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Research Article

Mathematical Modeling of Tumor-Immune Interaction with Optimal Control in the Human System

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Abstract

This paper presents a mathematical analysis of the immune response to tumor growth, conceptualized through the lens of predator-prey interactions. We investigate a three-dimensional mathematical model that captures the complex dynamics between tumor cells (the prey), hunting immune cells (active predators), and resting immune cells (reservoir population). The model extends classical ecological frameworks to immunology, recognizing that tumors and immune cells engage in a continuous battle for survival within the human body much like species competing in an ecosystem. We first establish the biological validity of our model by proving that all solutions remain positive, exist uniquely, and stay bounded over time essential properties when modeling living systems where negative populations would make no sense. Our analysis reveals that this seemingly simple system harbors surprisingly rich dynamical behavior. Unlike earlier models based on mass-action kinetics, our formulation shows the existence of multiple equilibrium points, representing different disease outcomes: tumor elimination, uncontrolled growth, or chronic persistence. Most notably, we identify conditions under which Hopf bifurcations occur, giving rise to limit cycles periodic oscillations in tumor and immune cell populations that mirror clinical observations of cancer remission and relapse cycles. Recognizing that clinical reality demands more than just understanding these dynamics, we implement a feedback control strategy designed to stabilize tumor populations at clinically manageable levels. Rather than aiming for complete eradication (which may not always be achievable), this approach seeks to transform aggressive growth into a controlled, chronic condition. Numerical simulations demonstrate that our control mechanism can successfully stabilize otherwise unstable equilibria, effectively "taming" the tumor's behavior. Parameter sensitivity analysis reveals that the half-saturation constants play particularly crucial roles in determining system outcomes. These constants, which govern how quickly immune responses saturate with increasing tumor burden, emerge as potential therapeutic targets. The findings suggest that treatments modifying these immunological thresholds might be as important as those directly killing tumor cells a perspective that could inform future immunotherapy strategies. This work bridges ecological modeling, dynamical systems theory, and clinical oncology, offering both theoretical insights into tumor-immune interactions and practical tools for treatment optimization.

Keywords

Tumor Growth, Predator-Prey, Immune System, Stability, Optimal Control, Holling Type-II Functional Response, Hopf Bifurcation

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1. Introduction

Cancer is widely recognized as one of the world's leading causes of death, making the control of tumor growth a critical global health challenge. The World Health Organization (WHO) estimates that approximately six million people die yearly due to cancer, making it the second most fatal disease after cardiovascular diseases [30]. Consequently, understanding tumor dynamics and developing effective therapeutic strategies is of major public health interest. Cancer begins when the tightly regulated process of cell growth and division breaks down, leading to uncontrolled cell proliferation and the formation of a mass of extra tissue called a tumor [2, 4]. Tumors are classified as either benign (noncancerous) or malignant (cancerous). Malignant tumors are particularly dangerous because they can invade and destroy surrounding healthy tissue and metastasize, spreading through the bloodstream or lymphatic system to form secondary tumors in distant organs [19].

In human physiology, the immune system plays a crucial role in identifying and eliminating tumor cells when they are detectable as non-self [32-34]. The cellular immune response is primarily carried out by T lymphocytes, which include both resting T cells and hunting (cytotoxic) T cells [13-17]. Resting T cells recognize tumor antigens through major histocompatibility complex (MHC) molecules and produce cytokines, but they cannot directly kill tumor cells. These cytokines activate resting T cells to become cytotoxic T lymphocytes (hunting cells), which can eliminate tumor cells through cytotoxic reactions [29].

The tumor microenvironment encompasses immune cells, fibroblasts, endothelial cells, the extracellular matrix, and signaling molecules including chemokines, cytokines, and growth factors [9]. Findings from the last two decades have evolved the conceptual framework from "immunosurveillance" referring to the immune system's tumor-protective role to "cancer immunoediting," which describes its dual function in both protecting against and sculpting tumors [36, 38, 39].

Mathematical modeling has become an essential tool for understanding tumor-immune dynamics and designing therapeutic strategies [3, 20]. This paper investigates an ordinary differential equation model comprising three equations that describe the interactions among cancer cells and two classes of immune cells: resting and hunting T lymphocytes. The model's structure builds upon foundational frameworks [17, 19] and modifies previous approaches [10] by substituting mass-action functional responses with Holling's Type II response. This adjustment incorporates more biologically realistic growth dynamics and reveals novel dynamical scenarios unattainable under mass-action kinetics.

2. Model Formulation

Following the modeling methodology of previous studies [17, 19], we consider a prey-predator type model for the interaction between cancer cell population (prey) and hunting and resting effector cells (predators) [8, 10]:

$$\frac{dT}{dt} = q + rT\left(1 - \frac{T}{k_1}\right) - f(T)H$$

$$\frac{dH}{dt} = g(R)H - d_1H \tag{1}$$

$$\frac{dR}{dt} = sR\left(1 - \frac{T}{k_2}\right) - g(R)H - d_1R$$

All model parameters are positive constants. Since cell concentrations cannot be negative, the state space of system (1) is restricted to $T(t) \geq 0$, $H(t) \geq 0$, and $R(t) \geq 0$.

In equations (1):

1) $T(t)$ represents the tumor cell population at time t

2) $H(t)$ represents the hunting effector cell population at time t

3) $R(t)$ represents the resting effector cell population at time t

4) q is the conversion rate of normal cells to malignant ones

5) r is the intrinsic growth rate of tumor cells

6) k_1 is the carrying capacity of the tumor cell population

7) α is the killing rate of tumor cells by hunting cells

8) β is the conversion rate of resting cells to hunting cells

9) d_1 is the natural death rate of hunting cells

10) s is the growth rate of resting cells

11) k_2 is the carrying capacity of resting cells

12) d_2 is the natural death rate of resting cells

13) $f(T)$ denotes the functional response of hunting effector cells to tumor cell population

14) $g(R)$ represents the functional response of hunting effector cells to conversion of resting effector cells

Previous studies [10-12] considered linear functional responses:

$$f(T) = \alpha T,\ g(R) = \beta R \tag{2}$$

However, these forms are not biologically realistic as they describe unlimited killing capacity of hunting effector cells and unlimited conversion capacity of resting effector cells. More realistic functional responses exhibit saturation effects [1]. Therefore, we modify model (1) by incorporating Holling's Type-II functional responses:

$$f(t) = \frac{\alpha T}{a+T} \text{ and } g(t) = \frac{\beta R}{b+R} \tag{3}$$

Here, a represents the half-saturation population of tumor cells, the population at which the hunting effector cell's killing capacity reaches half its maximum. Similarly, b is the half-saturation population of resting effector cells. Substituting (3) into model (1), our main model becomes:

$$\frac{dT}{dt} = q + rT(1 - \frac{T}{k_1}) - \frac{\alpha T}{a + T} H$$

$$\frac{dH}{dt} = \frac{\beta}{b + \mathrm{R}} H - d_1 H \quad (4)$$

$$\frac{dR}{dt} = sR(1 - \frac{T}{k_2}) - \frac{\beta}{b + \mathrm{R}} H - d_2 R$$

Non-Dimensionalization

To reduce the number of system parameters, we introduce the following dimensionless variables:

$$t^* = \frac{qt}{k_1}, x_1 = \frac{T}{k_1}, x_2 = \frac{\alpha H}{q}, x_3 = \frac{R}{k_2}, c_1 = \frac{rk_1}{q}, c_2 = \frac{\beta}{q} k_1, c_3 = \frac{k_1}{q} d_1,$$

$$c_4 = s\frac{k_1}{q},\ c_5 = \beta\frac{k_1}{\alpha k_2},\ c_6 = \frac{d_2 k_1}{q}, w_1 = \frac{a}{k_1} \text{ and } w_2 = \frac{b}{k_2} \quad (5)$$

The biological interpretations of the dimensionless parameters are:

1) c_1: dimensionless tumor growth rate
2) c_2, c_5: dimensionless conversion rates
3) c_3, c_6: dimensionless death rates
4) c_4: dimensionless resting cell growth rate
5) w_1: dimensionless half-saturation constant for tumor cell killing
6) w_2: dimensionless half-saturation constant for resting cell conversion

Using these dimensionless variables and constants, system (4) reduces to:

$$\frac{dx_1}{dt} = 1 + a_1 x_1(1 - x_1) - \frac{x_1 x_2}{w_1 + \mathrm{x}_1}$$

$$\frac{dx_2}{dt} = \frac{a_2 x_2 x_3}{w_2 + \mathrm{x}_3} - a_3 x_2 \quad (6)$$

$$\frac{dx_3}{dt} = a_4 x_3(1 - x_3) - \frac{a_5 x_2 x_3}{w_2 + \mathrm{x}_3} - a_6$$

with non-negativity conditions $x_1(t) \geq 0$, $x_2(t) \geq 0$, and $x_3(t) \geq 0$.

3. Analysis of the Model

Theorem 3.1 (Positivity). All solutions $x_1(t)$, $x_2(t)$, and $x_3(t)$ of system (6) with non-negative initial conditions remain non-negative for all $t \geq 0$.

Proof: The first equation of system (6) can be written as:

$$\frac{dx_1}{x_1} = (a_1(1 - x_1) - \frac{x_2}{w_1 + \mathrm{x}_1})dt$$

Integration yields:

$$x_1(t) = x_1(0)exp[(a_1(1 - x_1(s)) - \frac{x_2(s)}{w_1 + \mathrm{x}_1(\mathrm{s})})\mathrm{ds}] \geq 0.$$

The second equation can be written as:

$$\frac{dx_2}{x_2} = (a_2 \frac{x_3}{w_2 + \mathrm{x}_3} - a_3)dt$$

which on integration yields:

$$x_2(t) = x_2(0)exp[\int_0^t (a_2 \frac{x_3(s)}{w_2 + \mathrm{x}_3(\mathrm{s})} - a_3)\ \mathrm{ds}] \geq 0.$$

The third equation can be written as:

$$\frac{dx_3}{x_3} = (a_4(1 - x_3) - \frac{a_5 x_2}{w_2 + \mathrm{x}_3} - a_6)dt$$

which on integration yields:

$$x_3(t) = x_3(0)exp[(a_4(1 - x_3(s)) - \frac{a_5 x_2(s)}{w_2 + \mathrm{x}_3(\mathrm{s})} - a_6)\mathrm{ds}] \geq 0.$$

Hence, system (6) maintains non-negativity for all $t \in [0, \infty)$.

Theorem 3.2 (Boundedness). All solutions of system (6) starting in R^3 *are uniformly bounded.*

Proof. 1. Upper Bound for $x_1(t)$:

From the first equation of (6), since $x_1 \geq 0$, $x_2 \geq 0$, $w_1 \geq 0$, the term: $-x_2/w_1 + x_1 < 0$

Thus,

$$\frac{dx_1}{dt} \leq 1 + a_1 x_1(1 - x_1)$$

Let $f(x_1) = 1 + a_1 x_1 - a_1 x_1^2$. This downward-opening parabola has positive root:

$$\mathrm{M_1}^* = \frac{a_1 + \sqrt{a_1^2 + 4a_1}}{2a_1}$$

If $x_1 > M_1^*$, then $\frac{dx_1}{dt} \leq 0$, so $x_1(t)$ is bounded above. We can choose $M_1 = \max\{x_1(0), M^*\} + \epsilon_1$ for some small $\epsilon_1 > 0$.

Upper Bound for $x_3(t)$:

From the third equation of (6):

$$\frac{dx_3}{dt} \leq x_3(a_4 - a_6 - a_4 x_3)$$

If $a_4 \leq a_6$, the $\frac{dx_3}{dt} < 0$ for $x_3 > 0$. If $a_4 > a_6$, Let $\mathrm{M_3}^* = \frac{a_4 - a_6}{a_4}$. For $\mathrm{x_3} > \mathrm{M_3}^*$ $\frac{dx_3}{dt} < 0$.

Thus $x_3(t)$ is bounded above by $M_3=\max\{x_3(0), \max\{0,\frac{a_4-a_6}{a_4}\}\}+\epsilon_3$.

Upper Bound for $x_2(t)$:

Define the composite function:

$$W(t) = \frac{a_5}{a_2}x_2(t) + x_3(t)$$

Taking the derivative and substituting from (6):

$$\frac{dW}{dt} = -\frac{a_5 a_3}{a_2}x_2 + a_4 x_3(1 - x_3) - a_6 x_3$$

Adding $a_3 W$ both sides:

$$\frac{dW}{dt} + a_3 W = -a_4 {x_3}^2 + (a_4 - a_6 - a_3)x_3 \leq M_3$$

Applying Gronwall's inequality:

$$W(t) \leq W_0 e^{-a_3 t} + \frac{M_3}{a_3}(1 - e^{-a_3 t})$$

As $t \to \infty$, $W(t) \leq \frac{M_3}{a_3}$ Since $W = \frac{a_5}{a_2}x_2 + x_3$ and both terms are non-negative, $x_2(t)$ is bounded. Therefore, all solutions are uniformly bounded [24-28].

Theorem 3.3 (Existence and Uniqueness). For any given non-negative initial conditions, system (6) has a unique solution that exists for all t and remains in R^3.

Proof. Let the system be denoted by $\frac{dx}{dt}$ =f(x) where x= $(x_1, x_2, x_3)^T$ and:

$$f_1(x_1, x_2, x_3) = 1 + a_1 x_1(1 - x_1) - \frac{x_1 x_2}{w_1 + x_1}$$

$$f_2(x_1, x_2, x_3) = \frac{a_2 x_2 x_3}{w_2 + x_3} - a_3 x_2$$

$$f_3(x_1, x_2, x_3) = a_4 x_3(1 - x_3) - \frac{a_5 x_2 x_3}{w_2 + x_3} - a_6$$

The functions f_1, f_2, f_3 are continuous in $\Omega = \{(x_1, x_2, x_3) \in R^3 | x_1 \geq 0, x_2 \geq 0, x_3 \geq 0\}$ since denominators $w_1 + x_1$ and $w_2 + x_3$ are always positive. All partial derivatives are continuous in Ω, implying f (x) is locally Lipschitz continuous. By the Picard-Lindelo¨f theorem [14], for any initial condition $x_0 \in \Omega$, there exists a unique local solution. Combined with boundedness, the solution exists globally.

To find equilibrium points of (6), we set all derivatives to zero:

$$1 + a_1 x_1(1 - x_1) - \frac{x_1 x_2}{w_1 + x_1} = 0$$

$$\frac{a_2 x_2 x_3}{w_2 + x_3} - a_3 x_2 = 0 \quad (7)$$

$$a_4 x_3(1 - x_3) - \frac{a_5 x_2 x_3}{w_2 + x_3} - a_6 = 0$$

From the second equation, we have two cases:

Case 1: $x_2 = 0$ (Hunting cells absent)

Substituting $x_2 = 0$ into the first equation gives:

$$1 + a_1 x_1(1 - x_1) = 0 \Rightarrow a_1 x^2 - a_1 x_1 - 1 = 0$$

The positive solution is:

$${x_{1,1}}^* = \frac{a_1 + \sqrt{{a_1}^2 + 4a_1}}{2a_1}$$

The third equation becomes:

$$x_3(a_4(1 - x_3) - a_6) = 0$$

This yields two possibilities:

Equilibrium E_1: $x_3 = 0$

$$E_1 = (\frac{a_1 + \sqrt{{a_1}^2 + 4a_1}}{2a_1}, 0, 0)$$

Equilibrium E_2: $a_4(1 - x_3) - a_6 = 0 \Rightarrow x_{3,2}{}^* = 1 - \frac{a_6}{a_4}$ (exists when $a_4 > a_6$)

$$E_2 = (\frac{a_1 + \sqrt{{a_1}^2 + 4a_1}}{2a_1}, 0, 1 - \frac{a_6}{a_4})$$

Case 2: $x_2 \neq 0$ and $\frac{a_2 x_3}{w_2 + x_3} - a_3 = 0$(Co-existence)

From $\frac{a_2 x_3}{w_2 + x_3} - a_3 = 0$:

$${x_{3,3}}^* = \frac{a_3 w_2}{a_2 - a_3}$$ (exists when $a_2 > a_3$)

From the third equation (dividing by $x_3 \neq 0$):

$$a_4 x_3(1 - x_3) - \frac{a_5 x_2}{w_2 + x_3} - a_6 = 0$$

Solving for x_2:

4. Equilibrium Points of the System

$${x_{2,3}}^* = \frac{w_2 + {x_{3,3}}^*}{a_5}(a_4(1 - {x_{3,3}}^*) - a_6)$$ (exists when $a_4(1 - {x_{3,3}}^*) - a_6 > 0$)

Substituting into the first equation gives a cubic equation for x_1:

$$a_1x_1^3 - (a_1 - a_1w_1)\, x_1^2 - (1 + a_1w_1 - x_{2,3}^*)\, x_1 - w_1 = 0 \quad (8)$$

This cubic can have one, two, or three positive real roots, leading to up to three coexistence equilibria $E_3 = (x_{1,i}^*, x_{2,3}^*, x_{3,3}^*)$

5. Local Stability Analysis

The Jacobian matrix of system (6) is:

$$J=\begin{pmatrix} a_1 - 2a_1x_1 - \frac{w_1x_2}{(w_1+x_1)^2} & \frac{-x_1}{w_1+x_1} & 0 \\ 0 & \frac{a_2x_3}{w_2+x_3} - a_3 & \frac{a_2w_2x_2}{(w_2+x_3)^2} \\ 0 & \frac{-a_5x_3}{w_2+x_3} & a_4 - 2a_4x_3 - a_5\frac{w_2x_2}{(w_2+x_3)^2} - a_6 \end{pmatrix} \quad (9)$$

5.1. Stability of E_1

At $E_1 = (x_{1,1}^*, 0, 0)$:

$$J(E_1) = \begin{pmatrix} -\sqrt{a_1^2 + 4a_1} & \frac{-x_{1,1}^*}{w_1+x_{1,1}^*} & 0 \\ 0 & -a_3 & 0 \\ 0 & 0 & a_4 - a_6 \end{pmatrix}$$

Eigenvalues: $\lambda_1 = -\sqrt{a_1^2 + 4a_1} < 0$, $\lambda_2 = -a_3 < 0$, $\lambda_3 = a_4 - a_6$.

E_1 is locally asymptotically stable if $a_4 < a_6$ and unstable if $a_4 > a_6$.

5.2. Stability of E_2

At $E_2 = (x_{1,1}^*, 0, x_{3,2}^*)$ where $x_{3,2}^* = 1 - \frac{a_6}{a_4}$

$$J(E_2) = \begin{pmatrix} -\sqrt{a_1^2 + 4a_1} & \frac{-x_{1,1}^*}{w_1+x_{1,1}^*} & 0 \\ 0 & \frac{a_2x_{3,2}^*}{w_2+x_{3,2}^*} - a_3 & 0 \\ 0 & \frac{-a_5x_{3,2}^*}{w_2+x_{3,2}^*} & -(a_4 - a_6) \end{pmatrix}$$

Eigen values are $\lambda_1 = -\sqrt{a_1^2 + 4a_1} < 0$, $\lambda_2 = \frac{a_2x_{3,2}^*}{w_2+x_{3,2}^*} - a_3$ and $\lambda_3 = -(a_4 - a_6) < 0$

E_2 is locally asymptotically stable if $\lambda_2 < 0$.i.e.

$$a_2\frac{1-\frac{a_6}{a_4}}{w_2+1-\frac{a_6}{a_4}} < a_3$$

5.3. Stability of E_3 (Co-existence Equilibrium)

At $E_3 = (x_{1,3}^*, x_{2,3}^*, x_{3,3}^*)$:

$$J(E_3) = \begin{pmatrix} J_{11} & J_{12} & 0 \\ 0 & 0 & J_{23} \\ 0 & J_{32} & J_{33} \end{pmatrix}$$

Where, $J_{11} = a_1 - 2a_1x_1^* - \frac{w_1x_2^*}{(w_1+x_1^*)^2}$

$$J_{12} = -\frac{x_1^*}{w_1+x_1^*}$$

$$J_{23} = a_2\frac{w_2x_2^*}{(w_2+x_3^*)^2} > 0$$

$$J_{32} = -a_5\frac{x_3^*}{w_2+x_3^*} < 0$$

$$J_{33} = a_4 - 2a_4x_3^* - a_5\frac{w_2x_2^*}{(w_2+x_3^*)^2} - a_6$$

The characteristic equation is: $(J_{11} - \lambda)\,\lambda^2 - J_{33}\lambda - J_{23}J_{32} = 0$

This gives one eigenvalue $\lambda_1 = J_{11}$ and two eigenvalues from $\lambda^2 - J_{33}\lambda + B = 0$ where

$$B = -J_{23}J_{32} > 0.$$

E_3 is locally asymptotically stable if:

1) $\lambda 1 = J11 < 0$

2) $J33 < 0$ (for the quadratic to have negative real parts)

When $J_{33} = 0$, the system undergoes a Hopf bifurcation, leading to limit cycle oscillations [35, 37].

From Descartes' rule of signs [27], cubic (8) has a single positive real root except when $w_1 < 1$ and $x^* > a_1w_1 + 1$, in which case multiple positive roots may exist.

Define the Hopf-bifurcations:

$$w_{21} = (\frac{a_2}{a_3} - 1)(1 - \frac{a_6}{a_4}) \quad (10)$$

$$w_{22} = a_3\frac{(\frac{a_2}{a_3}-1)(1-\frac{a_6}{a_4})}{a_2+a_3} \quad (11)$$

Then

1) For $w_2 > w_{21}$, only E_1 and E_2 exist, with E_2 stable

2) At $w_2 = w_{21}$, E_3 emerges (first bifurcation)

3) For $w_{22} < w_2 < w_{21}$, E_3 is stable

4) At $w_2 = w_{22}$, E_3 loses stability via Hopf bifurcation (second bifurcation)
5) For $w_2 < w_{22}$, E_3 is unstable and limit cycles appear

6. Optimal Control Problem

In this section, we study the optimal control of tumor model (6) about its equilibrium states using a feedback control approach [25]. Consider the controlled system:

$$\frac{dx_1}{dt} = 1 + a_1 x_1(1 - x_1) - \frac{x_1 x_2}{w_1 + x_1} + u_1$$

$$\frac{dx_2}{dt} = \frac{a_2 x_2 x_3}{w_2 + x_3} - a_3 x_2 + u_2 \quad (12)$$

$$\frac{dx_3}{dt} = a_4 x_3(1 - x_3) - \frac{a_5 x_2 x_3}{w_2 + x_3} - a_6 + u_3$$

where u_1, u_2, u_3 are control inputs representing therapeutic interventions (e.g., drugs, chemotherapy, radiotherapy) [5, 6]. We determine these controls to asymptotically stabilize the system about its non-negative equilibrium states.

Define perturbation variables:

$$\xi_1 = x_1 - \hat{x}_1,\ \xi_2 = x_2 - \hat{x}_2,\ \xi_3 = x_3 - \hat{x}_3 \quad (13)$$

where $\hat{x}_i$ are equilibrium coordinates of model (6). The perturbed system becomes:

$$\frac{d\xi_1}{dt} = a_1\xi_1(1 - 2\hat{x_1} - \xi_1) - \frac{\hat{x_1}\xi_1 + \hat{x_2}\xi_1 + \xi_1\xi_2}{w_1 + \xi_1 + \hat{x_1}}$$

$$+\frac{\hat{x_1}\hat{x_2}\xi_1 + \xi_1\xi_2}{(w_1 + \xi_1)(\hat{x_1} + w_1 + \xi_1)} + u_1$$

$$\frac{d\xi_2}{dt} = a_2\left(\frac{\hat{x_2}\xi_3 + \hat{x_3}\xi_2 + \xi_3\xi_2}{w_2 + \xi_3 + \hat{x_3}}\right) - \frac{a_2\hat{x_3}\hat{x_2}\xi_3}{(w_2 + \hat{x_3})(\hat{x_3} + w_2 + \xi_3)} - a_3\xi_3 + u_2 \quad (14)$$

$$\frac{d\xi_3}{dt} = a_4\xi_3(1 - 2\hat{x_3} - \xi_3) - a_6\xi_3 - a_5\left(\frac{\hat{x_2}\xi_3 + \hat{x_3}\xi_2 + \xi_3\xi_2}{w_2 + \xi_3 + \hat{x_3}}\right)$$

$$+\frac{a_5\hat{x_3}\hat{x_2}\xi_3}{(w_2 + \hat{x_3})(\hat{x_3} + w_2 + \xi_3)} + u_3$$

System (14) admits the trivial solution $\xi_1 = \xi_2 = \xi_3 = 0$ when $u_1 = u_2 = u_3 = 0$. The control problem is to find optimal nonlinear feedback control inputs that steer the system from an initial state to an equilibrium state while minimizing an integral performance measure [1, 18, 21].

We formulate the optimal control problem with the objective of minimizing tumor burden and treatment cost. Define the cost functional:

$$J(u_1, u_2, u_3) = \int_0^{t_f} [\xi_1^2 + \xi_2^2 + \xi_3^2 + \frac{1}{2}(r_1 u_1^2 + r_2 u_2^2 + r_3 u_3^2)]dt \quad (15)$$

subject to system (14), where r_1, r_2, $r_3 > 0$ are weight factors balancing control effort against state deviations [31]. By Pontryagin's maximum principle [27], we derive the optimal controls:

$$u_i^* = -\frac{1}{r_i}\frac{\partial H}{\partial u_i} \quad i = 1, 2, 3$$

where H is the Hamiltonian. The resulting optimal controls drive the system to equilibrium while minimizing the cost.

7. Numerical Simulations

We perform numerical simulations to validate our analytical findings. Using parameter values: $a_1 = 6.6$, $a_2 = 0.5$, $a_3 = 0.05$, $a_4 = 0.5$, $a_5 = 0.6$, $a_6 = 0.05$, and varying the half-saturation constants w_1 and w_2 [1, 22].

7.1. Equilibrium Analysis for Different Parameter Values

Case 1: $w_1 = 3.0$, $w_2 = 8.5$
Equilibrium points:
1) $E_1 \approx (1.1337, 0, 0)$
2) $E_2 \approx (1.1337, 0, 0.9)$
3) E_3 does not exist (since $w_2 > w_{21} \approx 0.9$)

Eigenvalues at $E_2 \approx (-8.36598, 0.22510, -0.45)$ - one positive eigenvalue makes E_2 un- stable. The hunting cell population collapses to zero, and the tumor approaches carrying capacity.

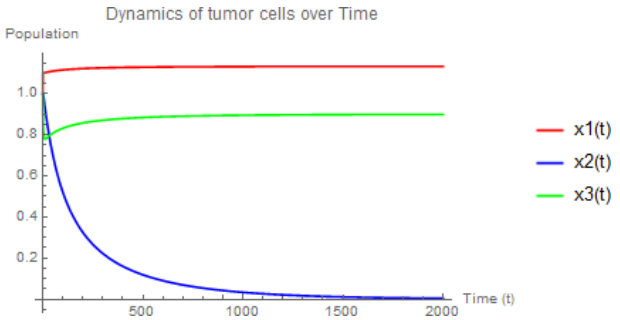

Figure 1. *$w_1 = 3.0$, $w_2 = 8.5$ - Hunting cells collapse.*

Case 2: $w_1 = 3.0$, $w_2 = 0.8$
Here $w_{22} \approx 0.7364 < w_2 = 0.8 < w_{21} \approx 0.9$, so E_3 exists and is stable:
$E_3 \approx (1.00690, 0.55776, 0.08182)$
The immune system controls but does not eradicate tumor cells, leading to stable coexistence. Initial oscillations dampen as the system approaches equilibrium.

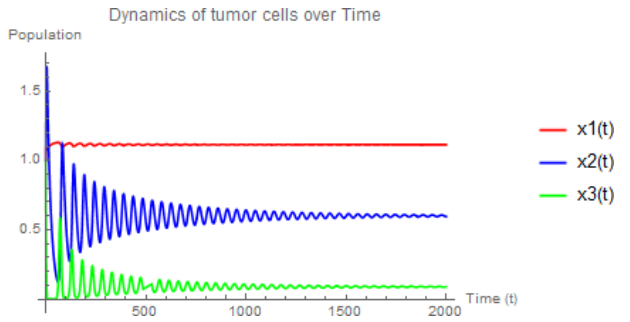

Figure 2. *$w_1 = 3.0$, $w_2 = 0.8$ - Stable coexistence equilibrium E_3.*

Case 3: $w_1 = 3.0$, $w_2 = 0.5$

Since $w_2 = 0.5 < w_{22} \approx 0.7364$, E_3 is unstable, and the system exhibits limit cycle oscillations:

1) Tumor population oscillates around a mean value
2) Hunting cells show large-amplitude oscillations (0.1 to 1.0)
3) Resting cells maintain low-level oscillations

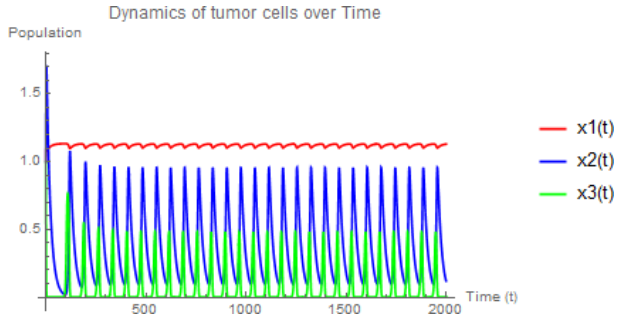

Figure 3. *$w_1 = 3.0$, $w_2 = 0.5$ - Unstable E_3 with limit cycle oscillations.*

Case 4: $w_1 = 0.2$, $w_2 = 1.0$

E_2 is stable:

1) Hunting cells behave like a drug-sensitive clone, eliminated quickly
2) Tumor cells reach near-carrying capacity
3) Resting cells coexist at reduced abundance

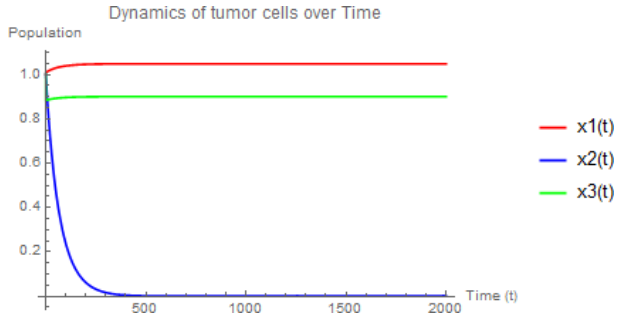

Figure 4. *$w_1 = 0.2$, $w_2 = 1.0$ - Stable E_2 with hunting cell elimination.*

Case 5: $w_1 = 0.2$, $w_2 = 0.8$

E_3 is stable, with hunting cells effectively controlling tumor growth:

1) Hunting cells reach system carrying capacity
2) Resting cells persist at low levels

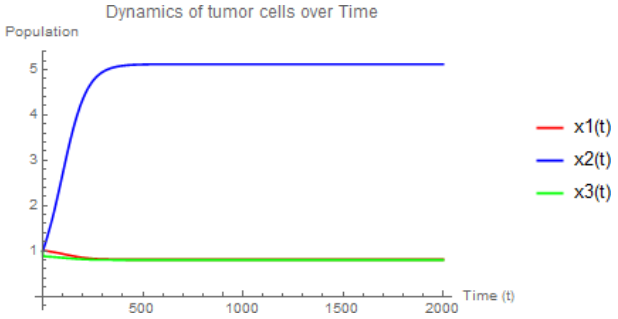

Figure 5. *$w_1 = 0.2$, $w_2 = 0.8$ - Stable E_3 with effective immune control.*

Case 6: Critical Parameters

At certain parameter values, all equilibria become unstable, leading to sustained regular oscillations:

1) Hunting cells show large amplitude oscillations (2 to 10)
2) Tumor and resting cells oscillate with the same period but smaller amplitude

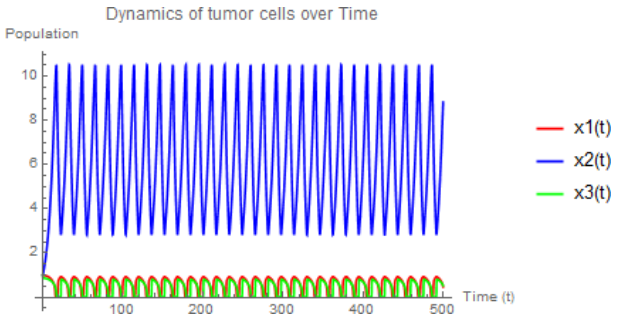

Figure 6. *All equilibria unstable - Sustained limit cycle oscillations.*

7.2. Numerical Solution of the Optimal Control

We now demonstrate the effectiveness of optimal control for stabilizing unstable equilibria. Using parameter values that yield unstable E_3: $a_1 = 6.6$, $a_2 = 0.5$, $a_3 = 0.05$, $a_4 = 0.5$, $a_5 = 0.6$, $a_6 = 0.05$, $w_1 = 0.1$, $w_2 = 0.7$.

The uncontrolled system exhibits oscillations. With optimal controls u_1^*, u_2^*, u_3^* derived from minimizing cost functional (15), the system stabilizes to equilibrium:

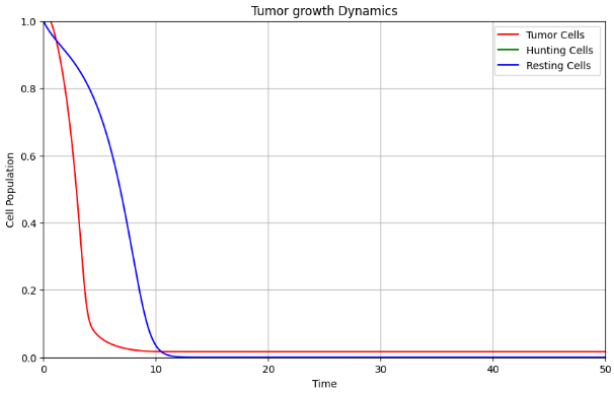

Figure 7. *Controlled system - Optimal controls stabilize the system to equilibrium.*

The control inputs initially apply strong therapy to dampen oscillations, then gradually reduce as the system approaches equilibrium. This demonstrates that optimal control theory can successfully design therapeutic interventions to stabilize tumor-immune dynamics [1, 31].

8. Discussion and Conclusion

This paper presents a mathematical model of tumor-immune interactions that incorporates biologically realistic Holling Type-II functional responses. Unlike previous mass-action model [10], our analysis reveals several novel dynamical features:

1) Multiple equilibria: The model can have none, one, or up to three positive coexistence equilibria, depending on parameter values.
2) Stability transitions: Coexistence equilibria can be stable or unstable, with stability determined by the half-saturation constants w_1 and w_2.
3) Hopf bifurcations: When coexistence equilibria lose stability, the system exhibits sustained limit cycle oscillations, representing periodic fluctuations in all three cell populations [35].
4) Threshold behavior: The half-saturation constant w_1 has a single threshold value of 1, while w_2 has two thresholds (w_{21} and w_{22}) that determine system dynamics:
   a) w2 > w21: Only E1 and E2 exist
   b) w22 < w2 < w21: Stable coexistence E3
   c) w2 < w22: Unstable E3 with limit cycles

The optimal control analysis demonstrates that therapeutic interventions can be designed to stabilize unstable equilibria, bringing tumor populations to manageable levels while minimizing treatment costs [1, 5].

Three important limitations and implications emerge:

First, the oscillatory dynamics predicted by the model, while mathematically interesting, lack empirical support in solid tumors. Further experimental validation is needed [9].

Second, administering anti-tumor treatments during oscillatory conditions presents clinical challenges. The optimal control framework developed here can guide treatment timing and dosage [6].

Third, the possibility of multiple tumor equilibrium values for fixed immune cell populations suggests an opportunity to contain cancer at the lowest equilibrium value through appropriate interventions [19, 23].

Future work should extend this model to include spatial effects, time delays [2, 7], and stochastic elements to capture more complex tumor-immune dynamics. Experimental vali dation of predicted bifurcations and optimal control strategies would strengthen the clinical relevance of this approach.

Author Contributions

Tewele Assefa Welu: Conceptualization, Formal analysis, Methodology, Software, Writing – original draft
Ataklti Araya: Data curation
Habtu Alemayehu: Supervision, Validation
Yohannes Yirga: Writing – review & editing
Subrata Kumar Sahu: Supervision, Validation

Conflict of Interest

The authors declare no conflict of interest.

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