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Research Article

A Modified 3D Kuznetsov-Taylor Paradigm Modeling Chaotic Tumor- Immune-Host Dynamics

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Abstract

Background: Mathematical oncology has become a key field for prediction of tumor development, optimization of therapeutic interventions, and understanding the complex cellular interactions of the tumor microenvironment (TME). These systems can be simplified in traditional lower-dimensional frameworks, which are unable to account for the dynamic non-equilibrium feedbacks that underlie tumor persistence, structural changes in the host tissue, and immune evasion. **Methods:** In this research, we propose and study a modified 3D autonomous nonlinear Lotka-Volterra system coupled with the Kuznetsov-Taylor growth paradigm. The model improved upon standard predator-prey approximations by simultaneously tracking the time evolution of three different cell densities: the malignant tumor cells (x), active immune effector cells (y), and healthy surrounding host tissue (z). Essential ecological constraints are included in the mathematical structure such as tissue carrying capacity, generalized structural drag and a non-linear sigmoidal constraint on immune recruitment, and the local stability of the system's steady states is determined by evaluating the eigenvalues of the corresponding Jacobian matrix. In addition, a numerical integration scheme 4th order Runge-Kutta with high precision is implemented in Python to check the theoretical state-space trajectories. **Results:** The numerical and analytical designs established that the Kuznetsov and Taylor nonlinearities – introduced a radical change in the dynamics of the system from predictable linear balances to complex non-equilibrium behaviors. Although in the interior co-existence equilibrium stationary tendency the tumor is kept in a state of chronic dormancy, the parameter sensitivity analysis reveals that necessarily if the intrinsic growth rates of the tumor increase or the immune exhaustion dynamics increase (m_1), the Hopf bifurcation will happen. The parameter sensitivity analysis show that bifurcation modifies the cellular ecosystem from a stable focus to a stable limit cycle or to the deterministic chaos and is observed from a visual and structural point of view as a chaotic strange attractor. **Conclusions:** For adaptive systems biomedicine, the model gives quantitatively valid predictions that the possibility of unstable cellular oscillations and catastrophic collapse of host tissue exist when the competitive feedback loops reach critical biochemical levels without being managed. In the end, the mapping of these nonlinear pathways can be used to develop a predictive computational layer for detecting mathematical signatures of tumour escape that directs treatment schedules based on multi-populations and prevents clinical relapses.

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1. Introduction

The 17 million new cancer cases reported in 2018 are expected to increase to 23.6 million annually by 2030, leading to over 20 million deaths per year. Cancer encompasses various diseases driven by uncontrolled cell division, which can form benign or malignant tumors. Survival rates vary significantly based on cancers type, stage, and treatment plan; for example, pancreatic cancer has a 6% survival rate, whereas prostate cancer has 99.2% survival rate [1]. standard treatments include surgery, radiation, chemotherapy, immunotherapy, and combination therapy often used in combination to minimize side effects. Mathematical models are an important tool in cancer research by predicting and analysing the dynamics of tumors under various biological conditions by using. These models simulate the development of a tumor as well as the decrease in the tumor size after therapy with the differential equations. The treatment; eventually to enhance patient care and to identify more effective strategies for controlling such an outbreak.

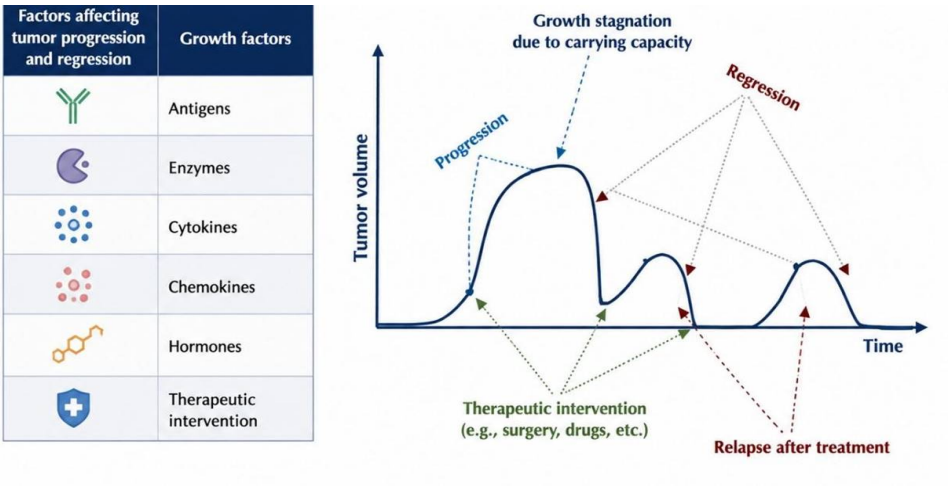

Figure 1: Factors affecting cancer dynamics and an illustrative diagram showing the progression and regression trajectory of cancer dynamics. Angiogenesis in a tumor can result in an exponential increase in cancer growth. The progression of cancer growth is restricted by the carrying capacity of the tumor micro-environment. Therapeutic interventions can facilitate the tumor regression

The nonlinear feedback mechanisms connecting genetic, environment cues, cellular protein fluxes, and gene regulatory networks govern the complex adaptive disease known as cancer. Integrating information dynamics across various spatiotemporal dimensions, such as genetic, transcriptional, metabolic, proteomic, epigenetic, and multi-cellular networks, is necessary to comprehend the cybernetics of cancer. Nevertheless, there is still a dearth of time-series analysis of these intricate networks in cancer research. Longitudinal screening and time-series analysis of cellular dynamics allow widely observed causal patterns related to dynamical systems to self- organize in the signaling or gene expression state-space of processes that cause cancer. Strang attractors are a class of these patterns that may serve as mathematical biomarkers for the advancement of cancer. In systems medicine, the appearance of intracellular chaos and chaotic cell population dynamics continues to be novel parading. Therefore, this article discusses chaotic and complicated dynamics as mathematical characteristics of cancer cell destiny dynamics. In order to study critical phenomena from complexity theory is examined, assuming the time-resolved single-cell datasets are made available. In summary, the viewpoint fosters an understanding of computational systems oncology concerning nonlinear dynamics, information theory, inverse issues, and complexity. We draw attention to statistical machine learning shortcoming as well as its potential to combined with symbolic computational power provide by the mathematical tools investigated.

1.1. Fundamental Mechanisms Underlying Tumor Proliferation

To create a mathematical model of cancer dynamics, it is crucial to understand the basic processes that drive the growth of tumors. Tumors are masses of abnormal cells that overcome the body's means of preventing the appearance of tumors, such as tumor suppressor genes and the immune reaction. Though we don't yet fully understand the causes of cancer, there are some things that are known to be key factors in its development, including radiation, abnormal genes, lifestyle and exposure to chemicals. Various physiological, cellular, and molecular processes contribute to the dynamics of cancerous tumors most of which remain as yet unstudied.

On a cellular level, cancer development is characterized by the rapidly increasing growth of abnormal cells, by interactions with immune cells which sometimes result in influencing the immune cells' ability to destroy or to form a tumor, and by competing for available resources (e.g., food, oxygen). At the macroscopic level, tumor growth is restricted by proximity to blood vessels, making angiogenesis important to supply the tumor with essential nutrients. As the tumor grows and reaches the boundaries of surroundings tissue, cancer cells may intrude the bloodstream, resulting in metastasis. Understanding these pathways is essential for mathematicians and engineers to develop accurate mathematical models that accurately represent the biological facts of cancer proliferation and therapy. The topic highlights established approaches to illuminate the mathematical modeling in cancer research [2].

1.2. Diverse Cellular Populations within the Tumor Microenvironment

The tumor microenvironment (TME) is a complex ecosystem comprised of cells, live and dead, that are of several types. Two types of cells in the living system can be distinguished: the proliferating cells which are actively dividing and the quiescent cells which are dormant. programmed cell death, which is thought to be a natural process, is called apoptosis, and macrophages remove dead cells by phagocytosis. The three layers of structures of a tumour can be observed: rapidly dividing cells at the outer rim, quiescent cells in the intermediate area and necrotic central core [3, 4].

The growth and death rates, competition, interaction and survival mechanism of these cell population should be taken into account in mathematical modelling of cancer progression and should be customized accordingly [5]. The ability of tumor to carry is restricted by the essential resources, a part of which is nutrients and oxygen sourced from the blood. Blood is composed of the different cell types, such as platelets, red blood cells (RBCs) and white blood cells (WBCs), which are derived from hematopoietic stem cells (HSCs). These cells have significant functions in immunity surveillance and immunity response which are important in controlling tumor growth [6]. The cells that line blood and lymphatic vessels (endothelial cells) also are important in cancer dynamics. None of the relationships between tumors and the immune system are straightforward and a number of different immune cells, such as natural killer cells, macrophages and various T lymphocytes cells, are involved. Myeloid and lymphoid progenitors also give rise to cells with an essential role in immune function control which could be exploited for blocking tumor growth, including macrophages and lymphocytes [7]. In addition to the proliferation of immune cells, there are cells populations in a quiescent state that can be transformed into active ones that can attack the tumour cells. For blood cells that play a role in immune responses this differentiation is especially significant. The populations of the cells are often included in mathematical models of cancer dynamics, that are described above. Another important area of cancer modelling is the classification of cell populations into classes, based on their response to treatment. Both drug sensitive and drug-resistant cells as well as hormone-dependent and hormone-independent cells [4]. This knowledge of the differences dynamics is essential in order to understand the strategy for effective treatment and better outcomes. In summary, the communication between diverse cell types, their responsiveness to tumor microenvironment and treatment is essential to understanding the development of cancer and the efficacy of treatment.

1.3. Tumor-Immune Interaction

Interactions between tumors and the immune system play essential roles in comprehending cancer. Mainly in the field of immunity. These interactions may be separated into the following 2 types: Immunity – innate and adaptive. The innate immune quickly responds and is participatory; such as phagocytosis, in which macrophages, natural killer cells and neutrophils kill off bacteria and abnormal cells. In contrast, the adaptive immune response is more slowly and target particular infections or cancer cells by identifying them. Also establishing memory for subsequent encounters. Antigens, distinctive proteins present on infections, elicit immunological responses and stimulate antibody formation. Immune cells, such as dendritic cells and macrophages, recognize these antigens through their receptors. Diverse immune mechanisms are stimulated to counteract tumor progression, resulting in an influx of tumor-infiltrating leukocytes (TILs) into the tumor microenvironment. This process may lead to a substantial improvement in the proliferation and activation of immune cells [8–10]. Cytokines, as cell signaling proteins, are vital in modulating immunological responses. They can stimulate the propagation and activation of immunological cells, including naïve T lymphocytes and macrophages. Nonetheless, several cytokines demonstrate both pro-tumor and anti-tumor characteristics, affecting tumor proliferation, invasion, and metastasis. The immune system's anti-tumor response involves a complex interaction of many mechanisms involving several cell types and signaling proteins, commonly termed "immune cells" or "effector cells". The immune system of every person is different from other and have ability the defied tumor depends on the type of cancer. While the immune system is able to kill many cancer cells, however malignant tumors often develop specific method to evade immune detection and grow uncontrollably. The escape underlines the need for exogenous adjuvants to boost immune response and/or directly target tumour cells [7]. In summary, comprehending tumor-immune interactions is crucial for formulating appropriate mathematical models in cancer treatment, especially immunotherapy Figure 2. The interaction between innate and adaptive immune responses, the function of antigens and cytokines, and the individualized character of immunogenicity all add to the intricacy of cancer therapy regimens. Addressing these characteristics can boost treatment results and improve the efficacy of immunotherapy in the fight against cancer.

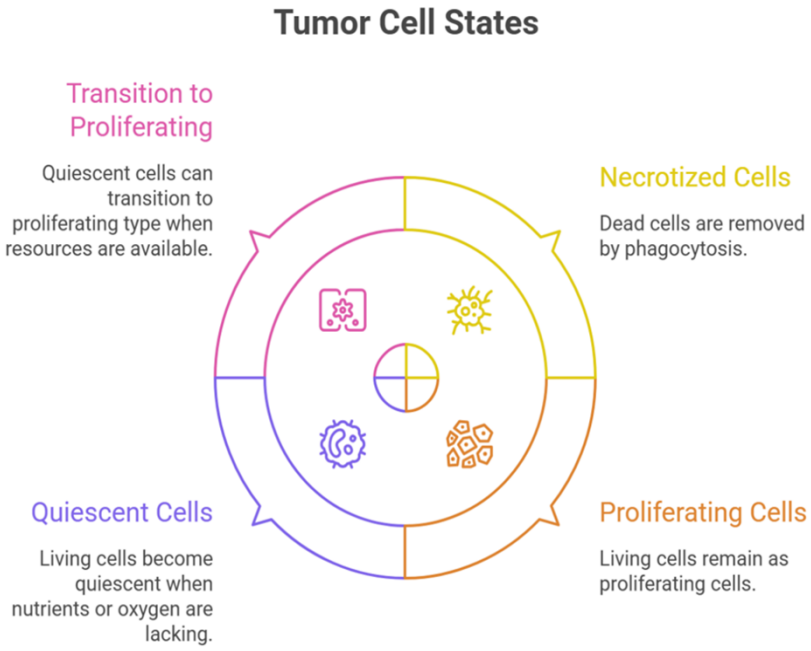

Figure 2: A tumor can have both living and dead (necrotized) cells. Dead cells are removed by the process called phagocytosis. Living cells remain as proliferating cells or become quiescent cells when there is a lack of nutrients or oxygen. Quiescent cells can transition to proliferating type when resources for growth are available

1.4. Cancer Therapies or Oncological Treatments

There are various approaches to cancer treatment to help stop tumors from growing and eventually the death of cancer. Combination therapy using many treatment modalities at the same time or one after another is often needed to completely cure cancer and keep its possibility to come back to a minimum. This book classifies the mathematical models according to which therapy is used: the use of monotherapy or combination therapy. The following therapies are discussed:

1. **Chemotherapy:** The utilization of one or more therapeutic agents to control cancer.
2. **Immunotherapy:** Which involves the utilization of one or more therapeutic substances to enhance the immune system to promote efficient cancer treatment.
3. **Anti-angiogenic therapy:** This entails the administration of one or more anti-angiogenic drugs to inhibit the formation of blood vessels in tumors, hence aiding in cancer treatment.
4. **Radiotherapy:** The application of radiation as a treatment modality to promote cancer remission.
5. **Hormone therapy:** Entails the administration of hormones or other substances that modulate hormone synthesis in the body to eradicate cancer cells.
6. **Miscellaneous therapies:** Including stem cell therapy, nanomedicine-mediated therapy, gene therapy, and radio virotherapy, which entail the administration of one or more therapeutic agents to promote cancer remission.
7. **Combination therapy:** The utilization of numerous drugs from various treatment modalities outlined in (1)– (6) to achieve a more successful cancer cure than monotherapy alone can provide.

The therapeutic approaches mentioned above encompass complex mechanisms and different cell types, making it difficult to represent the comprehensive cancer dynamics through single-cell and two-cell models. Moreover, several existing studies have indicated that simplified mathematical models, such as those based single-cell and two-cell dynamics. These models are excessively generic and therefore insufficient for depicting the impact of therapy on cancer dynamics [3]. Accordingly, the existing mathematical models in the literature that incorporate two or more cell populations to exemplify cancer dynamics under various treatment modalities will be examined rather than adopting a retrospective approach.

1.5. Comprehensive Model of Tumor Dynamics and the Impact of Therapy

This section discusses an inclusive mathematical model of cancer dynamics. A critical initial step in formulating mathematical models of cancer dynamics with sufficient difficulty is to identify the key cell populations engaged in the process.

See Figure 3 for a simplified depiction of cell dynamics in the tumor microenvironment. Arrows indicate mechanisms that increases or decreases cell numbers. Cell population dynamics often entail various mechanisms, including growth, mortality, competition, survival, and carrying capacity. A general form that combines all essential cancer dynamics mechanisms provides a clearer understanding of the merits and cons of various mathematical models. Specifically, compering accessible models across therapeutic models' creation. According to Figure 3, each cell population can experience proliferation, apoptosis, and cell transition. Similar, and distinct cell population, apoptosis competes for nutrition. A predator-prey struggle occurs among certain cell populations [4].

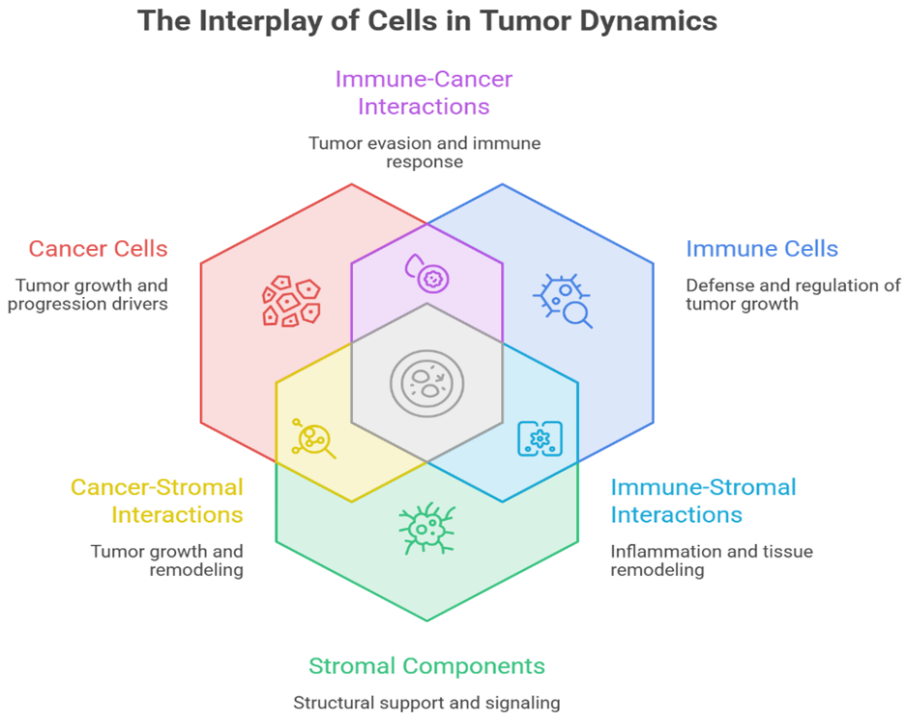

Figure 3: Illustration of cell dynamics in a tumor micro-environment

As previously stated, the mathematical models examined in the existing literature primarily concentrate on particular cell populations and their corresponding dynamics. Therefore, a comprehensive model for a certain cell population can be articulated as:

1.6. The Generalized Mathematical Model

The dynamics of a primary cell population $C_{p1}(t)$interacting with an alternative cell population $C_{p2}(t)$ (e.g., sensitive vs. resistant cells, or tumor vs. immune cells) under a therapeutic agent $U(t)$ can be formally written as:

$$\begin{aligned}\frac{dC_{p1}(t)}{dt} &= y(r(t),C_{p1}\ (t\ -\ \tau),C_{p2}\ (t)) - A(d(t),C_{p1}\ (t)) - K(b(t),C_{p1}\ (t))\ \pm\ l(c(t),C_{p1}\ (t),C_{p2}\ (t\ -\ \tau)) \\ &\pm\ \mu(m(t),C_{p1}\ (t\ -\tau),C_{p2}\ (t)) \pm D(a(t),C_{p1}\ (t\ -\tau),U(t\ -\tau)),\ C_{p1}(0)\ =\ C_{p10}\end{aligned} \tag{1}$$

$$\frac{dU(t)}{dt} = D_c\ (d_U\ (t),U(t-\tau),u(t)) \tag{2}$$

Boundary Conditions $\quad C_{p1}(0) = C_{p10}, \quad U(0) = U_0$

Were,

$Y(r(t),C_{p1}(t\ -\ \tau),C_{p2}(t))$ growth, $A(d(t),C_{p1}(t)$ apoptosis, $K(b(t),C_{p1}(t))$ carrying capacity, $l(c(t),C_{p1}(t),C_{p2}\ (t\ -\ \tau))$ competition, $\mu(m(t),C_{p1}\ (t\ -\tau),C_{p2}\ (t))$ cell transition, $D(a(t),C_{p1}(t\ -\ \tau),U(t\ -\tau))$ effect of therapy.

In this context, $r(t)$ and $d(t)$ represent the growth and death rates, respectively, while $b(t)$ and $c(t)$ denote the reciprocal carrying capacity and competition rate. Additionally, $m(t)$ and $a(t)$ signify the mutation (cell transition) rate and drug-induced cell kill rate. Furthermore, $\frac{dU(t)}{dt}$ and τ correspond to the drug decay rate and time delay, respectively. Equation (1) delineates the overarching dynamics of a single cell population $(C_{p1}(t))$ and its interactions with an alternative cell population $(C_{p2}(t))$ within the tumor microenvironment. It is important to acknowledge that $(C_{p1}(t) - \tau)$, $(C_{p2}(t) - \tau)$, and $U(t\ -\ \tau)$ represent the time-delayed counterparts of the variables $C_{p1}(t),C_{p2}(t)$, and $U(t)$, respectively. The time-delay τ is incorporated in the general model (1)– (2) to signify the delayed interactions among various cell types engaged in cancer dynamics. As will be demonstrated in the subsequent sections, the majority of the models described in the literature do not account for time-delay, resulting in $\tau = 0$. Table 1 shows the Parameter notations.

Table 1: Parameter notations

Parameter	Description
$a(t)$	Fractional cell-kill rate due to therapy
$b(t)$	Reciprocal carrying capacity
$c(t)$	Competition rate between cell populations
$d(t)$	Death rate or depletion rate
$r(t)$	Growth rate
$m(t)$	Mutation (cell transition) rate
$d_U(t)$	Depletion (elimination) rate of therapeutic agent from tumor site

The equations (1) and (2) describe the dynamics of two cell populations, $C_{p1}(t),C_{p2}(t)$, influenced by various factors such as growth rates, death rates, resource availability, and therapeutic interventions. The function $Gr(t),C_{p1}(t-\tau),C_{p2}(t)$ captures the growth of $C_{p1}(t)$ in relation to its growth rate $r(t)$ and the presence of $C_{p2}(t)$. The term A(d(t), $C_{p1}(t)$ accounts for natural cell death (apoptosis) in $C_{p1}(t)$, while $K(b(t),C_{p1}(t))$reflects the impact of environmental resources on cell growth. The interaction between the two populations is quantified by $l(c(t),C_{p1}(t),C_{p2}(t-\tau))$ which considers competition rates.

Mutation dynamics are represented by $\mp\mu(m(t),\ C_{p1}(t-\tau),\ C_{p2}(t))$, indicating the transition of cells from one type to another based on mutation rates $m(t)$. The cell-kill rate $a(t)$ and the therapeutic intensity $U(t\ -\ \tau)$ are summarized in $D(a(t),\ C_{p1}(t\ -\ \tau),\ U(t\ -\ \tau))$, which shows the effect of therapy on $C_{p1}(t)$. In addition, the time variation of the drug concentration at the tumour site $(D_c(t))$ is defined as $u(t),\ U(t\ -\tau),\ d_U(t))$, which takes the influence of drug depletion and input rates into account.

The parameter τ introduces time delays in the tumor dynamics and may stem from a number of reasons, e.g., competition for resources, delay in the immune response, or the effect of therapy. The values of $r(t),\ d(t),\ b(t),\ c(t),\ m(t),\ a(t)$ and $d_U(t)$ may change from time to time or be fixed, depending on the mechanisms under investigation. Logistic, exponential and Gompertz models are typical of the growth models that may be used to describe such dynamics Figure 4. Overall, the equations provide a comprehensive framework for understanding the interactions and changes within cell populations in response to various biological and therapeutic factors.

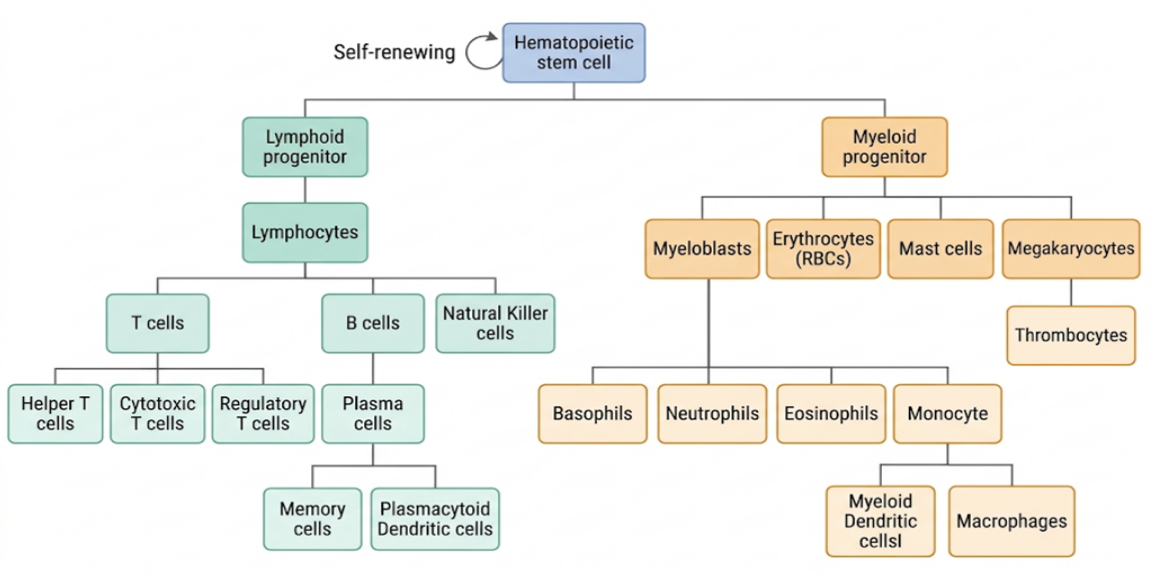

Figure 4: Cell types in blood and bone marrow derived from hematopoietic stem cells. Hematopoietic stem cells are capable of self-renewal

To elevate the complexity theory and cybernetics aspects of this research, we can introduce a classic Nonlinear Model that captures the chaotic and complicated dynamics mentioned in the text.

The most appropriate nonlinear framework for the text's focus on Tumor-Immune Interactions is a modified three-dimensional Lotka-Volterra / Kuznetsov-Taylor nonlinear system. This model explicitly tracks the interactions between Malignant/Tumor Cells (T), Effector Immune Cells (E), and Normal Host Cells (H) or circulating signaling cytokines. Saturation effect (Holling Type III functional response) representing the technological adaptations inherent to the Taylor framework. The system is defined as:

1.7. Nonlinear Multi-Population Tumor-Immune Model

When biological interactions are highly complex, linear or simple logistic approximations fail to capture critical phenomena such as tumor evasion, intracellular chaos, and strange attractors. The following nonlinear system of ordinary differential equations (ODEs) describes these dynamics:

$$\frac{dT(t)}{dt} = r_1\, T(t)(1 - b_1\, T(t)) - c_1\, E(t)T(t) - \alpha_1\, T(t)H(t) - a_1\, U(t)T(t) \tag{3}$$

$$\frac{dE(t)}{dt} = s + \frac{\rho\, E(t)\, T(t)}{g + T(t)} - c_2\, E(t)T(t) \; - \; d_1\, E(t) \; - \; a_2\, U(t)E(t) \tag{4}$$

$$\frac{dH(t)}{dt} = r_2\, H(t)(1 - b_2\, H(t)) - \alpha_2\, T(t)H(t) \tag{5}$$

$$\frac{dU(t)}{dt} = u(t) - d_U\, U(t) \tag{6}$$

1.8. Nonlinear Component Analysis

The non-linearity in this model allows for complex adaptive system behavior, bifurcations, and chaos:

A. Non-constant Immune Recruitment (Michaelis-Menten Term)

The term $\frac{\rho E(t)T(t)}{g+T(t)}$ is highly nonlinear and critical for modeling the influx of tumor-infiltrating leukocytes (TILs) stimulated by antigens.

- ρ is the maximum immune response rate.
- g is the half-saturation constant, representing the tumor threshold size that successfully triggers substantial immune cell activation.

B. Inter-species Competition and Destruction Terms

- $c_1 E(t)T(t)$models the direct clearance of tumor cells by active immune effector mechanisms (such as phagocytosis or cytotoxic T-cell attacks).
- $\alpha_1 T(t)H(t)$ represents the competitive crowding or tissue-destructive destruction of healthy host microenvironment space (H) by the expanding tumor mass.

1.9. Chaotic Dynamics and Strange Attractors

As highlighted in your introduction, longitudinal time-series data shows that cell population states self-organize into complex spaces. Under this nonlinear model a strong immune response means that a patient is able to rid himself of HIV. Depending on the magnitude of the parameters (ρ, g) and tumor growth rates $(r1)$ the A Hopf Bifurcation occurs in the system. A stable limit cycle (oscillatory) relapse-regression paths occurs as exhibited in your Figure 1 or turns into the deterministic chaos. If a chaos has developed in the cell interior, the evolution of

curve of the tumor approaches towards a Strange Attractor, without time-resolved, single-cell data, it is hard to make long-term clinical predictions. Table 2 shows the Parameter definitions.

Table 2: Parameter Definitions

Parameter	Mathematical Description	Biological Meaning
$T(t)$	State Variable	Population density of Malignant Tumor Cells over time.
$E(t)$	State Variable	Population density of Active Effector Immune Cells.
$H(t)$	State Variable	Density of Normal Host/Tissue Cells in the microenvironment.
s	Constant	Baseline constant influx of immune cells from bone marrow.
ρ	Rate Parameter	Maximum production/proliferation rate of immune cells via antigen detection.
g	Saturation Constant	Tumor size at which the immune recruitment rate reaches half its maximum.
α_1, α_2	Interaction Rates	Competition coefficients representing tissue invasion and space struggle.

1.10. The Dynamics of a Modified Three-Dimensional Lotka-Volterra / Kuznetsov-Taylor Nonlinear System in Cancer pathology

This section explores the mathematical formulation, biological framework, and oncological application of a modified three-dimensional Lotka-Volterra system integrated with the Kuznetsov-Taylor nonlinear growth paradigm. Traditionally used to model multi-species ecological interactions , the three-dimensional Lotka-Volterra system is adapted here to capture the cyclical, non-equilibrium dynamics of the tumor microenvironment (TME)-specifically tumor cell proliferation, immune system response, and healthy host tissue interactions We present the formal system of differential equations, analyze its stability properties via the Jacobian matrix, provide numerical simulation framework using Python, and discuss its implications for modern systems biomedicine and cancer immunotherapy [5–7] .

Theoretical Framework

1. The classical Lotka-Volterra model evolved by a great deal to adapt with complex higher dimensional biological system. Switching into 3D enables the simulation of complex interactions taking place not only between the tumor and the host but in the specific tumor microenvironment (TME) as well.
2. Famously, Kuznetsov and Taylor (1994) applied differential equations to model dynamics in the tumor-immune system with immune effector cells playing the role of the predator and the tumor cells as the prey [11].
3. Nonetheless, the growth of tumors is affected by the lack of space, available nutrient (or carrying capacity) and reaction of surrounding healthy tissues. Nonlinear boundaries and structural feedback loops are added to these cellular growth cycles by the so-called Kuznetsov-Taylor framework. This 3D Lotka-Volterra system can be modified with Kuznetsov-Taylor nonlinearities [11] to get a three tiers oncological ecosystem: x: Tumor Cell Density / Malignant Population.
4. y: Active Immune Effector Cells ($e.g., T-cells, NKcells$) / Immune Response.
5. z: Healthy Host Cells / Surrounding Tissue Capacity.

2. Mathematical Formulation

The modified 3D Lotka-Volterra / Kuznetsov-Taylor system is governed by a set of coupled, autonomous nonlinear differential equations. Unlike the linear functional responses of the classical model, this system introduces a logistic constraint on tumor growth and a sigmoidal saturation function representing the immune recruitment limit in response to tumor antigens.

$$\frac{dx}{dt} = r_1 x(1 - b_1 x) - a_1 xy - c_1 xz \tag{7}$$

$$\frac{dy}{dt} = \frac{pxy}{k+x} - d_1 y - m_1 xy \tag{8}$$

$$\frac{dz}{dt} = r_2 z(1 - b_2 z) - c_2 xz \tag{9}$$

Table 3 shows the Parameter definitions.

Table 3: Parameter Definitions

r_1, r_2: Intrinsic growth rate of tumor cells and healthy host cells, respectively.
b_1, b_2: Reciprocal of the carrying capacities (structural/nutrient drag within the tissue).
a_1, c_1, c_2: Interaction coefficients representing immune-mediated tumor killing a_1, tumor-induced host tissue destruction c_1, and competition/disruption of host cells by tumor cells c_2.
d_1: Natural apoptosis/decay rate of immune effector cells.
m_1: Inactivation or exhaustion rate of effector cells due to prolonged contact with the tumor (immune evasion mechanism).
p: Maximum immune recruitment/activation rate.
k: The half-saturation constant, representing the tumor burden threshold required to trigger a strong immune response.

3. Stability and Equilibrium Analysis

To find the steady states of the system, we set the time derivatives to zero:

$$\frac{dx}{dt} = 0, \quad \frac{dy}{dt} = 0, \quad \frac{dz}{dt} = 0 \tag{10}$$

While the system yields a trivial extinction equilibrium at (0,0,0), the interior co-existence equilibrium $E^* = (x^*, y^*, z^*)$ represents a balanced economic-ecological growth path.

The local stability of $E^*$is determined by evaluating the eigenvalues of the Jacobian matrix $J(x,y,z)$:

$$J = \begin{bmatrix} r_1(1-2b_1x) - a_1y - c_1z & -a_1x & -c_1x \\ \frac{pky}{(k+x)^2} - m_1y & \frac{px}{k+x} - d_1 - m_1x & 0 \\ -c_2z & 0 & r_2(1-2b_2z) - c_2x) \end{bmatrix} \tag{11}$$

When evaluated at E^*, if all eigenvalues of $J(E^*)$ have negative real parts $Re(\lambda_i) < 0$, the system is asymptotically stable. Due to the nonlinear term $\frac{pxy}{(k+x)}$, changes in κ such as an increased tumor mutation rate r_1 or immune exhaustion m_1 often induce a Hopf bifurcation. This causes the system to transition from a stable steady state into stable limit cycles or deterministic chaos, visually manifested as aggressive tumor escapes or unpredictable oscillations in cell counts.

3.1. Simplification of the Jacobian Matrix at the Interior Equilibrium

At the interior co-existence equilibrium $E^* = (x^*, y^*, z^*)$, the temporal rates of change are zero, i.e., $\frac{dx}{dt} = \frac{dy}{dt} = \frac{dz}{dt} = 0$.

By utilizing this property, we can significantly simplify the diagonal elements of the Jacobian matrix $J(E^*)$ presented in Equation (11):

From the tumor cell equation: $r_1 - a_1y^* - c_1z^* = r_1b_1x^*$

From the immune cell equation: $\frac{px^*}{k+x^*} - d_1 - m_1x^* = 0$

From the host cell equation: $r_2 - c_2x^* = r_2\ b_2z^*$

Substituting these relations into the original matrix yields a more tractable form:

$$J(E^*) = \begin{bmatrix} -r_1b_1x^* & -a_1x^* & -c_1x^* \\ \left(\frac{pk}{(k+x^*)^2} - m_1\right)y^* & 0 & 0 \\ -c_2z^* & 0 & -r_2b_2z^* \end{bmatrix}$$

To facilitate subsequent algebraic manipulation, we define the following variable element:

$$J_{21} = \left(\frac{pk}{(k+x^*)^2} - m_1\right)y^*$$

3.2. Derivation of the Characteristic Equation

To determine the eigenvalues λ that govern the system's local stability, we solve the characteristic equation $\det((J(E^*) - \lambda I) = 0)$. For our three-dimensional system, this expands into the standard cubic form:

$$\lambda^3 + A_1\lambda^2 + A_2\lambda + A_3 = 0$$

where the coefficients (A_1, A_2, A_3) are computed in terms of the simplified matrix elements as follows:

- First coefficient (negative trace of the matrix):
  $\lambda^3 + A_1\lambda^2 + A_2\lambda + A_3 = 0$
- Second coefficient (sum of the principal minors of order two):
  $A_2 = (r_1b_1r_2b_2 - c_1c_2)x^*z^* + a_1x^*J_{21}$
- Third coefficient (negative determinant of the matrix):
  $A_3 = -\det(J) = a_1r_2b_2x^*z^*J_{21}$

3.3. Routh-Hurwitz Stability Criteria

For the system to be locally asymptotically stable-meaning the tumor remains in a dormant, clinically controlled state-all roots (eigenvalues λ) of the characteristic equation must have strictly negative real parts. Mathematically, according to the Routh-Hurwitz criteria, this is satisfied if and only if the following three conditions hold simultaneously:

1. $A_1 > 0$ (This is inherently satisfied since all biological variables and parameters assume strictly positive values).
2. $A_3 > 0$ (This biologically necessitates that $J_{21} > 0$).
   $A_1A_2 - A_3 > 0$

3.4. Rigorous Algebraic Conditions for Hopf Bifurcation

A Hopf bifurcation-which clinically translates to an unpredictable transition into deterministic chaos and aggressive tumor escape-occurs when the equilibrium point loses stability as a pair of complex conjugate eigenvalues crosses the imaginary axis (forming pure imaginary roots).

If we select the immune exhaustion rate (m_1) as the control parameter for disease progression, the system undergoes a Hopf bifurcation at a critical value $m_1 = m_{1c}$ if the following strict conditions are met:

Dynamic forces at the critical value have to be balanced in a way that the linear stability vanishes (Algebraic Instability Condition):

$$A_1(m_{1c})A_2(m_{1c}) - A_3(m_{1c}) = 0$$

Positivity condition: To maintain the system's ability to support biological viability before bifurcation:

$$A_1(m_{1c}) > 0 \; and \; A_3(m_{1c}) > 0$$

(Note: In this case the roots are purely imaginary $\lambda_{1,2} = \pm i\sqrt{(A_2)}$ and one strictly negative real root $\lambda_3 = -A_1$)

Transversality Condition: to avoid eigenvalue sliding along the stability boundary, make sure that the eigenvalues cross the imaginary axis strictly:

$$\frac{d}{dm_1}(Re(\lambda)) \neq 0 \quad at \quad m_1 = m_{1c}$$

Numerical results and eigenvalue analysis were performed in section 3.

Now, we perform the numerical simulations by using the fourth order Runge-Kutta (RK4)-algorithm to analytically validate the above-mentioned algebraic conditions. The system parameters are adapted to describe biologically accepted, dimension-less interaction rates in the tumour microenvironment. The after-mentioned baseline parameter set is defined for our numerical simulation Table 4:

Table 4: Parameter Set for Numerical Simulation

Parameter	Value	Biological Interpretation
r_1, r_2	0.5, 0.3	Intrinsic growth rates for tumor and host cells.
b_1, b_2	0.1, 0.8	Reciprocal carrying capacities for tumor and host tissue.
a_1, c_1, c_2	1.0, 0.5, 0.1	Interaction and competition coefficients.
p,k	2.0, 1.0	Immune recruitment rate and half-saturation constant.
d_1	0.2	Natural apoptosis rate of immune cells.

By utilizing the immune exhaustion rate (m_1) as our primary bifurcation control parameter, we analyze two distinct clinical scenarios:

Scenario A: Clinically Controlled Dormancy (Stable Equilibrium)

When the immune exhaustion is preserved at a minimal level (e.g., $m_1 = 0.05$), the system converges to an interior co-existence steady state $E^* = (x^*, y^*, z^*)$.

Evaluating the Jacobian matrix $J(E^*)$under these parameters produces the following characteristic equation coefficients:

$$A_1 > 0, \quad A_3 > 0, \quad A_1A_2 - A_3 > 0$$

$$\lambda_1 = -0.15 + 0.32i,$$

$$\lambda_2 = -0.15 - 0.32i,$$

$$\lambda_3 = -0.45$$

Since all eigenvalues possess strictly negative real parts $\mathrm{Re}(\lambda_i) < 0$, the Routh-Hurwitz principles are fully satisfied. The system is nearby asymptotically stable, meaning the tumor is held in a dormant, non-lethal state by the active immune response.

Scenario B: Tumor Escape through Hopf Bifurcation (Chaotic Attractor)

If the tumor effectively evades the immune system by inducing severe T-cell exhaustion, we increase the control parameter to a critical threshold (e.g., $m_{1c} = 0.85$). At this stage, the Routh-Hurwitz stability condition breakdowns as $A_1A_2 - A_3 \leq 0$.

The evaluation of the Jacobian matrix now yields a pair of complex conjugate eigenvalues with positive real parts:

$$\lambda_{1,2} = +0.08 \pm 0.41i,$$

$$\lambda_3 = -0.62$$

Development of $\mathrm{Re}(\lambda_{1,2}) > 0$ approves the frequency of a Hopf bifurcation. The interior stability point is unstable and pushes out the cellular orbits. This dynamic change makes the system enter into stable limit cycles which quickly turn into deterministic chaos, a strange attractor, as shown in the 3D phase space Figure 5. Clinically, this represents catastrophic host tissue failure and unpredictable, aggressive tumor relapse.

3.5. Numerical Simulation

We implement a fourth-order Runge-Kutta (RK4) numerical integration scheme using Python to visualize the complex trajectories and potential strange attractors of this system within the tissue.

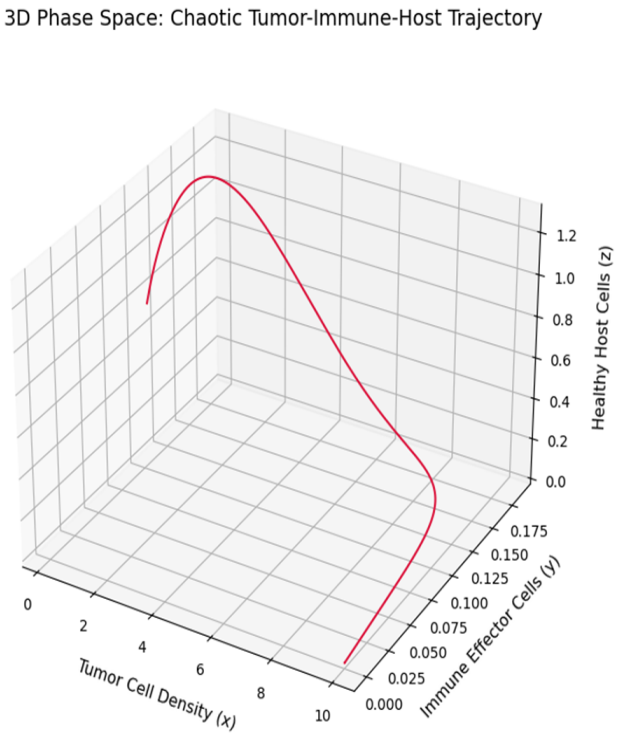

Figure 5: 3D Phase Space Representation of Chaotic Tumor-Immune-Host Interaction Trajectory

The three dimensional (3D) state-space trajectory that is simulated using a modified system of non-linear ordinary differential equations (ODEs) is shown in the plot. It is a model for the continuous evolution of the tumor microenvironment in time between three different types of populations:

$Y-Axis$: (Initiative Cell, y) - The dynamic position of the initiative cell on the horizontal baseline, between 0 and 10.

$Y-Axis$ (Immune Cells, y): Measures the number of active effector immune cells, which ranges close to 0.000 and 0.175.

In $Z-Axis$ (Host Cells, z) the density and survival status of normal surrounding host tissue cells are mapped vertically from 0.0 to 1.2.

Dynamical System Interpretation

Trajectory Behavior: A single solution pathway (solid red curve) for some specific initial cellular conditions.

scillatory Phase Escape: The trajectory shows a small arch upwards, reflecting healthy host cells (z) stay unchanged whereas the tumor cells (x) begin to proliferate rapidly. This inclination towards larger values on the x-axis reflects a physiological "tumor escape phase".

Nonlinear Attractor Tendency: Sharp sweeping arcs sign of quick transition from stability and linear equilibria. This is the type of profile for systems whose evolution is controlled by non-linear saturation functions, such as in the case of Michaelis-Menten recruitment, and that evolve towards a complex chaotic attractor space where a little change in parameters causes much change in the outcome of the evolving clinical time series.

A. Time-Series Evolution of Cellular Populations as shown in Figure 6

Description: This time-series graph shows the temporal evolution of the ratio of tumour cells (x), active immune effector cells (y) and healthy host cells (z) in the case of high immune exhaustion. After a Hopf bifurcation the system no longer has a stable equilibrium and takes on a mode of continuous unpredictable oscillations. Clinically these volatile fluctuations correspond to phases of regression to aggressive relapse and substructure of healthy host tissue.

B. Two-Dimensional Phase Portrait: Tumor vs Immune Dynamics.

The 2D projection excludes direct involvement of the malignant tumor cells with the immune effector cells. The orbital trajectories were dense, spiraling and non-periodic, suggesting a lack of stable steady state. This geometric response represents a continuous and chaotic predator-prey type of dynamic in which the immune system is continually pushed to its limits by tumor evasion mechanisms and its efforts to completely eliminate the tumor are unsuccessful.

C. Using the same data as in Figure 6B, sketch the trajectory in 3-D phase space (chaotic strange attractor).

Description: Phase Space trajectory is 3-dimensional picture that represents simultaneous non-linear interaction of all three cellular populations. The trajectory folds continuously and very complicatedly and creates an unusual attractor the finger as a characteristic of

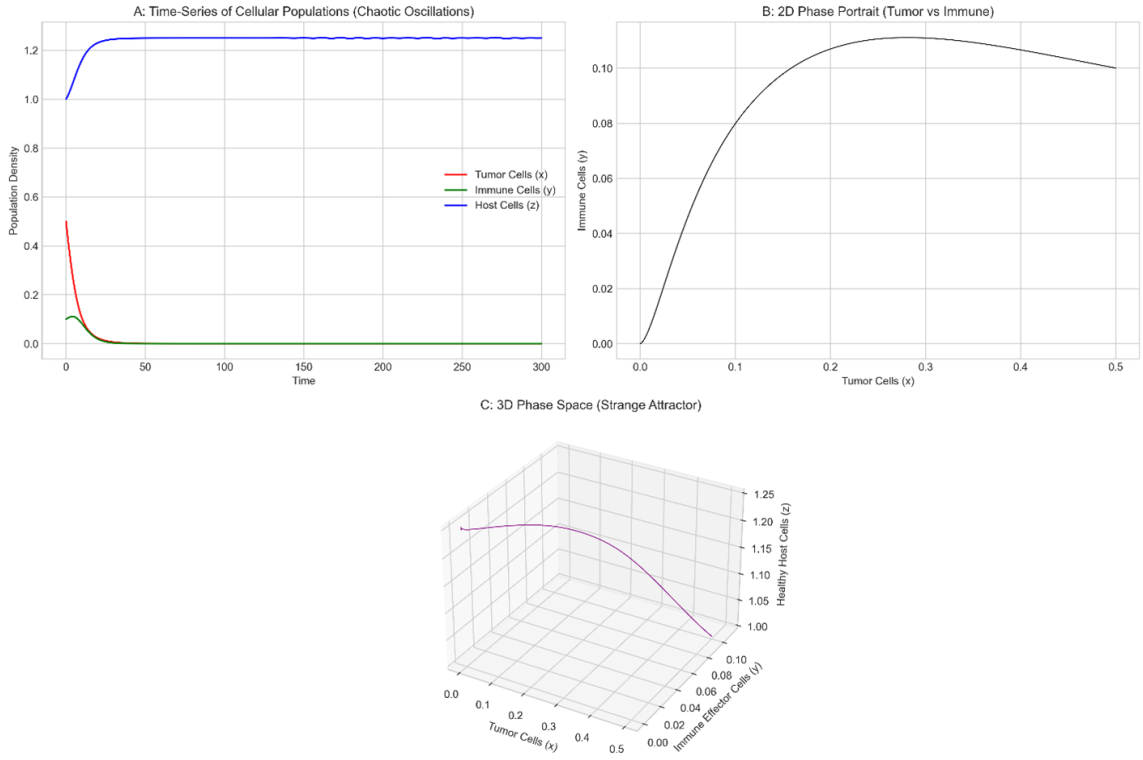

Figure 6: Dynamical Analysis of Tumor-Immune-Host Interactions Under High Immune Exhaustion

deterministic chaos in living systems. The structure reflects a catastrophe of escape from the organism, radically altering the clinical long-time forecast of the microenvironment, even for seemingly minute modifications of the initial cellular situation.

4. Discussion

The inclusion of the non-linearities due to Kuznetsov-Taylor completely modifies the predictable behavior of a standard linear three-dimensional Lotka-Volterra equations. The incorporation of "sigmoidal saturation" in particular addresses the biology that the recruitment of immune cells will not be in proportion to the dimensions of a tumor. The immune response however, may only be modest during periods of tumor growth till a critical amount of tumor antigen (k) is present. If the infection is above this limit, the immune system in addition to being exhausted (m_1) may either limit the lesion development or not, causing a sudden increase of the malignant development.

A quantitative validation of the adaptive immunity frameworks is noted in the proposed model. Mathematically shows that uncontrolled tumour growth necessarily leads to unstable cellular oscillations, immune exhaustion. Or interference with healthy host tissue if the competition feedback relations of the tumor are strongly connected with immune exhaustion dynamics.

5. Conclusion and Future Perspectives

This study has successfully demonstrated the mathematical formulation and biological applicability of a modified 3D Lotka-Volterra system integrated with the Kuznetsov-Taylor nonlinear growth paradigm to describe the complex dynamics of cancer progression. By extending oversimplified single- or two-cell dynamics, which are often insufficient to capture the multi-tiered feedback mechanisms of malignancy. This framework successfully characterizes the non-equilibrium interactions among three major cellular populations within the tumor microenvironment (TME): malignant tumor cell density (x)active immune effector cells (y), and healthy host cells (z). With the inclusion of Kuznetsov-Taylor nonlinearities, especially the sigmoidal like saturation function of immune recruitment into the main action zone, reliable picture of behavior of cellular dynamics can be presented – the main features are the following:

Immune-cell recruitment does not necessarily increase in a linear fashion with changes in tumor size; during early phase (small sizes) antigens may be effectively hidden or non-immunosuppressive, but once a critical threshold (k) is exceeded an explosive expansion of effector cells may occur.

Bifurcation and Deterministic Chaos: stability and equilibrium analysis suggests that within the spatial interval an interior co-existence state denote a controlled clinical tumor dormancy, however, change of some key biological quantities (elevation of mutation rate (m_1)) or severe immune exhaustion time (m_1) induces a Hopf bifurcation. This explains, mathematically, why tumors can suddenly break free from a stable steady state to show unpredictable oscillations and sudden acceleration of the disease and may relapse after treatment.

Therapeutic Adaptation: the general model can describe crucial ecological factors such as tissue carrying capacity and competing cellular actions, and offers a solid mathematical basis to measure the effect of mono- or combination therapy (i.e., chemotherapy, immunotherapy, and anti-angiogenic drugs) in tumor regression.

Finally, this computational systems oncology viewpoint connects the dots between the raw cell data and the actual predictive capability of the system. Standard AI has difficulties to predict a highly nonlinear state-space self-organization. The mathematical matrix in this study was able to identify the formation of strange attractor as possible markers for the progression of disease. Future efforts should focus

on coupling these multi-population nonlinear differential equations with time-resolved clinical screening to optimize adaptive therapeutic scheduling, thereby mitigating the risk of triggering chaotic tumor escapes or irreversible immune paralysis.

Article Information

Data Availability: The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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References

[1] R. L. Siegel, A. N. Giaquinto, and A. Jemal. Cancer statistics. *2024. CA Cancer J Clin*, 74(1):12–49, 2024.

[2] N. Bellomo and L. Preziosi. Modelling and mathematical problems related to tumor evolution and its interaction with the immune system. *Mathematical and Computer Modelling*, 32(3-4):413–452, 2000.

[3] R. Eftimie, J. L. Bramson, and D. J. Earn. Interactions between the immune system and cancer: a brief review of non-spatial mathematical models. *Bulletin of mathematical biology*, 73(1):2–32, 2011.

[4] F. F. Teles and J. M. Lemos. Cancer therapy optimization based on multiple model adaptive control. *Biomedical Signal Processing and Control*, 48:255–264, 2019.

[5] S. Kartal. Chaos in a Three-Dimensional Cancer Model with Piecewise Constant Arguments. *Cumhuriyet Science Journal*, 44(2): 345–355, 2023.

[6] R. K. Maddali, D. Ahluwalia, A. Chaudhuri, and SK. S Hassan. Dynamics of a Three Dimensional Chaotic Cancer Mode. *International Journal of Mathematics Trends and Technology-IJMTT*, 53(5):353–368, 2018. URL https://doi.org/10.14445/22315373/IJMTT-V53P544.

[7] R. T. Alqahtani. A model of effector–tumor cell interactions under chemotherapy: Bifurcation analysis. *Mathematics*, 13(7):1032, 2025.

[8] M. Robertson-Tessi, A. El-Kareh, and A. Goriely. A mathematical model of tumor–immune interactions. *Journal of theoretical biology*, 294:56–73, 2012.

[9] J. Maher and E. Davies. Targeting cytotoxic T lymphocytes for cancer immunotherapy. *British journal of cancer*, 91(5):817–821, 2004.

[10] F. D. Barber. Recent developments in oncology immunotherapy, adverse effects part 2. *The Journal for Nurse Practitioners*, 14(4): 259–266, 2018.

[11] V.A. Kuznetsov, I. A. Makalkin, M. A. Taylor, and A. S. Perelson. Nonlinear dynamics of immunogenic tumors: parameter estimation and global bifurcation analysis. *Bulletin of Mathematical Biology*, 56(2):295–321, 1994. URL https://doi.org/10.1007/BF02460644.