immunotherapy treatment parameter to eradicate gastric cancer. Finally, we perform numerical simulations and discuss the biological implications of our results.

Keywords. Mathematical modelling, gastric adenocarcinoma, adoptive cellular immunotherapy, localizing domain, global stability.

1 Introduction

Currently, cancer-related rates of incidence, prevalence, and mortality at global level have increased considerably, the latter represents a problem for every health system. According to the incidence and mortality statistics from GLOBOCAN in 2020, approximately 19.3 million diagnoses and 9.9 million deaths were attributed to cancer [35]. Furthermore, according to statistics from the International Agency for Research on Cancer (IARC) [13], lung, colorectum, liver, stomach, and breast cancers were associated with the highest deaths that year.

The high percentage of detection in advanced or metastatic stages is one of the main factors that influence the survival of many types of cancer, as in the case of gastric cancer, which has one of the highest mortality rates worldwide [13].

Gastric cancer, often known as stomach cancer, is the third most common cause of cancer death [2, 13], the survival of affected patients rarely exceeds 12 months [33]. The highest incidence and mortality from gastric cancer occurs in developing countries that are part of Central and South America, as well as developed countries in East Asia, and Central and Eastern Europe [2].

The vast majority of malignant tumors of the stomach are adenocarcinomas produced in gastric epithelia where there is an uncontrolled proliferation of epithelial cells. Histologically, adenocarcinomas are classified into intestinal and diffuse types [2]. Intestinal type of gastric adenocarcinoma is the most usual in countries with a high incidence of gastric cancer [2]. The most common cause for the formation of this tumor is associated with a chronic bacterial infection of the gastric epithelium linked with *Helicobacter Pylori* (H. Pylori) [2, 37].

H. Pylori is a bacterium known for its association with chronic gastritis, peptic ulcers and the tumorigenesis of gastric adenocarcinomas [37]. It has been theorized that H. Pylori infection affects gastric epithelial cells, causing them to mutate and proliferate uncontrollably [5, 37]. H. Pylori successfully performs a persistent bacterial infection despite the presence of a rigorous immune response

that generally favors its colonization. Prolonged exposure to this bacterium can cause glandular atrophy or metaplasia, greatly increasing the risk of gastric cancer [37]. However, the action-specific mechanism of this bacterium in the tumor remains unclear [25].

Traditional gastric cancer treatments, such as surgery, radiotherapy, and chemotherapy are not entirely effective [2] and their results are not very encouraging during the metastatic phase. Another novel strategy is immunotherapy, which has been applied effectively and safely in patients with other types of tumors, generating significant interest for its application to treat gastric cancer [38]. Concerning the current types of immunotherapies, Adoptive Cellular Immunotherapy (ACI) is one of the most effective for the treatment of malignant tumors. This therapy works by injecting modified T cells at the tumor site, whose purpose is to stimulate an immune response. The modified T cells have the same impact as regular T cells in combating the immune evasion and suppression of gastric cancer cells. However, research is still needed to determine the best mode of treatment due to limited knowledge of the interactions between tumor evolution and the immune system [24, 38].

Cancer research is focused to some extent on tumor survival mechanisms such as immune evasion and suppression, angiogenesis, metastasis, and recently, cannibalism [3, 11, 27]. These mechanisms make cancer biology a complex process to understand. This is demonstrated in the problems surrounding laboratory tests and clinical trials for this disease [24, 30, 39]. Nonetheless, it has been shown that the application of biomathematics in oncology provides scientists and doctors a powerful tool that enables them to determine useful information on tumor growth and its response to diverse treatments [10]. Hence, assumptions are established to simplify the complexity of cancer and mathematical models may be formulated to achieve a qualitative view of this disease.

The tumor growth and its interaction with the immune system can be interpreted using a system of first-order ODEs and, through mathematical analysis and *in silico* experimentations, predictions are performed at different stages of cancer evolution as well as the response to treatments that would be difficult to reproduce in a real-life scenarios [10]. Many mathematical models of tumor growth are formulated from empirical data and clinical results, in order to fit the model to experimental data and obtain an adequate estimation for the parameters involved. Some examples of these types of models are [8, 21, 22]. Other models have been proposed without using empirical data, in order to capture the cancer complexity through the application of dynamical systems theory, chaos theory, control theory and game theory, among other approaches [10, 39]. Some examples of these models are [4, 9, 14, 23]. In general, the importance of these cancer models lies in studying the qualitative dynamics of tumor growth, analyze the critical parameters through a sensitivity and bifurcation analysis, and exploring numerous scenarios such as drug dosing and combination of treatments [8, 39].

In virtue of the application of biomathematics to investigate tumor-immune dynamics, the focus of our work is to analyze mathematically, the long-term dynamics of intestinal-type gastric adenocarcinoma and its interaction with the immune system under ACI treatment. Although, literature on mathematical models that generally describe these interactions is limited, we propose a mathematical model composed of three nonlinear first-order ODEs, capable of reflecting tumor response when considering an immunotherapy treatment application. The model consists of three types of cell populations: gastric adenocarcinoma cells (gastric cancer cells), antigen-presenting cells (dendritic cells), and effector cells of the adaptive immune response (T cells). Furthermore, we cover interesting aspects such as cell cannibalism and the prolonged presence of H. Pylori that could stimulate tumor growth and survival beyond its initial carrying capacity. The model was designed based on set of assumptions describing tumor-immune dynamics and treatment application. In order to study the qualitative properties of our model, we analyzed its global dynamics by appliying the Localization of Compact Invariant Sets (LCIS) method [18, 19, 34] and stability theories such as the direct Lyapunov method and the LaSalle's invariance principle [16]. This approach allows us to establish sufficient conditions on the ACI treatment to eliminate the gastric cancer cell population. We expect our work to

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be helpful in better understanding the dynamics of gastric cancer and the effect of immunotherapy on its long-time evolution, which could lead to the design of personalized strategies for treatment administration.

The remainder of this paper proceeds as follows. In section 2 we show the assumptions for the model formulation and describe each equation. In section 3, we analyze the stability of some equilibrium points. In section 4 we provide the mathematical preliminaries on the LCIS method and compute the bounds of the so-called localizing domain. In section 5, we establish conditions for the elimination of gastric cancer cell population with the imunotherapy treatment. In section 6, we illustrate the results of our analysis by performing numerical simulations and discuss the biological implications. Finally, the conclusions of our results are given in section 7.

2 Mathematical Model

The limited efficacy of gastric cancer treatments has promoted research for new strategies across different areas of science and engineering. Due to the usefulness of the biomathematics to modelling and analyzing oncological dynamics, we decided to propose a qualitative mathematical model in order to investigate the response of intestinal-type gastric adenocarcinoma to ACI treatment. In this way, we expect to provide useful information concerning gastric cancer evolution and the effects of the ACI treatment. It should be noted that the model takes place on a cellular scale and it was formulated to describe some survival mechanisms in the gastric adenocarcinoma growth. In order to construct our model, assumptions are established which we explain in detail in the following subsection, as well as the description of each equation and all parameters.

2.1 Biological Assumptions

The biological assumptions made are based on literature concerning gastric cancer biology, tumor immunology and mathematical oncology. The assumptions are as follows:

1. In the absence of an immune response and a proper treatment, the gastric adenocarcinoma grows logistically, as this is the most accepted growth law to describe a solid tumor [10].

2. There is evidence in [3, 11] to support the statement that gastric cancer cells cannibalize neutrophils. Further, in other tumor types, malignant cells have also been shown to cannibalize other effector cells such as cytotoxic T cells [11, 27]. Therefore, cannibalism is considered as a mechanism to suppress the immune response.

3. There is an abnormal proliferation of gastric epithelial cells due to the presence of bacterium H. Pylori, which may contribute to the formation of gastric adenocarcinoma [5, 37]. Hence, we assume H. Pylori stimulates the proliferation of gastric cancer cells [5, 25].

4. The main antigen-presenting cells, Dendritic Cells (DCs), remain in a homeostatic state. Nonetheless, these cells become activated through stimulation of their cellular receptors by identifying tumor antigens of gastric cancer cells [36]. We assume that the population of DCs grows logistically in response to the cancer cell presence. The latter allows us to consider a maximum carrying capacity for these population.

5. The mature DCs die by apoptosis after presenting tumor antigens to the T cells [36].

6. T cells are activated and are capable of eliminating gastric cancer cells by interacting with them. We describe this process by the law of mass action.

7. There is natural death of T cells. Furthermore, such cells are eventually inactivated after a certain number of encounters with gastric cancer cells [10, 24, 36].

8. The total tumor cells population eliminated by ACI treatment is a factor of the number of T cells supplied which we represent as a treatment parameter.

2.1.1 Model Equations

Under the assumptions above, the model that describes the interactions between the immune system and gastric cancer cells is represented by the following system of three nonlinear first-order ODEs:

$$\dot{x} = \alpha_x x(1-\beta_x x) + \eta_x x + \delta_x xz - \gamma_x xz, \quad (1)$$

$$\dot{y} = \alpha_y y(1-\beta_y y) + \delta_y xy - \gamma_y yz, \quad (2)$$

$$\dot{z} = \delta_z yz - \gamma_z xz - \mu_z z + \alpha_z, \quad (3)$$

where the amount of cells populations over time t are denoted by $x(t)$ as the gastric cancer cell population, $y(t)$ as the DCs population, and $z(t)$ as the T cells population. This set of equations has the general initial conditions $x(0) = x_0$, $y(0) = y_0$ and $z(0) = z_0$. It should be noted that the dynamics of the system is located in the nonnegative orthant defined by:

$$\mathbf{R}^3_{+,0} = \{x(t) \geq 0,\ y(t) \geq 0,\ z(t) \geq 0\}, \quad (4)$$

under the positivity property for dynamical systems established by De Leenheer et al. [7]. The positivity of the system implies that, given the initial nonnegative conditions, all solutions to Eqs. (1)-(3) will be forward positively invariant in $\mathbf{R}^3_{+,0}$.

Equation (1) describes the rate of change of the gastric cancer cell population, where the first term represents the logistic growth of $x(t)$ in which $1/\beta_x$ is the maximum carrying capacity. The term $\eta_x x$ symbolizes the increase of gastric cancer cells by stimulation of an H. Pylori population attached to the infected mucosa. We emphasize that the mechanisms involved in colonization of the gastric mucosa by H. Pylori are not examined in this work, but an interesting example can be found in [17]. The third term $\delta_x xz$ represents T cell cannibalism by gastric cancer cells, which benefits tumor survival. Finally, gastric cancer cells death due to an immune response by T cells is considered through the law of mass action by the term $\gamma_x xz$.

Equation (2) describes the rate of change of the DCs population and is mainly governed by a logistic growth, considering a maximum carrying capacity $1/\beta_y$. The immune response is carried out by the DCs activation in the term $\delta_y xy$ due to their interaction with gastric cancer cells. Logistic growth is assumed for the sake of simplicity and to limit the maximum amount of this cell population during the immune response. The term $\gamma_y yz$ symbolizes the death of mature DCs by presenting peptides derived from tumor-associated antigens to T cells.

Equation (3) describes the rate of change of the T cells population. The term $\delta_z yz$ symbolizes the activation of T cells by mature DCs. The term $\gamma_z xz$ is the reduction or inactivation of T cells by each interaction with gastric cancer cells. The term $\mu_z z$ represents the natural death of T cells. The external supply, α_z, represents the parameter of ACI treatment. The designed T cells are injected into the tumor site in large numbers of approximately 10^{11} cells for successful treatment [15]. In this sense, it is understood that α_z symbolizes the addition of T cells designed by ACI treatment, and a sufficient value for this parameter will be computed through our mathematical analysis. The reason for having selected this type of immunotherapy is due to its effectiveness for the treatment of malignant tumors [38].

Our model explores the case of an advanced gastric adenocarcinoma due to the observations of survival mechanisms in this type of advanced tumors [3, 5, 24, 25]. In relation to this, we established a population of 10^{11} cancer cells (approx. 100 g) to represent an advanced tumor, before causing the death of the patient with 10^{12} cancer cells (approx. 1 kg) [12]. This depends on the type of tumor, but it is reasonable to allow this to be on the order of 10^{11} cells [9]. Therefore, the dimension per unit for all cell populations is 10^{11} cells, and the time scale is considered to be in months. Figure 1 illustrates an overview of the development of a gastric adenocarcinoma, as well as the interactions between cells populations, H. Pylori, and the treatment.

The description, values, and units of the parameters are shown in Table 1. To estimate the parameter values, we used an artificial intelligence software based on genetic algorithms called Eureqa [32]. For practical purposes and to obtain qualitative values for the parameters, we take the nonlinear model proposed by Llanos-Perez et al. [26] and, subsequently, we enter its time series data into Eureqa to generate our system of Eqs.

(1)-(3). In this way, we adapt and parameterize the ODEs generated by Eureqa based on our biological assumptions to obtain our system (1)-(3). Since our model is qualitative, rather than quantitative, the values acquired by Eureqa may be used for *in silico* experimentation and mathematical analysis concerning asymptotic stability. Hence, we expect our model to be helpful in exploring the long-term evolution of this disease by means of numerical simulations considering diverse scenarios for hypothetical patients.

3 Equilibrium Points and Local Stability

The calculation of equilibrium points allows us to understand the long-term dynamics of the system of Eqs. (1)-(3) through a subsequent analysis of local and global stability. By calculating these points in tumor-immune systems we can identify those states of interest, such as the *tumor-free* and the *tumor persistence* equilibrium point. Equilibrium points are obtained by solving the following system of equations:

$$\begin{aligned} \alpha_x x(1-\beta_x x)+\eta_x x+\delta_x xz-\gamma_x xz &= 0,\\ \alpha_y y(1-\beta_y y)+\delta_y xy-\gamma_y yz &= 0,\\ \delta_z yz-\gamma_z xz-\mu_z z+\alpha_z &= 0. \end{aligned}$$

By solving for each variable, the following expressions are obtained:

$$\begin{aligned} x &= 0 \quad \text{and} \quad x=\frac{\alpha_x+\eta_x}{\alpha_x\beta_x}-\left(\frac{\gamma_x-\delta_x}{\alpha_x\beta_x}\right)z,\\ y &= 0 \quad \text{and} \quad y=\frac{1}{\beta_y}+\frac{\delta_y x-\gamma_y z}{\alpha_y\beta_y},\\ z &= \frac{\alpha_z}{\mu_z-\delta_z y+\gamma_z x}. \end{aligned}$$

From the intersection of the previous expressions, we are able to determine seven equilibrium points denoted as $P_i = (x_i^*, y_i^*, z_i^*)$ where $i = 0, 1, ..., 6$. For $i = 0, 1, 2$ are defined the tumor-free equilibria ($x_0^* = 0$, $x_1^* = 0$, $x_2^* = 0$). Numerically, depending on the parameter values presented in the Table 1, most of the equilibrium points of the system (1)-(3) are unstable. The local stability is determined by evaluating each equilibrium point in the Jacobian matrix of the system (1)-(3) and, later, analyzing the signs of their associated eigenvalues. The general expression of the Jacobian matrix of the system is:

$$J(x,y,z)=\begin{bmatrix} A & 0 & -x(\gamma_x-\delta_x)\\ \delta_y y & B & -\gamma_y y\\ -\gamma_z z & \delta_z z & C \end{bmatrix},$$

where:

$$\begin{aligned} A &= \alpha_x(1-2\beta_x x)-z(\gamma_x-\delta_x)+\eta_x,\\ B &= \alpha_y(1-2\beta_y y)+\delta_y x-\gamma_y z,\\ C &= \delta_z y-\gamma_z x-\mu_z. \end{aligned}$$

We focus our work on the analysis of one tumor-free equilibrium point. In the absence of ACI treatment ($\alpha_z = 0$), the tumor-free equilibrium is the trivial state $P_0 = (0, 0, 0)$ where all the populations are zero and the system (1)-(3) is always an unstable saddle-node.

In another scenario, when there is a treatment supply, that is, $\alpha_z > 0$, the tumor-free equilibrium point is now:

$$P_0=\left(0,0,\frac{\alpha_z}{\mu_z}\right).$$

The eigenvalues associated with the equilibrium P_0:

$$\begin{aligned} \lambda_1 &= (\alpha_x+\eta_x)-\frac{\alpha_z}{\mu_z}(\gamma_x-\delta_x),\\ \lambda_2 &= -\mu_z,\\ \lambda_3 &= \alpha_y-\frac{\alpha_z\gamma_y}{\mu_z}. \end{aligned}$$

The equilibrium P_0 will be locally asymptotically stable if $\lambda_1 < 0$ and $\lambda_3 < 0$. To establish a sufficient condition for local asymptotic stability, the following must be fulfill:

$$\alpha_z > \max\left\{\frac{\mu_z(\alpha_x+\eta_x)}{\gamma_x-\delta_x}, \frac{\alpha_y\mu_z}{\gamma_y}\right\}, \tag{5}$$

by assuming the following condition also holds:

$$\gamma_x > \delta_x. \tag{6}$$

If $\gamma_x > \delta_x$, it would imply that the death rate of gastric cancer cells by T cells must be greater than

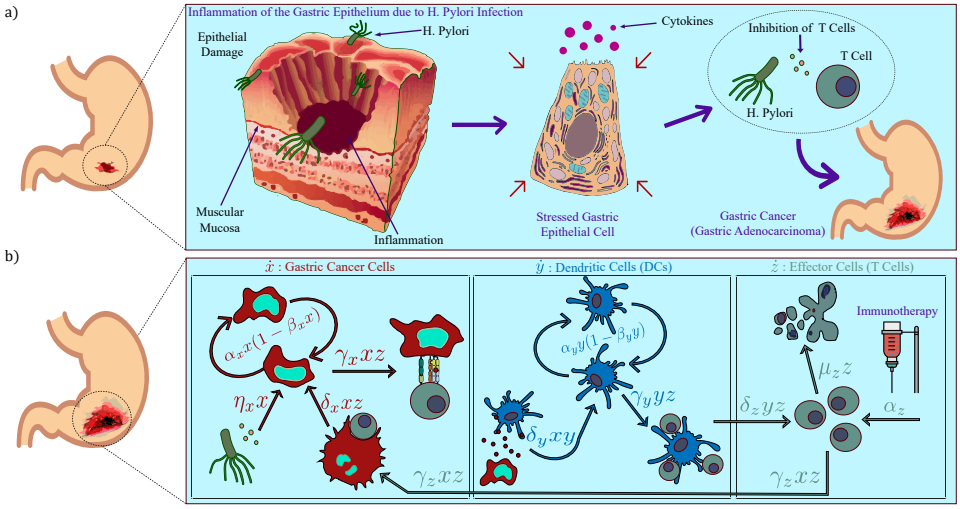

Fig. 1. Diagram of the gastric adenocarcinoma development and the cellular interactions of our mathematical model. Section a) Illustrates the inflammation process of the gastric epithelium derived from H. Pylori infection. Due to the damage caused by H. Pylori, gastric epithelial cells become stressed and release cytokines to generate an immune response [24, 37]. However, the mechanisms of immune evasion of the bacteria prevent a rigorous immune response, therefore, gastric adenocarcinoma originates at the infection site. Section b) shows the interactions between gastric cancer cells [$x(t)$], DCs [$y(t)$], effector cells [T cells, $z(t)$] and the ACI treatment

the rate of cell cannibalism performed by cancer cells. To get local asymptotic stability of the system in equilibrium P_0, α_z must be greater than the maximum value of the condition (5). Intuitively, this implies that the administration of ACI treatment is capable of eliminating the tumor by converging the trajectory $x(t)$ in $x = 0$.

With the stability results, it is concluded that the tumor-free equilibrium P_0 is the only steady-state biologically feasible. Based on the local stability analysis performed, the following result is concluded.

Result 1. *Suppose that conditions (5) and (6) are satisfied in the intestinal-type gastric adenocarcinoma system with ACI (1)-(3). Then, the tumor-free equilibrium point* $P_0 = \left(0, 0, \frac{\alpha_z}{\mu_z}\right)$ *is locally asymptotically stable.*

The latter establishes the clearance for a short initial tumor burden because the stability analysis is local, that is, a region around of P_0. In subsequent sections, we analyze the global dynamics of the model with the LCIS method and we find a sufficient condition to eliminate all gastric adenocarcinoma burden.

4 Boundedness of the Solutions

We use the LCIS method and Lyapunov's stability theory to study the short- and long-term behavior, and global stability of the system (1)-(3). The LCIS method was proposed by Krishchenko in [18] and optimized by Krishchenko and Starkov in [19]. Through this method, lower and upper bounds are calculated that define the so-called *localizing domain*, which establishes a bounded region in the state-space where all compact invariant sets of the system are located. The LCIS method has been successfully applied in different dynamical systems, i.e., the Lorenz chaotic system [19], a permanent-magnet motor system [6] and recently in biomathematics for models that describe the tumor-immune dynamics and their treatments [34, 20, 29, 30, 31], among others. The following, we present the mathematical preliminaries and notations of the LCIS method, and subsequently

Table 1. Description, values and units of parameters

Parameter Dimension and Units	Description	Value
α_x unit time^{-1}	Population growth rate of gastric cancer cells	8.0504
β_x cells^{-1}	Inverse carrying capacity of gastric cancer cells	0.1273
η_x unit time^{-1}	Rate of gastric cancer cells proliferation by H. Pylori stimulation	2.1979
δ_x cells^{-1} per unit time^{-1}	Cellular cannibalization rate of T cells by gastric cancer cells	0.1249
γ_x cells^{-1} per unit time^{-1}	Death rate of gastric cancer cells by activated T cells	3.5
α_y unit time^{-1}	Proliferation rate of DCs induced by growth factors	3.5976
β_y cells^{-1}	Inverse carrying capacity of DCs	0.1461
δ_y cells^{-1} per unit time^{-1}	Rate of DCs activation when capturing tumor antigens created by gastric cancer cells	0.1709
γ_y cells^{-1} per unit time^{-1}	Rate of DCs apoptosis when presenting tumor antigens to T cells	1.4818
δ_z cells^{-1} per unit time^{-1}	Rate of preparation and activation of T cells due to their interaction with DCs	1.5255
γ_z cells^{-1} per unit time^{-1}	Inactivation rate of T cells by its interaction with gastric cancer cells	0.2498
μ_z unit time^{-1}	Natural death rate of activated T cells in tumor	0.4171
α_z 10^{11} cells/mg of dose	Immunotherapy treatment parameter	To be estimated

we show its application for the model proposed in this work.

4.1 Localization of Compact Invariant Sets Method

The LCIS method it is useful to study the short- and long-time dynamics of any ODEs system by computing the localizing domain. Equilibrium points, periodic, homoclinic and heteroclinic orbits, limit cycles and chaotic attractors are examples of compact invariant sets.

Let us take an autonomous nonlinear ODEs system of the form $\dot{x} = f(x)$, where $f(x)$ is a C^∞-differentiable vector function and $x \in \mathbf{R}^n$ is the state vector. Let $h(x) : \mathbf{R}^n \to \mathbf{R}$ be a C^∞-differentiable function, by $h\big|_S$ we denote the restriction of $h(x)$ on a set $S \subset \mathbf{R}^n$. The function $h(x)$ used in this statement is called *localizing* and we assume that $h(x)$ is not the first integral of $f(x)$. By $S(h)$ we denote the set $\{x \in \mathbf{R}^n \mid L_f h(x) = 0\}$, where $L_f h(x)$ represents the Lie derivative of $f(x)$ and is given by: $L_f h(x) = (\partial h/\partial x)\, f(x)$. Now, let us define $h_{\text{inf}} := \inf\{h(x) \mid x \in S(h)\}$ and $h_{\text{sup}} := \sup\{h(x) \mid x \in S(h)\}$. Then, the General Theorem concerning the localization of all compact invariant sets of a dynamical system establishes the following:

General Theorem. [19]. *Each compact invariant set Γ of $\dot{x} = f(x)$ is contained in the localizing domain:*

$$K(h) = \{h_{\text{inf}} \leq h(x) \leq h_{\text{sup}}\}.$$

Localizing functions are selected by a heuristic process, this means that one may need to analyze

several functions in order to find a proper set that will allow to fulfill the General Theorem. If we consider the location of all compact invariant sets inside the domain $U \subset \mathbf{R}^n$ we have the set $K(h) \cap U$. It is evident that if all compact invariant sets are located in the sets $K(h_i)$ and $K(h_j)$, with $K(h_i)$,$K(h_j) \subset \mathbf{R}^n$, then they are located in the set $K(h_i) \cap K(h_j)$ as well. Furthermore, a refinement of the localizing domain $K(h)$ is realized with help of the Iterative Theorem stated as follows:

Iterative Theorem. [19]. *Let $h_m(x)$,$m = 0, 1, 2, ...$ be a sequence of C^∞-differentiable functions. Sets:*

$$K_0 = K(h_0), \quad K_m = K_{m-1} \cap K_{m-1,m}, \quad m > 0,$$

with:

$$\begin{aligned} K_{m-1,m} &= \{x : h_{m,\text{inf}} \leq h_m(x) \leq h_{m,\text{sup}}\}, \\ h_{m,\text{sup}} &= \sup_{S(h_m) \cap K_{m-1}} h_m(x), \\ h_{m,\text{inf}} &= \inf_{S(h_m) \cap K_{m-1}} h_m(x), \end{aligned}$$

contain any compact invariant set of the system $\dot{x} = f(x)$ and:

$$K_0 \supseteq K_1 \supseteq \cdots \supseteq K_m \cdots .$$

4.2 Localizing Domain

The LCIS method is applied to define the solutions or trajectories of the system (1)-(3) in a domain delimited by upper and lower limits. The limits are given as inequalities in terms of the variables and parameters of the system and are obtained through four localizing functions.

In order to obtain the maximum value for the gastric cancer cell population $x(t)$, we propose the localizing function:

$$h_1 = x.$$

The Lie derivative of h_1 is given by:

$$L_f h_1 = \alpha_x x(1 - \beta_x x) + \eta_x x + \delta_x xz - \gamma_x xz,$$

and from which the set $S(h_1) = \{L_f h_1 = 0\}$ is established, and can be calculated as follows:

$$S(h_1) = \{\alpha_x x(1 - \beta_x x) + \eta_x x + \delta_x xz - \gamma_x xz = 0\}.$$

It becomes clear that x is a common factor in $S(h_1)$. Therefore, we obtain the union of two sets:

$$S(h_1) = \{\alpha_x(1 - \beta_x x) + \eta_x + \delta_x z - \gamma_x z = 0\} \cup \{x = 0\}.$$

Performing the corresponding algebraic operations, we obtain the following solution:

$$S(h_1) = \left\{x = \frac{\alpha_x + \eta_x}{\alpha_x \beta_x} - \frac{\gamma_x - \delta_x}{\alpha_x \beta_x} z\right\} \cup \{x = 0\},$$

where to determine the maximum limit of x in $S(h_1)$, the condition (6) must be fulfilled. Based on the above, the following result is established:

$$K_1(h_1) = \left\{x(t) \leq x_{\text{max}} = \frac{\alpha_x + \eta_x}{\alpha_x \beta_x}\right\}. \qquad (7)$$

The maximum densities for the population of DCs can be determined with the function:

$$h_2 = y,$$

whose the Lie derivative is given by:

$$L_f h_2 = \alpha_y y(1 - \beta_y y) + \delta_y xy - \gamma_y yz,$$

and set $S(h_2) = \{L_f h_2 = 0\}$ is presented as:

$$S(h_2) = \{\alpha_y y(1 - \beta_y y) + \delta_y xy - \gamma_y yz = 0\}.$$

The dependent variable is identified as a common factor in $S(h_2)$, therefore, performing the corresponding algebraic operations the following union of two sets is obtained:

$$S(h_2) = \left\{y = \frac{1}{\beta_y} + \frac{\delta_y}{\alpha_y \beta_y} x - \frac{\gamma_y}{\alpha_y \beta_y} z\right\} \cup \{y = 0\},$$

then, negative terms are discarded and the Iterative Theorem is applied with the set $K_1(h_1)$, that is, $S(h_2) \cap K_1(h_1)$, getting the next maximum limit for the DCs population:

$$K_1(h_2) = \left\{y(t) \leq y_{\text{max}} = \frac{1}{\beta_y} + \frac{\delta_y}{\alpha_y \beta_y} x_{\text{max}}\right\},$$

if condition (6) holds.

Following the same path of the results shown above, we analyze the localizing function:

$$h_3 = z,$$

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to calculate the lower limit of the T cell population. Consequently, the Lie derivative of the function h_3 is:

$$L_f h_3 = \delta_z yz - \gamma_z xz - \mu_z z + \alpha_z,$$

and from which the set $S(h_3) = \{L_f h_3 = 0\}$ is given by:

$$S(h_3) = \{\delta_z yz - \gamma_z xz - \mu_z z + \alpha_z = 0\}.$$

Through algebraic calculations, we can obtain the set:

$$S(h_3) = \left\{ z = \frac{\alpha_z}{\mu_z + \gamma_z x} + \frac{\delta_z yz}{\mu_z + \gamma_z x} \right\},$$

then discarding the second term in the set $S(h_3)$ and applying the Iterative Theorem with the set $K_1(h_1)$, that is, $S(h_3) \cap K_1(h_1)$, in order to calculate the next lower bound for T cells population:

$$K_1(h_3) = \left\{ z(t) \geq z_{\text{inf}} = \frac{\alpha_z}{\mu_z + \gamma_z x_{\text{max}}} \right\}, \quad (8)$$

if condition (6) is fulfilled.

Now, trying to obtain the upper bound for the gastric cancer cell population, we take the set $S(h_1)$ and apply the Iterative Theorem with the set $K_1(h_3)$, that is, $S(h_1) \cap K_1(h_3)$, we get the following localizing set for all nondivergent solutions to $\dot{x}(t)$:

$$K_x = \left\{ 0 \leq x(t) \leq x_{\text{sup}} = \frac{\alpha_x + \eta_x}{\alpha_x \beta_x} - \frac{(\gamma_x - \delta_x)}{\alpha_x \beta_x} z_{\text{inf}} \right\}. \quad (9)$$

The upper bound for the DCs population is solved in a similar way to the previous case. We take the set $S(h_2)$ and apply the Iterative Theorem with the set $K_1(h_3)$, that is, $S(h_2) \cap K_1(h_3)$, obtaining the next localizing set for all nondivergent solutions to $\dot{y}(t)$:

$$K_y = \left\{ 0 \leq y(t) \leq y_{\text{sup}} = \frac{1}{\beta_y} + \frac{\delta_y}{\alpha_y \beta_y} x_{\text{max}} - \frac{\gamma_y}{\alpha_y \beta_y} z_{\text{inf}} \right\}. \quad (10)$$

Now, we can establish the upper bound for the T cells population using the following localizing function:

$$h_4 = \Upsilon y + z,$$

with $\Upsilon > 0$. The Lie derivative of the function h_4 is given:

$$L_f h_4 = \Upsilon \left(\alpha_y y(1 - \beta_y y) + \delta_y xy - \gamma_y yz \right) + \left(\delta_z yz - \gamma_z xz - \mu_z z + \alpha_z \right),$$

hence,set $S(h_4) = \{L_f h_4 = 0\}$ is defined as:

$$S(h_4) = \{\alpha_y \Upsilon y(1 - \beta_y y) + \delta_y \Upsilon xy - \gamma_y \Upsilon yz + \delta_z yz - \gamma_z xz - \mu_z z + \alpha_z = 0\}.$$

Through algebraic operations, we obtain the next set:

$$S(h_4) = \left\{ z = \frac{1}{\mu_z} \left(\alpha_y \Upsilon y(1 - \beta_y y) + \delta_y \Upsilon xy - \gamma_y \Upsilon yz + \delta_z yz - \gamma_z xz + \alpha_z \right) \right\}.$$

Now, the localizing function h_4 is rewritten and it is solved for z obtaining as result $z = h_4 - \Upsilon y$, which allows us to formulate the following set:

$$S(h_4) = \left\{ h_4 - \Upsilon y = \frac{1}{\mu_z} \left(\alpha_y \Upsilon y(1 - \beta_y y) + \delta_y \Upsilon xy - \gamma_y \Upsilon yz + \delta_z yz - \gamma_z xz + \alpha_z \right) \right\},$$

which implies that:

$$S(h_4) = \left\{ h_4 = \frac{\alpha_y}{\mu_z} \Upsilon y - \frac{\alpha_y \beta_y}{\mu_z} \Upsilon y^2 + \frac{\delta_y}{\mu_z} \Upsilon xy - \frac{\gamma_y}{\mu_z} \Upsilon yz + \frac{\delta_z}{\mu_z} yz - \frac{\gamma_z}{\mu_z} xz + \frac{\alpha_z}{\mu_z} + \Upsilon y \right\}.$$

Then, we group similar terms and apply the algebraic technique completing the square. In order to calculate an upper bound for z, we define a function $\Lambda(x, y, z)$ as:

$$\Lambda(x, y, z) = \frac{\alpha_y \beta_y}{\mu_z} \Upsilon \left(y - \frac{\mu_z + \alpha_y + \delta_y x}{2\alpha_y \beta_y} \right)^2 + \left(\frac{\gamma_y}{\mu_z} \Upsilon - \frac{\delta_z}{\mu_z} \right) yz + \frac{\gamma_z}{\mu_z} xz,$$

and if we impose the next condition for the second term of the function $\Lambda(x, y, z)$:

$$\Upsilon \geq \frac{\delta_z}{\gamma_y}, \quad (11)$$

and we get the following result:

$$S(h_4) = \left\{ h_4 = \frac{\alpha_z}{\mu_z} + \frac{\Upsilon\left(\mu_z + \alpha_y + \delta_y x\right)^2}{4\alpha_y\beta_y\mu_z} - \Lambda(x,y,z) \right\},$$

therefore, the function $\Lambda(x,y,z)$ is discarded for being negative and we obtain the following subset:

$$S(h_4) \subset \left\{ h_4 \leq \frac{\alpha_z}{\mu_z} + \frac{\Upsilon\left(\mu_z + \alpha_y + \delta_y x\right)^2}{4\alpha_y\beta_y\mu_z} \right\}.$$

Now, by substituting $\Upsilon y + z$ in h_4 and solving for z, we get the following subset:

$$S(h_4) \subset \left\{ z \leq \frac{\alpha_z}{\mu_z} + \frac{\Upsilon\left(\mu_z + \alpha_y + \delta_y x\right)^2}{4\alpha_y\beta_y\mu_z} - \Upsilon y \right\}.$$

Finally, if we discard the negative term of the subset and apply the Iterative Theorem with the set $K_1(h_1)$, we can establish the upper bound for T cells population and the following localizing set for all nondivergent solutions to $\dot{z}(t)$:

$$K_z = \left\{ z_{\text{inf}} = \frac{\alpha_z}{\mu_z + \gamma_z x_{\max}} \leq z(t) \leq z_{\text{sup}} = \frac{\alpha_z}{\mu_z} + \frac{\Upsilon\left(\mu_z + \alpha_y + \delta_y x_{\max}\right)^2}{4\alpha_y\beta_y\mu_z} \right\}, \quad (12)$$

if conditions (6) and (11) are satisfied.

The upper and lower bounds of the system (1)-(3), define the domain of maximum and minimum densities of cells populations. It is important to mention that the condition (6) affects the sets K_x, K_y and K_z of the system. Based on the results that have been shown in this subsection, the following Theorem is established.

Localizing Domain Theorem. *If conditions (6) and (11) are satisfied, then all compact invariant sets of the intestinal-type gastric adenocarcinoma system with ACI (1)-(3) are located either inside or at the boundaries of the following compact localizing domain:*

$$K_{xyz} = K_x \cap K_y \cap K_z,$$

where:

$$\begin{aligned} K_x &= \{0 \leq x(t) \leq x_{\text{sup}}\}, \\ K_y &= \{0 \leq y(t) \leq y_{\text{sup}}\}, \\ K_z &= \{z_{\text{inf}} \leq z(t) \leq z_{\text{sup}}\}, \end{aligned}$$

with:

$$x_{\text{sup}} = \frac{\alpha_x + \eta_x}{\alpha_x\beta_x} - \frac{(\gamma_x - \delta_x)}{\alpha_x\beta_x} z_{\text{inf}}, \quad (13)$$

$$y_{\text{sup}} = \frac{1}{\beta_y} + \frac{\delta_y}{\alpha_y\beta_y} x_{\max} - \frac{\gamma_y}{\alpha_y\beta_y} z_{\text{inf}}, \quad (14)$$

$$z_{\text{inf}} = \frac{\alpha_z}{\mu_z + \gamma_z x_{\max}}, \quad (15)$$

$$z_{\text{sup}} = \frac{\alpha_z}{\mu_z} + \frac{\Upsilon\left(\mu_z + \alpha_y + \delta_y x_{\max}\right)^2}{4\alpha_y\beta_y\mu_z}. \quad (16)$$

The bounds (13)-(16) define a compact domain in $\mathbf{R}^3_{+,0}$ where all compact invariant sets of the system (1)-(3) are located. In section 5, the bounds (7) and (15) are applied using the direct Lyapunov method in order to establish sufficient conditions to define the appropriate dose of immunotherapy for tumor clearance.

5 Tumor Clearance and Global Stability

The main objective of this section is to present sufficient conditions of attraction to the tumor-free equilibrium point P_0 and global stability in $\mathbf{R}^3_{+,0}$.

The conditions are established in the form of an inequality on the parameter α_z. With this, we seek that all the solutions of Equation (1) will go to the tumor-free invariant plane given by $x = 0$. The candidate Lyapunov function must be a continuously differentiable function that satisfies $h_5(x_0^*) = 0$ and $h_5(x) > 0$ if $x \neq x_0^*$. For simplicity of global stability analysis, we propose the next candidate Lyapunov function:

$$h_5 = x,$$

whose the Lie derivative is given by:

$$L_f h_5 = \alpha_x x\left(1 - \beta_x x\right) + \eta_x x + \delta_x xz - \gamma_x xz,$$

and when grouping similar terms we have:

$$L_f h_5 = -\alpha_x\beta_x x^2 + x\left(\alpha_x + \eta_x\right) - xz\left(\gamma_x - \delta_x\right).$$

Now, we look for a non-positive upper limit with $L_f h_5 \leq 0$ that allows us to fulfill the Lyapunov conditions for global asymptotic stability. We can find a solution evaluating our results of the Localizing Domain Theorem. Notice that condition (6) is

present in the third term of the previous expression, thus we may consider the following upper bound for function $L_f h_5$ as indicated below:

$$L_f h_5 \leq x\left[(\alpha_x + \eta_x) - z_{\text{inf}}\left(\gamma_x - \delta_x\right)\right] \leq 0. \quad (17)$$

If we satisfy the inequality (17), the next constraint must also be fulfilled:

$$(\alpha_x + \eta_x) - z_{\text{inf}}\left(\gamma_x - \delta_x\right) < 0. \quad (18)$$

Rewriting the expression (18), we achieve the following inequality:

$$(\alpha_x + \eta_x) - \left(\frac{\alpha_x \beta_x \alpha_z}{\alpha_x \beta_x \mu_z + \gamma_z\left(\alpha_x + \eta_x\right)}\right)\left(\gamma_x - \delta_x\right) < 0.$$

Solving for the ACI treatment parameter α_z, the next condition is determined:

$$\alpha_z > \frac{\mu_z\left(\alpha_x + \eta_x\right)}{\gamma_x - \delta_x} + \frac{\gamma_z\left(\alpha_x + \eta_x\right)^2}{\alpha_x \beta_x\left(\gamma_x - \delta_x\right)}, \quad (19)$$

by assuming (6) holds.

Condition (19) implies that ACI treatment is able to clear the gastric cancer cell population. If the conditions (19) and (6) are fulfilled, with LaSalle's Invariance Principle [16] we can conclude that any trajectory derived from an initial condition $x(0)$ to the Eq. (1), will go to the tumor-free invariant plane $x = 0$ where:

$$\lim_{t \longrightarrow \infty} x(t) = x_0^* = 0.$$

Hence, we establish the following theorem.

Theorem 2. *If the conditions (19) and (6) are satisfied, then the plane $x^* = 0$ is asymptotically stable in the domain K_{xyz}, which implies tumor elimination by ACI treatment in the intestinal-type gastric adenocarcinoma system (1)-(3).*

Additionally, if condition (19) holds, this inequality is a condition of non-existence of compact invariant sets (see definition in [31]) in the set $\mathbf{R}^3_{+,0} \cap \{x > 0\}$ of the system (1)-(3). Let us remind the upper bound of the gastric cancer cell population:

$$x_{\text{sup}} = \frac{\alpha_x + \eta_x}{\alpha_x \beta_x} - \frac{(\gamma_x - \delta_x)}{\alpha_x \beta_x} z_{\text{inf}},$$

where by substituting the bounds z_{inf} and $x_{\max}$, we get:

$$x_{\text{sup}} = \frac{\alpha_x + \eta_x}{\alpha_x \beta_x} - \frac{\alpha_z(\gamma_x - \delta_x)}{\left(\alpha_x \beta_x \mu_z + \gamma_z\left(\alpha_x + \eta_x\right)\right)}.$$

Then, if the condition (19) is fulfilled, the result in the upper bound of the cancer cell population is $x_{\text{sup}} \leq 0$. Biologically, this means that the condition (19) does not allow the existence of tumor persistence dynamics, for example, tumor latency (oscillations). Mathematically, this implies that all types of compact invariant sets (equilibrium points, limit cycles, and periodic orbits) that the system can exhibit (1)-(3), they will be tumor-free dynamics. Based on these results, we conclude with the following result.

Result 2. *If condition (19) is satisfied, then all compact invariant sets of the intestinal-type gastric adenocarcinoma system with ACI (1)-(3), will be located in the domain $\mathbf{R}^3_{+,0} \cap \{x = 0\}$.*

6 Discussion and Biological Interpretations

Immunotherapy is considered a good alternative for the treatment of various types of cancer, and currently, it has generated significant interest for its application in patients with gastric cancer [38]. However, knowledge of the tumor-immune interactions and other factors related to this disease is still limited. Today mathematical oncology has become a fundamental area for understanding complex oncological phenomena and their interactions with the immune system.

Using deterministic models, it is possible to provide valuable information related to tumor growth, as well as its response to treatments such as ACI [10, 39]. Therefore, exploring different scenarios and types of cancer with these tools is only a first step on understanding tumor evolution, which will eventually lead to the development and evaluation of appropriate treatments with the greatest decrease in tumor burden.

In this work, we propose a qualitative mathematical model composed of the system of Eqs.

(1)-(3) that describes the growth of an intestinal-type gastric adenocarcinoma, covering interesting aspects such as H. Pylori infection and cellular cannibalism. Furthermore, we explore the effects of ACI treatment by incorporating the parameter α_z into the Eq. (3) of the T cell population. When there is a treatment supply ($\alpha_z > 0$), the tumor-free equilibrium point P_0 is locally asymptotically stable if the conditions (5) and (6) hold. This result establishes the clearance of a limited tumor burden around the equilibrium point P_0 because the stability analysis is local, that does not necessarily imply a global elimination for any solution or trajectory of the system (1)-(3).

One of the main foci of our work was to apply the LCIS method, due to the utility of this methodology to understand long-term tumor dynamics [34, 30, 31]. With the results obtained, we define the bounds of the localizing domain K_{xyz} where all compact invariant sets of the system (1)-(3) are located. The importance of these bounds relies in the fact that cell populations will not grow beyond their upper bounds, only if the conditions of the Localizing Domain Theorem hold. Also, by applying Lyapunov's stability theory and LaSalle's Invariance Principle, a sufficient condition on α_z was determined for gastric adenocarcinoma clearance and global asymptotic stability in the tumor-free equilibrium point P_0. The latter implies that any trajectory of the system (1)-(3) will go to the tumor-free invariant plane $x = 0$.

Both the stability of the equilibrium P_0 and the limits of the localizing domain are subject to the condition (6). This condition implies that the rate of cancer cell death from an immune response is greater than its rate of cannibalism by engulfing T cells. It is theorized that cannibal activity in cancer cells could be a way of neutralizing the immune response to engulf effector cells, assuming a morphological appearance called *cell-in-cell* [11, 27]. This cannibalistic activity is linked to a poor prognosis in the health of patients [11]. Therefore, if we seek to eradicate gastric cancer with ACI treatment, the immune response must be stronger than the cannibalistic activity by cancer cells. Cannibalism has been found at high levels in some cases of gastric cancer cells that cannibalize infiltrating neutrophils [3], however, more research is needed regarding the relationship of cannibalistic activity of gastric cancer cells to other immune cells.

Focusing directly on the treatment, we obtained two important conditions for the local and global stability of the system in the tumor-free equilibrium P_0. With the local stability analysis of P_0, we calculate the following result from condition (5):

$$\alpha_z > \max\left\{\frac{\mu_z\left(\alpha_x+\eta_x\right)}{\gamma_x-\delta_x}, \frac{\alpha_y\mu_z}{\gamma_y}\right\}.$$

With the upper and lower bounds of the model, we achieve the global asymptotic stability condition for tumor clearance from condition (19):

$$\alpha_z > \frac{\mu_z\left(\alpha_x+\eta_x\right)}{\gamma_x-\delta_x} + \frac{\gamma_z\left(\alpha_x+\eta_x\right)^2}{\alpha_x\beta_x\left(\gamma_x-\delta_x\right)}.$$

The second term of the global condition offers the system a faster convergence to the tumor-free equilibrium, that is, when considering a higher dose of immunotherapy, it is theoretically possible to decrease the tumor burden. The next phase is to verify these results with *in silico* experiments using numerical simulations.

Figure 2 shows the temporal dynamics of the system (1)-(3) without and with ACI treatment. With $\alpha_z = 0$, the system exhibits periodic oscillations related to a periodic orbit, see panels a to c of Figure 2. The tumor gastric mass is cycled in approximately 9 months. During 2 or 3 months, the tumor reaches a value close to its maximum carrying capacity and then descends to almost zero in a state known as tumor latency [9, 10, 22, 36]. These oscillations of tumor recurrence partially coincide with the time observed clinically in subjects diagnosed with gastric adenocarcinomas and treated with preoperative chemotherapy and a gastrectomy to decrease their tumor burden [28]. The tumor recurrence phenomenon has devastating implications in early and advanced gastric cancer. Patients with untreated early gastric cancer will survive 5 years without treatment, where 70% will have already developed advanced gastric cancer [1]. On the other hand, the survival for patients diagnosed with advanced gastric cancer does not exceed 12 months [33].

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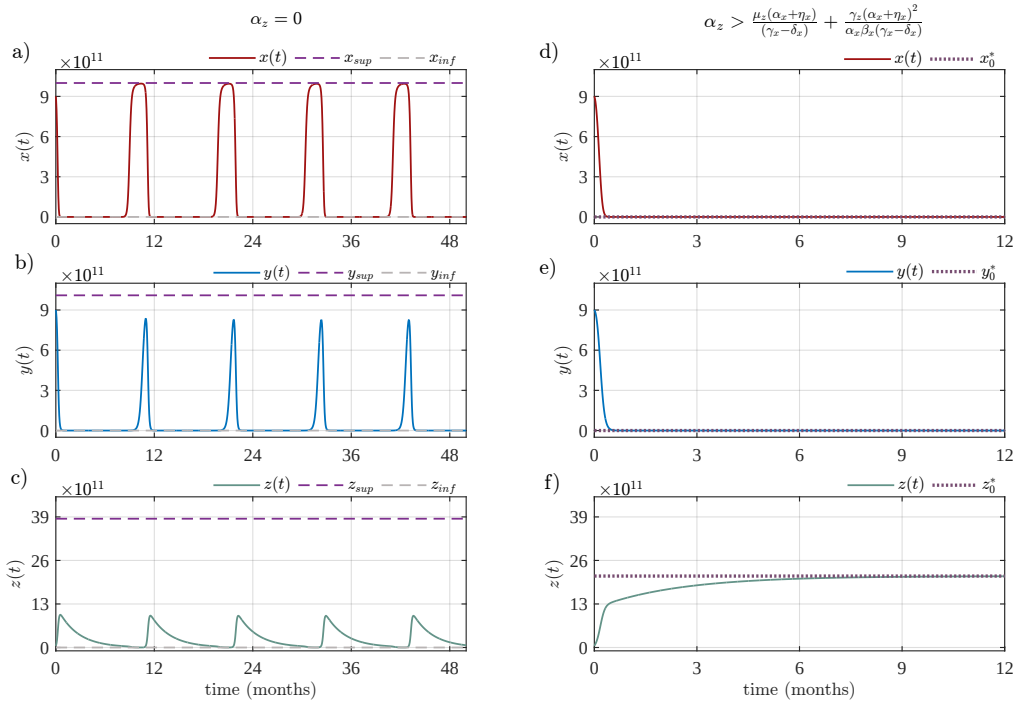

Fig. 2. Solutions of the three cell populations. For $\alpha_z = 0$, the solutions of the system (1)-(3) are shown in panels a to c. For $\alpha_z = 8.9$, the solutions are shown in panels d to f. All solutions with the stability condition (19) are directed to the tumor-free equilibrium point P_0. The time units in the six panels are in months and the assumed dimension for the cell populations is 10^{11} cells

Gastric cancer cells and immune cells can coexist for quite a long time and this is shown in the periodic oscillations of panels a to c of Figure 2. Similar oscillations have been reported in various works in other tumors [9, 22, 34]. It is worth mentioning that, as the value of the parameter γ_x increases, the magnitude and the period of these oscillations shorten until the size of the tumor becomes small.

Panels d to f of Figure 2 illustrate the response of the system (1)-(3) to ACI treatment when condition (19) is satisfied. The solution of the cancer cell population converges to zero in short time with ACI treatment. The active DCs response is reflected only at the time of the immune response against the tumor. Instead, activated T cells grow to converge to a homeostatic state, derived from treatment. This value of ACI ensures the global asymptotic stability of the $x(t)$ solutions to the plane $x = 0$, which implies the elimination of the tumor. These results indicate that ACI treatment could play an important role in the regression of gastric cancer. Additionally, in Figure 3 we illustrate the dynamics of the system (1)-(3) in the phase space for the cases of $\alpha_z = 0$ and $\alpha_z > 0$. Panels a) to b) of Figure 3 show that given any nonnegative initial condition inside the domain K_{xyz} (polytope), the trajectories remain inside for all future time.

One important aspect of our model is to include the saturation effects on the activation of the immune cell populations. As future work, we will include the Michaelis-Menten saturation function to describe the growth of these cells, to achieve a more realistic view of gastric cancer. Another aspect is related to the parameter values presented in Table 1. With those values, the model exhibits a periodic orbit in its solutions, however, as future work, it is planned to determine values that describe a quantitative dynamics on the evolution

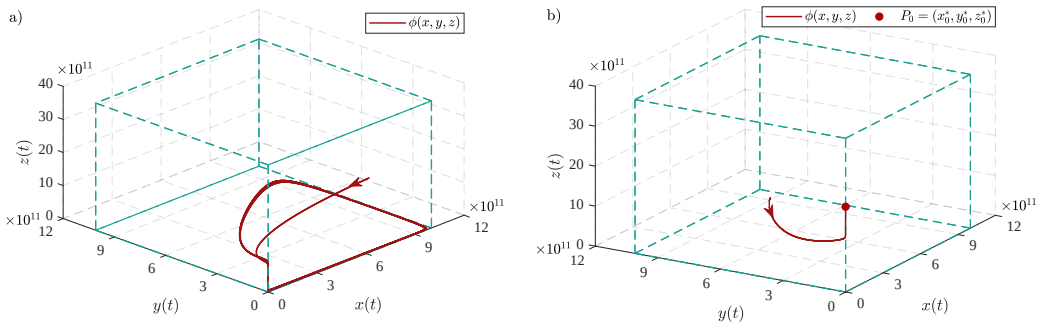

Fig. 3. Trajectories of the system (1)-(3) in the phase space. Panel a) of Figure 3 illustrates the periodic orbit of the system when $\alpha_z = 0$. Panel b) of Figure 3 presents the system dynamics when condition (19) is satisfied, where the system trajectory converges in the healthy tumor-free equilibrium point P_0. In these numerical simulations, we illustrate that given any nonnegative initial condition inside the domain K_{xyz} (polytope) all trajectories will be attracted to the largest compact set within that domain and remain inside for all future time

of intestinal-type gastric adenocarcinoma. At the same time, we will redesign the model to approach the infection of the gastric mucosa by H. Pylori. Finally, it is necessary to evaluate different treatments and carry out combinations of them to advise in gastric cancer related clinical trials.

7 Conclusion

Mathematical models are not only practical strategies to achieve a simpler qualitative vision of cancer, they are also crucial for understanding the tumor-immune system and advancing the research and implementation of treatments for this disease. Models have been developed from different scales, approaches, mathematical theories, and computational tools. In this work, we propose and analyze a qualitative mathematical model composed of first-order ODEs that describes the interactions between a population of gastric cancer cells and two populations of immune cells in the growth of intestinal-type gastric adenocarcinoma with ACI treatment.

The ACI parameter α_z was added to the model in order to establish a sufficient concentration of treatment to ensure the elimination of a gastric adenocarcinoma. In the absence of treatment, the model exhibits periodic oscillations that allow predicting the tumor latency and recurrence.

We were able to decrease the tumor burden in the model through a global asymptotic stability condition on the parameter α_z, the latter was based on the limits of the localizing domain K_{xyz}, Lyapunov's stability theory, and LaSalle's Invariance Principle. These statements imply that intestinal-type gastric adenocarcinoma is eliminated in approximately the first month of treatment, as illustrated in Figure 2, panels d to f. Although these theoretical results derived in this paper provide qualitative information that helps us understand tumor-immune interactions in gastric cancer, some limitations were discussed in the previous section. With the latter, some necessary improvements to the model will be considered, which will be reflected in future works.

We expect that the approach presented in this work be an initial guide to understand the effect of immunotherapy on gastric cancer evolution.

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