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Local Controllability Analysis for a Tumor Dynamics Model

Análise de Controlabilidade Local para um Modelo de dinâmica Tumoral

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ABSTRACT

This study investigates the local controllability of a mathematical model describing tumor dynamics, incorporating cellular competition and external interventions represented by a control variable. The model analyzed is a modified version of the formulation proposed by Gatenby (1996), and its dynamics are explored through linearization around equilibrium points. Using the Kalman rank condition, we establish the circumstances under which the system exhibits local controllability. The results provide a theoretical foundation for understanding how external stimuli can steer the system between distinct biological states, particularly in the context of interactions between healthy and tumor cells. The work bridges concepts from control theory and mathematical oncology, aiming to support the development of more effective clinical intervention strategies. Our analysis offers insights into identifying scenarios in which treatment, modeled as an external control input, can effectively stabilize or even reverse tumor growth.

keywords cancer modeling, controllability theory, Kalman rank condition, mathematical oncology

RESUMO

Este estudo investiga a controlabilidade local de um modelo matemático que descreve a dinâmica tumoral, incorporando a competição entre células e a atuação de intervenções externas representadas por uma variável de controle. O modelo adotado consiste em uma modificação da formulação proposta por Gatenby (1996), cuja dinâmica é analisada por meio da linearização em torno dos pontos de equilíbrio. A partir do critério de posto de Kalman, são estabelecidas condições sob as quais o sistema apresenta controlabilidade local. Os resultados obtidos oferecem uma base teórica para compreender de que forma estímulos externos podem conduzir o sistema entre distintos estados biológicos, especialmente no contexto das interações entre células tumorais e saudáveis. O trabalho articula conceitos de controle não linear e modelagem matemática aplicada à oncologia, com o objetivo de contribuir para o desenvolvimento de estratégias clínicas mais eficazes. Nossa análise fornece subsídios para identificar cenários nos quais um tratamento, modelado como controle externo, pode efetivamente estabilizar ou até reverter o crescimento tumoral.

palavras-chave modelagem do câncer, teoria da controlabilidade, posto de Kalman, oncologia matemática

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Introduction

Salvador and Arenales (2022) emphasize that mathematical modeling of biological systems is a rich and active research area, with numerous models developed to describe population dynamics. Addressing a biological phenomenon involves understanding and defining it as precisely as possible, selecting the necessary information. Transposing this phenomenon into a problem using appropriate mathematical language contributes to its understanding, equation-solving, simulation, and resolution.

In particular, Lotka–Volterra-type models have received significant attention, as stability analyses within optimal control frameworks yield valuable insights into their dynamics (El-Gohary & Yassen, 2001; Wang et al., 2016; Zhang et al., 2022). One important application of these models is in the study of tumor growth.

Cancer remains the foremost public health challenge worldwide and one of the leading causes of death. Despite extensive research efforts, several fundamental aspects of the disease, including its origin, the mechanisms of progression, and its behavior in specific tissues, are still not fully understood (Bray et al., 2021; Rodrigues et al., 2011). From the perspective of mathematical modeling, this complexity is reflected in the difficulty of constructing models entirely grounded in experimentally validated biological mechanisms. As highlighted by Murray (2002), most available tumor growth models are based on empirical curve fitting, simplified assumptions, or computational heuristics, which limits their biological and clinical applicability.

Nevertheless, mathematical modeling has proven to be an indispensable tool for understanding tumor dynamics and devising therapeutic strategies. Models based on ordinary differential equations (ODEs), in particular, have been widely used to simulate tumor progression, angiogenesis, and the effects of therapies (Byrne & Chaplain, 1995; Cristini & Lowengrub, 2010; Roose et al., 2007). These models offer both qualitative and quantitative insights into the mechanisms involved in tumor development, as well as enabling the incorporation of control theory concepts to assess the impact of therapeutic interventions as highlighted by De Pillis and Radunskaya (2003) and Nave (2022).

A notable example in this direction is the model introduced by Gatenby and Gawlinski (1996), which describes the competitive interaction between normal cells (N_1) and tumor cells (N_2) in a tissue. This formulation draws inspiration from ecological modeling principles, treating the tumor as an invasive species competing for space and resources. This approach has inspired a series of studies on tumor–host interactions and control possibilities, as discussed in Bellomo et al. (2008).

In this work, we analyze a dynamic tumor model that incorporates both cellular competition and external interventions represented by a control variable (u). In particular, we study a perturbation of the model originally proposed by Gatenby (1996), now extended with a control term representing therapeutic action. Our main objective is to investigate the *local controllability* of this system, understood as the ability to steer the dynamics locally between biologically meaningful states through appropriate control inputs. Puma and Henarejos (2024) present this type of analysis for a classical Lotka-Volterra model.

Based on the Kalman rank condition, we establish criteria under which local controllability is guaranteed. These results provide a theoretical foundation for understanding how therapeutic interventions, such as drug administration, can locally guide the biological system between different stages of tumor–healthy tissue interaction. Our analysis offers insights into identifying conditions under which treatment can effectively stabilize or reverse tumor growth, thus contributing to the development of mathematical approaches to support cancer therapy.

Based on the above and the author's knowledge, it is observed that, in the existing studies on the perturbed Gatenby model, there is no analysis from the perspective of local controllability. Therefore, the contributions of this work can be summarized as follows:

1. To formulate the local controllability problem of the control system in the neighborhood of its equilibrium points;

2. To identify specific equilibrium regions in which the dynamics of the control system ensure local controllability.

Throughout this paper, $\mathbf{P} \in \mathbb{R}^{n\times m}$ denotes a matrix, and $\mathbf{P}^\top$ its transpose. $\mathbb{R}_+$ denotes the set of positive real numbers and $\mathbb{R}_-$ the set of negative real numbers. To $N(t) \in \mathbb{R}^{n\times 1}$, the notation $\dot{N}(t)$ denotes its derivative. Moreover, it is denoted $\sigma(\mathbf{A})$ as the eigenvalues set of matrix $\mathbf{A} \in \mathbb{R}^{n\times n}$.

Material and methods

The methodology of this work consists of the formulation, analysis, and application of control theory tools to the study of the mathematical model that describes the competitive interaction between normal cells (N_1) and tumor cells (N_2). The competition between the cell populations (N_1, N_2) is modeled analogously to the Lotka–Volterra model, incorporating resource limitation effects and interspecies interaction, Gatenby (1996). The model is then modified to include a control function $u(t)$, representing the therapeutic action applied to the system (e.g., chemotherapy or another pharmacological agent).

The control system can be generically expressed as:

$$\begin{cases} \dot{N}_1 &= f_1(N_1, N_2), \\ \dot{N}_2 &= f_2(N_1, N_2) - u(t). \end{cases} \tag{1}$$

In the system described by equation (1), f_1 and f_2 represent the natural dynamics of the model, and $-u(t)$ models the effect of the external intervention. For simplicity, we denote $x = (N_1, N_2)^\top$, $\mathbf{B} = (0, -1)^\top$, and $f(x) = (f_1(x), f_2(x))^\top$. We now consider the equation

$$\dot{x} = f(x) + \mathbf{B}u. \tag{2}$$

Equation (2) is a rewrite of equation (1) and from now on we will use this notation.

Definition 1. Let $\mathcal{V}$ be an open subset of $\mathbb{R}^n$, $f : \mathcal{V} \to \mathbb{R}^n \in C^1$, and $\mathbf{B} \in \mathbb{R}^{n\times m}$ a constant matrix. An **Equilibrium Point** or **Equilibrium Solution** of the system, given by equation (2), is a pair $(x^*, h) \in \mathcal{V}\times\mathbb{R}^m$ such that

$$f(x^*) + \mathbf{B}h = 0. \tag{3}$$

The notion of Local Controllability via trajectories for a system given by the equation (2) is defined in Coron (2007), since an equilibrium solution (x^*, h), defined by the equation (3), is a type of constant trajectory.

Definition 2. Let (x^*, h) be an equilibrium point of the control system by equation (2). Such a system is said to be *locally controllable* at the equilibrium (x^*, h) if, for every real number $\epsilon > 0$, there exists a real number $\eta > 0$ such that, for every $x_0 \in B_\eta(x^*) := \{x \in \mathbb{R}^n \mid \|x - x^*\| < \eta\}$ and for every $x_1 \in B_\eta(x^*)$, there exists a measurable function $u : [0, \epsilon] \to \mathbb{R}^m$ such that

$$||u(t) - h|| \leq \epsilon, \quad \forall t \in [0, \epsilon], \tag{4}$$

and the solution to the Cauchy problem

$$\dot{x} = f(x) + \mathbf{B}u(t), \quad x(0) = x_0 \tag{5}$$

satisfies

$$x(\epsilon) = x_1. \tag{6}$$

No checkable necessary and sufficient condition is known for small-time local controllability for general control systems, even for analytic systems. However, there are powerful sufficient conditions (Coron, 2007).

On the other hand, for linear vector fields, i.e., $f(x) = \mathbf{A}x$, there is a result that characterizes controllability, known as the Kalman Theorem. As stated in Baumeister and Leitão (2014), this theorem asserts that:

Theorem 1. The *Kalman Test*

$$\text{rank}\,\left[\mathbf{B}\;\; \mathbf{AB}\;\; \mathbf{A}^2\mathbf{B}\;\; \cdots\;\; \mathbf{A}^{n-1}\mathbf{B}\right] = n, \tag{7}$$

is a necessary and sufficient condition for the system $\dot{x} = \mathbf{A}x + \mathbf{B}u$ to be controllable. That is, for every $x_0, x_1 \in \mathbb{R}^n$, there exists a measurable and essentially bounded function $u : [0, \epsilon] \to \mathbb{R}^m$ such that the solution to the Cauchy problem

$$\dot{x} = \mathbf{A}x + \mathbf{B}u, \quad x(0) = x_0 \tag{8}$$

satisfies

$$x(\epsilon) = x_1. \tag{9}$$

The system of equations, (8) and (9), is called a linear control system and u is the control function so that the trajectory starts at x_0 and ends at x_1.

Definition 3. Let (x^*, h) be an equilibrium point of the control system by equation (2). The linearized control system at (x^*, h) is the linear control system:

$$\dot{x} = Df(x^*)x + \mathbf{B}u, \tag{10}$$

where, at time t, the state is $x(t) \in \mathbb{R}^n$ and the control is $u(t) \in \mathbb{R}^m$.

The local controllability analysis of system given by equation (2) can be carried out by means of the linearization of the system around an equilibrium point (x^*, h). Coron (2007) demonstrated this with the following theorem:

Theorem 2. Let (x^*, h) be an equilibrium point of the control system by equation (2). Suppose that the linearized control system (10) at (x^*, h) is controllable. Then, the nonlinear control system $\dot{x} = f(x) + \mathbf{B}u$ is *locally controllable* at that equilibrium.

Theorem 2, which is straightforward and natural, is very useful. It is worth recalling that the controllability of the linearized system at (x^*, h) can be easily verified using the Kalman rank condition (Theorem 1), as also employed by Puma and Henarejos (2024).

Analysis of Equilibrium and Stability

Competition between species for space and limited resources is a central phenomenon in ecology, Murray (2002). To study the interactions between populations and predict their dynamic behaviors, mathematical models such as the system Lotka (1925) and Volterra (1931) are widely employed. A relevant application of these models arises in the context of cancer Rodrigues et al. (2011). We analyze the following system:

$$\begin{cases} \dot{N}_1 = \alpha N_1 \left(1 - \dfrac{N_1}{k_1} - \dfrac{a_{12}N_2}{k_1}\right) \\ \dot{N}_2 = \beta N_2 \left(1 - \dfrac{N_2}{k_2} - \dfrac{a_{21}N_1}{k_2}\right) - u(t) \end{cases} \tag{11}$$

where N_1 and N_2 represent healthy and tumor cells respectively, with growth rates α, β, and carrying capacities k_1, k_2. The parameters a_{12} and a_{21} represent interspecific competition, while the input $u(t)$ models the effect of an external treatment.

To find the equilibria $(e, h) \in \mathbb{R}^2 \times \mathbb{R}$ of (11), we solve $\dot{N}_1 = 0$ and $\dot{N}_2 = 0$. The equilibrium points $e(h) = (N_1^*(h), N_2^*(h))$, with h being the harvesting parameter ($u = h$), are as follows:

a) **Total extinction:**

$$e_1 = (0, 0). \tag{12}$$

b) **Competitive exclusion:**

$$e_2 = (k_1, 0). \tag{13}$$

c) **Competitive exclusion:** $e_3^+(h)$ and $e_3^-(h)$ where

$$e_3^+(h) = (0, k_2^+(h)) = \left(0\,, \frac{k_2}{2} + \sqrt{\left(\frac{k_2}{2}\right)^2 - \frac{k_2}{\beta}h}\right) \;;\; h \in \left[0, \frac{k_2\beta}{4}\right]. \tag{14}$$

$$e_3^-(h) = (0, k_2^-(h)) = \left(0\,, \frac{k_2}{2} - \sqrt{\left(\frac{k_2}{2}\right)^2 - \frac{k_2}{\beta}h}\right) \;;\; h \in \left(0, \frac{k_2\beta}{4}\right). \tag{15}$$

d) **Coexistence:** $e_4^+(h)$ and $e_4^-(h)$, represent positive equilibria.

$$e_4^+(h) = (N_1^+(h), N_2^+(h)), \quad a_{12} < \frac{k_1}{k_2} < \frac{1}{a_{21}} \text{ and } h \in \left(0, \frac{\beta(1-a_{12}a_{21})}{4k_2} R_2^2\right] \tag{16}$$

$$e_4^-(h) = (N_1^-(h), N_2^-(h)), \quad a_{12} < \frac{k_1}{k_2} < \frac{1}{a_{21}} \text{ and } h \in \left(0, \frac{\beta(1-a_{12}a_{21})}{4k_2} R_2^2\right) \tag{17}$$

where $N_1^\pm(h) = k_1 - a_{12}N_2^\pm(h)$, $N_2^\pm(h) = \dfrac{R_2}{2} \pm \sqrt{\left(\dfrac{R_2}{2}\right)^2 - \dfrac{k_2 h}{\beta(1-a_{12}a_{21})}}$ and $R_2 = \dfrac{k_2 - a_{21}k_1}{1 - a_{12}a_{21}}$.

Lemma 1. Let

$$I = \left(0, \frac{\beta(1-a_{12}a_{21})}{4k_2} R_2^2\right) \quad \text{and} \quad R_1 = \frac{k_1 - a_{12}k_2}{1 - a_{12}a_{21}}.$$

If $a_{12} < \dfrac{k_1}{k_2} < \dfrac{1}{a_{21}}$, then:

1. $\left(N_1^+(0), N_2^+(0)\right) = (R_1, R_2) \in (0, k_1) \times (0, k_2)$.
2. $\left(N_1^\pm(h), N_2^\pm(h)\right) \in (0, k_1) \times (0, k_2)$ for all $h \in I$.

Proof. We will prove the statements in parts.

1. First, we show that $\left(N_1^+(0), N_2^+(0)\right) = (R_1, R_2) \in (0, k_1) \times (0, k_2)$. Indeed,

$$R_1 = \frac{k_1 - a_{12}k_2}{1 - a_{12}a_{21}},$$

and by the condition $a_{12} < \dfrac{k_1}{k_2}$, we have $k_1 - a_{12}k_2 > 0$. Moreover, $1 - a_{12}a_{21} > 0$ since $a_{12}a_{21} < \dfrac{k_1}{k_2}a_{21} < 1$. Thus, $R_1 > 0$.

On the other hand,

$$R_1 < k_1 \iff k_1 - a_{12}k_2 < k_1(1 - a_{12}a_{21}) \iff \frac{k_1}{k_2} < \frac{1}{a_{21}},$$

which is exactly one of the assumptions of the lemma. Hence, $0 < R_1 < k_1$.

Similarly, $R_2 \in (0, k_2)$.

2. Next, we show that $\left(N_1^\pm(h), N_2^\pm(h)\right) \in (0, k_1) \times (0, k_2)$ for all $h \in I$. The choice of the interval

$$I = \left(0, \frac{\beta(1-a_{12}a_{21})}{4k_2} R_2^2\right)$$

ensures that

$$0 < \left(\frac{R_2}{2}\right)^2 - \frac{k_2 h}{\beta(1-a_{12}a_{21})} < \left(\frac{R_2}{2}\right)^2, \quad \forall h \in I,$$

or equivalently,

$$0 < \sqrt{\left(\frac{R_2}{2}\right)^2 - \frac{k_2 h}{\beta(1-a_{12}a_{21})}} < \frac{R_2}{2}.$$

Thus,

$$-\frac{R_2}{2} < \pm\sqrt{\left(\frac{R_2}{2}\right)^2 - \frac{k_2 h}{\beta(1-a_{12}a_{21})}} < \frac{R_2}{2},$$

and consequently,

$$0 < \frac{R_2}{2} \pm \sqrt{\left(\frac{R_2}{2}\right)^2 - \frac{k_2 h}{\beta(1-a_{12}a_{21})}} < R_2.$$

Therefore, $N_2^{\pm}(h) \in (0, R_2)$.

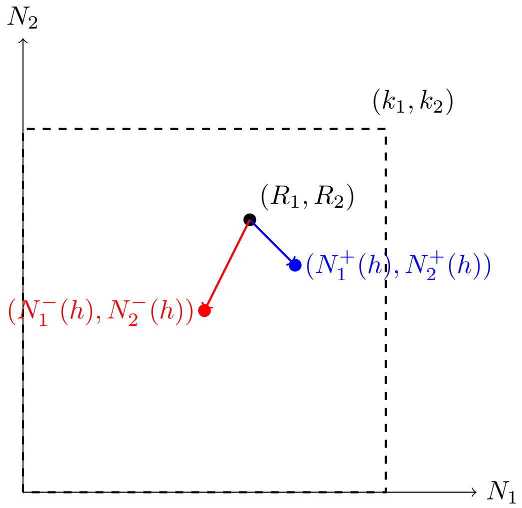
On the other hand, $a_{12} < \dfrac{k_1}{k_2}$ implies $R_2 = \dfrac{k_2 - a_{21}k_1}{1 - a_{12}a_{21}} < \dfrac{k_1}{a_{12}}$. Using $N_2^{\pm}(h) < R_2 < \dfrac{k_1}{a_{12}}$, we obtain

$$0 < N_2^{\pm}(h) < \frac{k_1}{a_{12}} \Longrightarrow 0 < a_{12}N_2^{\pm}(h) < k_1 \Longrightarrow 0 < k_1 - a_{12}N_2^{\pm}(h) < k_1.$$

Hence, $N_1^{\pm}(h) \in (0, k_1)$ for all $h \in I$.

In this way we complete the proof of Lemma 1. Furthermore, Figure 1 illustrates the result of the lemma, that is, the control equilibrium invariance property for $h \in I$.

Figure 1 - $(N_1^{\pm}(h), N_2^{\pm}(h))$ remain inside the rectangle $(0, k_1) \times (0, k_2)$ as h varies in the interval I.



The **linearized system** by equation (11) around $(e, h) = ((N_1^*, N_2^*), h)$ is defined as:

$$\begin{bmatrix} \dot{N}_1 \\ \dot{N}_2 \end{bmatrix} = \underbrace{\begin{bmatrix} \alpha\left(1 - \dfrac{2N_1^*}{k_1} - \dfrac{a_{12}N_2^*}{k_1}\right) & -\dfrac{\alpha a_{12}N_1^*}{k_1} \\ -\dfrac{\beta a_{21}N_2^*}{k_2} & \beta\left(1 - \dfrac{2N_2^*}{k_2} - \dfrac{a_{21}N_1^*}{k_2}\right) \end{bmatrix}}_{Df(e)} \begin{bmatrix} N_1 \\ N_2 \end{bmatrix} + \begin{bmatrix} 0 \\ -1 \end{bmatrix} u \tag{18}$$

By direct calculation, we obtain the Jacobian matrices $\mathbf{J}_i = Df(e_i)$ for each equilibrium point e_i, defined by equations (12) to (17).

$$\mathbf{J}_1 = \begin{bmatrix} \alpha & 0 \\ 0 & \beta \end{bmatrix}; \tag{19}$$

$$\mathbf{J}_2 = \begin{bmatrix} -\alpha & -a_{12}\alpha \\ 0 & -\beta\left(a_{21}\dfrac{k_1}{k_2} - 1\right) \end{bmatrix}; \tag{20}$$

$$\mathbf{J}_3^+(h) = \begin{bmatrix} -\alpha\left(a_{12}\dfrac{k_2^+(h)}{k_1} - 1\right) & 0 \\ -a_{21}\beta\dfrac{k_2^+(h)}{k_2} & -\beta\left(\dfrac{2k_2^+(h)}{k_2} - 1\right) \end{bmatrix}, \quad h \in \left[0, \frac{k_2\beta}{4}\right]; \tag{21}$$

$$\mathbf{J}_3^-(h) = \begin{bmatrix} -\alpha\left(a_{12}\frac{k_2^-(h)}{k_1} - 1\right) & 0 \\ -a_{21}\beta\dfrac{k_2^-(h)}{k_2} & -\beta\left(\dfrac{2k_2^-(h)}{k_2} - 1\right) \end{bmatrix}, \quad h \in \left(0, \frac{k_2\beta}{4}\right); \tag{22}$$

$$\mathbf{J}_4^+(h) = \begin{bmatrix} -\dfrac{\alpha}{k_1}N_1^+(h) & -\dfrac{\alpha\, a_{12}}{k_1}N_1^+(h) \\ \\ -\dfrac{\beta\, a_{21}}{k_2}N_2^+(h) & -\dfrac{\beta}{k_2}N_2^+(h) + \dfrac{h}{N_2^+(h)} \end{bmatrix}, \quad h \in I \text{ and } a_{12} < \frac{k_1}{k_2} < \frac{1}{a_{21}}\,; \tag{23}$$

$$\mathbf{J}_4^-(h) = \begin{bmatrix} -\dfrac{\alpha}{k_1}N_1^-(h) & -\dfrac{\alpha\, a_{12}}{k_1}N_1^-(h) \\ \\ -\dfrac{\beta\, a_{21}}{k_2}N_2^-(h) & -\dfrac{\beta}{k_2}N_2^-(h) + \dfrac{h}{N_2^-(h)} \end{bmatrix}, \quad h \in I \text{ and } a_{12} < \frac{k_1}{k_2} < \frac{1}{a_{21}}\,. \tag{24}$$

For example, in equation (23), it is straightforward to verify that $e_4^+(0) = (R_1, R_2)$ yields the following matrix:

$$\mathbf{J}_4^+(0) = \begin{bmatrix} -\dfrac{\alpha}{k_1}R_1 & -a_{12}\dfrac{\alpha}{k_1}R_1 \\ \\ -a_{21}\dfrac{\beta}{k_2}R_2 & -\dfrac{\beta}{k_2}R_2 \end{bmatrix}. \tag{25}$$

The Jacobian matrices given for (19) to (24) define linearized systems and it is important to know their stability properties to deduce the stability of the original system by equations (11). This analysis will be based on definitions and results in the following section.

Stability analysis of the equilibrium of the uncontrolled system

We analyze the following system:

$$\begin{cases} \dot{N}_1 = \alpha N_1 \left(1 - \dfrac{N_1}{k_1} - \dfrac{a_{12}N_2}{k_1}\right) \\ \dot{N}_2 = \beta N_2 \left(1 - \dfrac{N_2}{k_2} - \dfrac{a_{21}N_1}{k_2}\right) \end{cases} \tag{26}$$

Definition 3. Let $\mathcal{V} \subset \mathbb{R}^2$ be open, $f : \mathcal{V} \to \mathbb{R}^2$ of class C^1, and e^* an equilibrium of $\dot{N} = f(N)$. Then

(a) We say that e^* is a *stable equilibrium* if, given $\epsilon > 0$, there exists $\delta = \delta(\epsilon) > 0$ such that for any initial condition $N(0)$ satisfying $||N(0) - e^*|| < \delta$, the trajectory $N(t)$ satisfies:

$$||N(t) - e^*|| < \epsilon\,,\ \forall\, t \geq 0. \tag{27}$$

An equilibrium e^* is said to be *unstable* if it is not stable.

(b) We say that e^* is an *asymptotically stable equilibrium* if, in addition to being stable, it satisfies the following condition:

$$\lim_{t\to\infty} ||N(t) - e^*|| = 0. \tag{28}$$

The local stability around an equilibrium e^* can be classified by analyzing the nature of the eigenvalues of the Jacobian matrix $Df(e^*)$ associated with it. Below, we present results from stability theory Doering and Lopes (2016).

Theorem 3. Let $\mathcal{V} \subset \mathbb{R}^2$ be open, $f : \mathcal{V} \to \mathbb{R}^2$ of class C^1, e^* an equilibrium state of the system $\dot{N} = f(N)$, and $Df(e^*) = \mathbf{J} \in \mathbb{R}^{2\times 2}$ the associated Jacobian matrix.

1. If all eigenvalues of $\mathbf{J}$ have negative real parts, then e^* is an asymptotically stable equilibrium.
2. If $\mathbf{J}$ has at least one eigenvalue with positive real part, then e^* is an unstable equilibrium.

The equilibrium point is now classified by analyzing the nature of the eigenvalues of the corresponding matrix $\mathbf{J}$. For this, it is sufficient to use the matrices defined by equations (19) to (24):

$$\text{Eigenvalues of } \mathbf{J}_1 = \{\alpha, \beta\}, \tag{29}$$

$$\text{Eigenvalues of } \mathbf{J}_2 = \left\{-\alpha, -\beta\left(a_{21}\frac{k_1}{k_2} - 1\right)\right\}, \tag{30}$$

$$\text{Eigenvalues of } \mathbf{J}_3^+(0) = \left\{-\alpha\left(a_{12}\frac{k_2}{k_1} - 1\right), -\beta\right\}, \tag{31}$$

$$\text{Eigenvalues of } \mathbf{J}_4^+(0) = \left\{\lambda \in \mathbb{C} \,\middle|\, \lambda^2 + \left(\frac{\alpha R_1}{k_1} + \frac{\beta R_2}{k_2}\right)\lambda + \frac{\alpha R_1}{k_1}\frac{\beta R_2}{k_2}(1 - a_{12}a_{21}) = 0\right\}. \tag{32}$$

From now on, we denote $\mathbf{J}_3^+(0)$ and $\mathbf{J}_4^+(0)$ by $\mathbf{J}_3$ and $\mathbf{J}_4$, respectively. In the following section we present the stability results of these equilibria and from the perspective of controllability we compare both notions.

Results and discussion

We present the main results of the work. Firstly, the stability results corresponding to the uncontrolled system by equations (26).

Theorem 4. Consider the equilibria of system by equations (26): $e_1 = (0, 0)$, $e_2 = (k_1, 0)$, $e_3 = (0, k_2)$ and $e_4 = (R_1, R_2)$. Then

1. e_1 is unstable (local source).
2. If $\dfrac{1}{a_{21}} < \dfrac{k_1}{k_2}$ then e_2 is asymptotically stable (local attractor).
3. If $\dfrac{k_1}{k_2} < a_{12}$ then e_3 is asymptotically stable (local attractor).
4. If $\dfrac{k_1}{k_2} > a_{12}$ then e_3 is unstable (saddle).
5. If $\dfrac{1}{a_{21}} < \dfrac{k_1}{k_2} < a_{12}$ then e_4 is unstable (saddle).

Proof. Applying the results of local stability, Theorem 3, we obtain of result. That is, a simple observation on the sign of the eigenvalues in the matrices defined in (30) to (33) allows us to identify that:

1. $\sigma(\mathbf{J}_1) \subset \mathbb{R}_+$
2. $\sigma(\mathbf{J}_2) \subset \mathbb{R}_-$ since $\dfrac{1}{a_{21}} < \dfrac{k_1}{k_2}$.
3. $\sigma(\mathbf{J}_3) \subset \mathbb{R}_-$ since $\dfrac{k_1}{k_2} < a_{12}$.
4. $\mathbf{J}_3$ has one positive and one negative eigenvalue if $\dfrac{k_1}{k_2} > a_{12}$. Therefore e_3 is unstable (saddle) in this case.

5. If $\frac{1}{a_{21}} < \frac{k_1}{k_2} < a_{12}$ then $\mathbf{J}_4$ has a positive eigenvalue, $\lambda_1 \in \sigma(\mathbf{J}_4) \cap \mathbb{R}_+$. Therefore e_4 is unstable (saddle)

$$\lambda_1 = \frac{-\left(\frac{\alpha R_1}{k_1} + \frac{\beta R_2}{k_2}\right) + \sqrt{\left(\frac{\alpha R_1}{k_1} + \frac{\beta R_2}{k_2}\right)^2 + 4\frac{\alpha R_1}{k_1}\frac{\beta R_2}{k_2}(a_{12}a_{21} - 1)}}{2} > 0 \tag{33}$$

$$\lambda_2 = \frac{-\left(\frac{\alpha R_1}{k_1} + \frac{\beta R_2}{k_2}\right) - \sqrt{\left(\frac{\alpha R_1}{k_1} + \frac{\beta R_2}{k_2}\right)^2 + 4\frac{\alpha R_1}{k_1}\frac{\beta R_2}{k_2}(a_{12}a_{21} - 1)}}{2} < 0 \tag{34}$$

Theorem 5. Consider the equilibria of system by equation (11) with $a_{12} < \frac{k_1}{k_2} < \frac{1}{a_{21}}$. Then

1. The system is locally controllable around $(e_2, 0) = ((k_1, 0), 0)$.
2. It is locally controllable around $(e_4^+(h), h) = (N_1^+(h), N_2^+(h), h)$, for $h \in \left[0, \frac{\beta(1 - a_{12}a_{21})}{4k_2} R_2^2\right]$.
3. It is locally controllable around $(e_4^-(h), h) = (N_1^-(h), N_2^-(h), h)$, for $h \in \left(0, \frac{\beta(1 - a_{12}a_{21})}{4k_2} R_2^2\right)$.

Proof. Applying the results of Local Controllability (Theorem 2) for the system by equation (11) and consider that the Test Kalman (7) is equivalent to

$$\det\left[\mathbf{B} \quad \mathbf{J}_i\mathbf{B}\right] \neq 0,$$

for $\mathbf{B} = (0, -1)^\top$ and $\mathbf{J}_i = Df(e_i)$, we obtain the result.

Moreover, for $u(t) \equiv 0$, representing the uncontrolled tumor case, we recall the stability analysis of the equilibrium e_i presented in Rodrigues et al. (2011), and compare it with the corresponding controllable equilibrium $(e_i, 0)$. A summary of this comparison is provided in Table 1.

Table 1 - Local properties of system by equations (26) with $\frac{1}{a_{21}} < \frac{k_1}{k_2} < a_{12}$

	Equilibrium	**Stability**	**Controllability**
Total Extinction	$(0, 0)$	Source / Unstable	-
Competitive Exclusion	$(k_1, 0)$	Asymptotically Stable	Locally Controllable
Competitive Exclusion	$(0, k_2)$	Asymptotically Stable	-
Coexistence	(R_1, R_2)	Saddle / Unstable	Locally Controllable

In Figure 2, we observe the dynamics predicted in Table 1. Specifically, we consider the synthetic parameters $\alpha = 2.2$, $\beta = 1.1$, $k_1 = 60$, $k_2 = 10$, $a_{12} = 6.5$, and $a_{21} = 0.25$, which were assumed for the purpose of generating the corresponding numerical simulation and graphical representation, without any a priori biological interpretation.

With these values, we obtain the dynamics around the equilibria: $(0, 0)$ (unstable), $(60, 0)$ (asymptotically stable), $(0, 10)$ (asymptotically stable), and $(8, 8)$ (unstable). Also shown in Figure 3 is the corresponding trajectory $(N_1(t), N_2(t))$ (blue curve and orange curve, respectively).

Figure 2 - Phase-plane representation of the equilibria as indicated in Table 1.

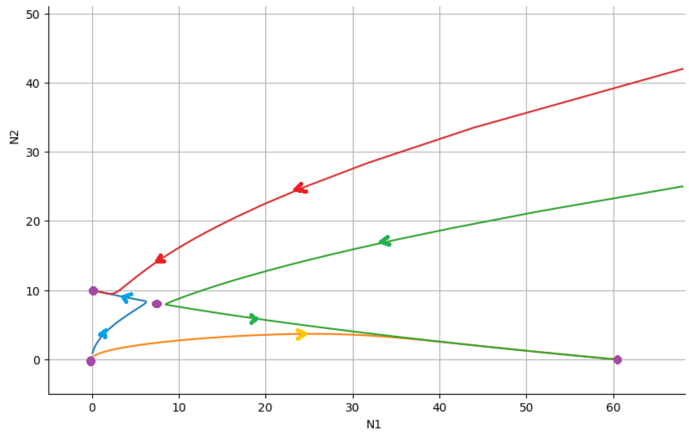
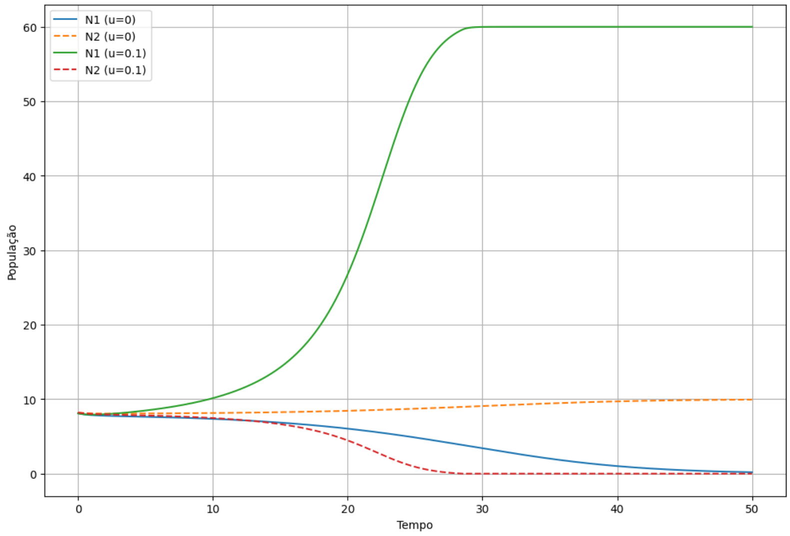


Figure 3 - Numerical solutions of the system given by equation (11) with parameters used in Figure 2.



Conclusions

We investigated the local controllability of a nonlinear tumor-normal cell interaction model under therapeutic control. By analyzing the linearized dynamics around multiple equilibrium configurations and applying the Kalman rank condition, we rigorously established conditions under which the system is locally controllable. These results confirm the ability of control actions to influence the state trajectory in the vicinity of equilibria, enabling a precise theoretical characterization of treatment effectiveness.

For instance, in Figure 3, when $u \equiv 0$, the numerical solution converges to the equilibrium corresponding to the exclusion of species N_1. However, under a constant harvesting rate $u = 0.1$, the system transitions to the equilibrium of extinction of species N_2. These findings underscore the potential of control strategies in modulating tumor–healthy cell interactions and point to the need for further studies on sustainable harvesting thresholds that could effectively reduce tumor cell populations while preserving the persistence of healthy cells N_1, with direct relevance to biomedical treatment planning.

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Author Contributions

F. F. C. Puma participated in: Conceptualization, Project managements, Formal Analysis, Data Curation, Investigation, Methodology, Supervision, Validation, Visualization and Writing – preparation of the original draft, revision and editing.

Conflicts of Interest

The author declare no conflict of interest.

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