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Bifurcation and Stability Analysis of Tumor–Immune Interaction Models under Chemotherapy

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Abstract: A nonlinear tumor-immune interaction model is used to show the effect chemotherapy has on the qualitative aspects of cancer cell proliferation. The model uses three coupled ordinary differential equations for tumor cells (T), effector immune cells (E) and chemotherapy (C). Tumor growth is modeled using a logistic equation; immune mediated killing of tumor cells (via a saturated response); stimulation of immune activity via tumor antigens; immunological exhaustion (i.e., reduction in immune activity due to chronic antigen presentation); cytotoxic effects of chemotherapy directly on tumors and indirect effects on the immune system leading to suppression. The mathematical nature of this system is studied in terms of its fundamental characteristics (positivity, boundedness and existence of an invariant set which satisfies biological constraints) so as to establish that the system will be well posed. In addition to establishing the existence of tumor free and co-existence steady-states, a linearization about each steady-state using the Jacobian matrix and application of the Routh-Hurwitz criteria are used to examine the local stability of the steady-states. Using the chemotherapy input rate as a control parameter to induce bifurcations within the system it is demonstrated that this model can exhibit transcritical and Hopf bifurcations. These types of bifurcations are shown to explain transitions in tumor burden (persistent or eliminated) in relation to levels of chemotherapy use, transitions between an immune controlled state of co-existence, oscillatory behavior related to remission-relapse patterns and complete tumor eradication. Numerical simulations were performed to confirm the results obtained through analytical techniques and to determine a critical chemotherapy dose level at which persistent tumor burden changes to tumor elimination. Finally, sensitivity analyses were conducted to demonstrate that treatment efficacy was dependent upon several factors, including intensity of chemotherapy, efficiency of the immune response against tumors, aggressiveness of the tumor population and toxic effects of chemotherapy.

Keywords: Tumor–immune interaction, chemotherapy, bifurcation analysis, local stability, tumor-free equilibrium, coexistence equilibrium, Hopf bifurcation, transcritical bifurcation, mathematical oncology, numerical simulation.

I. INTRODUCTION

Chemotherapy is one of the most common treatments for cancer. Chemotherapy is considered dualistic since it both kills (destroys) growing tumor cells, and simultaneously damages some of the immune cells that destroy (effector cells), thereby reducing the immune systems ability to fight the tumor. Since chemotherapy can either kill tumors or reduce the effectiveness of the body's own defenses, chemotherapy represents a non-linear dynamic process. The ultimate effect of chemotherapy is determined by two factors; namely, the amount of chemotherapy administered, and the relationship among three variables including tumor aggressiveness, immune strength, and toxicity associated with the treatment. In this regard, models describing tumor-immune interaction when treated with chemotherapy represent useful tools for explaining clinical observations regarding the treatment of cancer. These include: persistent tumor growth; partial control of tumor growth; temporary reduction of tumor size (remission); recurrence of previously reduced tumor size (relapse); and complete destruction of all cancerous tissue (complete eradication). Therefore, the goal of this research was to develop and analyze a nonlinear mathematical model consisting of tumor cells; immune effector cells; and concentration of chemotherapeutic agents, in order to determine at what equilibrium state(s) exist; how those equilibrium states are affected by stability characteristics; and how chemotherapy functions as a bifurcation parameter that can qualitatively affect disease processes. In addition to using positivity/boundedness results to describe the existence of solutions; equilibria and local stability analyses were performed to examine qualitative changes in the system. Bifurcation theory was applied to establish relationships among concentrations of chemotherapeutic agents and transitions from stable persistent tumor regimes to tumor free regimes. Finally, numerical simulations were performed to illustrate and visualize the effects of varying levels of chemotherapeutic agents and demonstrate oscillations between remission and relapse.

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Agarwal and Bhadauria (2015) represents one of the first uses of a mathematical model to assess how the use of exogenously generated T cells as part of the treatment of leukemia would affect the progression of the disease. The results indicated that when a sufficient number of therapeutic T cells are infused, they could have significant effects upon the relative levels of leukemic cells and host immune responses. The studies authors also found that such factors as treatment dosage, rates of immune cell recruitment, and coefficients describing the interactions between various populations of immune cells would determine if there was any net decrease or increase in the amount of leukemic cells present. These studies provide quantifiable evidence that links adoptively transferred T cells with the ability to modulate the level of leukemia in affected individuals, and demonstrate how mathematical modeling can assist researchers in developing more effective treatments using immunotherapy. **Eftimie *et al.* (2016)** reviewed the field of mathematical immunology and illustrated the power and applicability of mathematical modeling in studying the function of the immune system. They illustrated how mathematical models of varying degrees of complexity, ranging from simple deterministic models to complex stochastic models, can be used to understand the functioning of both normal and abnormal immune processes at multiple scales. The authors also discussed how models based on experimental data can be developed and calibrated to better describe real-world biological processes. They demonstrated that immunologically complex phenomena can be modeled mathematically in ways that are amenable to analytical solutions; therefore, they encourage others to develop cancer treatment models that incorporate both biologic knowledge and predictive analyses. **Elsayed *et al.* (2017)** assessed the efficacy of radiotherapy as a means of treating leukemia cutis. Their results indicate that although radiotherapy has largely been replaced by other forms of treatment as a primary mode of therapy for leukemia, it still provides a valuable method of controlling symptoms associated with cutaneous leukemia manifestations. Further, their results support previous findings suggesting that localized therapy should be considered as an adjunct to systemic therapies when managing skin manifestations of leukemia. **Lestari *et al.* (2019)** developed an analytical model of how the behavior of cancerous tumors is affected by chemotherapy in terms of how the effects of drugs change the rate of progression of the tumor as a function of time. They demonstrated how the effects of chemotherapy are dependent on the amount and type of drug administered, drug absorption into the body and the speed at which the tumor grows; thus, proper amounts of chemotherapy can effectively reduce the size of a tumor while improper administration could allow the tumor to grow back after treatment. Their work contributes to the literature by enhancing the application of differential equations to explain why patients respond differently to treatments and providing a basis for future research comparisons between chemotherapy and new immunotherapeutic approaches. **Rockne and Scott (2019)** defined the area of Mathematical Oncology and described how mathematical models can be used to describe both the growth and regression of tumors during cancer treatment and to predict when resistance will develop and lead to relapse. The authors were able to show that cancer is not just a biological process, but rather a complex system where all three elements, i.e., timing of treatment, amount of treatment given and patient specific factors affect what happens in the long term. Therefore, this article has provided value in framing the studies regarding Leukemia and interactions between tumors and the immune system in a much broader context than previously existed; specifically, in a frame that would ultimately enable researchers to provide personalized therapy based upon predictive models. **Zhao and Cao (2019)** presented information on engineered T-cell therapy in clinical oncology and have shown how this technology represents one of the most exciting developments in the treatment of various forms of cancer, particularly hematologic malignancies. The authors presented data demonstrating the potential therapeutic use of genetically modified T-cells in identifying and destroying malignant cells. In addition, they identified several key limitations to widespread successful utilization of these technologies, i.e., toxic side-effects, recurrence of cancer due to residual cancer stem cells being left behind after treatment, and limited utility against certain cancer types. Thus, their work has established a connection between clinical successes using T-cell therapies and the need for the development of mathematical models to assist in understanding efficacies of treatment, optimizing doses and predicting adverse events associated with treatment. **Khatun and Biswas (2020)** established a mathematical model that illustrated how T-cell adoptive immunotherapy could help decrease leukemia cell population sizes given certain biological and treatment parameters. Their results also showed that the effect of leukemia cells on T-cells as well as T-cells on leukemia cells was quite sensitive to changes in various parameters. When the level of immune response exceeded the rate of leukemia proliferation, then, the authors found that the disease would be reduced in an equilibrium state. This research was important because they provided a more precise representation of earlier models representing leukemia and immunotherapy; this study also supported the idea that using adoptive T-cell therapies can be examined with systematic mathematics-based evaluation. **Dhar and Gupta (2021)** modeled an example of a tumor-antibody model incorporating B-cells and monoclonal antibodies as therapeutic treatments. Using a combination of semi-analytic and numerical techniques, they were able to obtain solutions to the system of differential equations describing their model. The value of their research lies in expanding the commonly accepted traditional tumor-immune framework to include other aspects of the immune system and treatments. They have shown that adding antibody mediated treatments and supportive elements to the immune system can provide quantifiable benefit to overall cancer treatment. In addition, their use of computationally sophisticated tools to describe complex biological processes illustrates how such methodologies can contribute to understanding cancer treatments. León-**Triana *et al.* (2021)** developed a series of mathematical models that described CAR T-cell treatment in B-cell acute lymphoblastic leukemia. They demonstrated how interactions between tumor cells and CAR T cells determine whether CAR T cell treatments will result in either complete elimination of the tumor, partial control over the tumor, or little to no control. Their results suggest that there are three main factors determining if patients achieve long term remission after receiving CAR T-cell treatment. These factors include the ability of CAR T cells to expand, persist, and kill tumor cells. On the contrary, failure of CAR T cells to proliferate adequately or to exhaustively deplete tumor cells may ultimately result in incomplete control. **Perez-Garcia *et al.* (2021)** developed CAR T-Cell model in T-cell leukemias which is much harder than CAR T-Cell in malignancies where therapeutic T-cells could have bad effects upon both normal and malignant T-cell populations. They were able to show that the design of treatment in T-cell leukemia was more complicated and they demonstrated how mathematical analysis could provide insight into the delicate balance between anti-tumor efficacy and adverse biological limits. This work is significant since it represents an area of great challenge for cellular immunotherapies, specifically demonstrating the necessity for well-designed models for the therapy cell and the target cell to exhibit similar characteristics biologically. **Sterner and Sterner (2021)** discussed many of the current challenges and potential future directions of CAR-T Cell Therapy, specifically, toxicity, antigen escape, relapse, difficulty in manufacturing, and poor success rate in treating solid tumors. They clearly stated that while CAR-T Cells has improved some forms of blood cancers, there are many biological, technological, and clinical barriers to expanding CAR-T Cell therapies beyond these blood cancers. Therefore, this paper will be very useful to mathematical oncologists because it defines exactly what types of challenges that we need to use our quantitative models to solve, i.e., optimizing treatment protocols, reducing risks, and predicting long-term responses. **Van De Vyver *et al.* (2021)** studied cytokine release syndrome (CRS) induced by T-cell redirecting therapies and evaluated if CRS risk could be predicted and/or modulated. These authors illustrated the central role of hyperimmune activation as being responsible for treatment toxicities and highlighted the importance of understanding inflammation signaling pathways, individual patient variability and optimal times to intervene. In addition, this work highlights that effective treatment does not occur solely through tumor killing but through management of systemic immune related toxicities; factors which should be included within reasonable therapeutic models. **Xue *et al.* (2021)** studied whether or not chimeric antigen receptor T cell products would modulate their own associated inflammatory responses and toxicities by releasing IL-6-related "storm" in patients receiving cancer therapies for hematologic malignancies. They identified evidence supporting possible ways that engineered T cells interact with pathways of immune signaling could potentially affect both the effectiveness of the therapy as well as the toxicities of engineered T cell products. Their findings also highlight that CAR-T therapy research may have many complexities in that immune mediated adverse events are not necessarily independent of the therapeutic effect. Consequently, they provide data suggesting that cytokine dynamics should be represented within models designed to simulate leukemia therapy. **Karim *et al.* (2025)** modeled the distribution of leukemia viruses using a fractional order mathematical model capable of representing "memory" effects and hereditary properties of systems in a way superior to that of traditional integer-order models. As such, this study shows how fractional dynamic studies may be useful for enhancing our understanding of the progression of diseases and stability characteristics in those cases in which the present states of the systems are heavily influenced by prior biological histories. Of significant importance is the fact that this study will allow for more flexibility in the mathematical representation of various leukemia phenomenon as well as the ability to develop additional detail regarding the progression, persistence and response to therapy. **Putignano *et al.* (2025)** indicated the growing need for computational and mathematical approaches to understand the kinetic features of CAR-T therapies; specifically, cell proliferation/decline, toxicity and individualized/personalized medicine based on therapeutic design. Additionally, their paper illustrates a maturation stage of the field in which mathematical models are becoming essential tools for interpreting both clinical and experimental data versus merely supportive. Ultimately, the importance of this work rests in its demonstration that there is increasing convergence of translational immunotherapy and computational oncology. **Karim *et al.* (2026)** demonstrated that the immune-therapy approach may be able to achieve more substantial and long-lasting reductions in leukemic cells than chemotherapy alone if appropriately applied. Their model included susceptible cells, infected cells, leukemic cells, immune cells, cytokines, and the concentration of a chemotherapeutic agent. With this comprehensive formulation of the model, they were able to investigate stability, bifurcations, and treatment responses. They determined that sufficient levels of immune-stimulation will promote systemic stability; additionally, the introduction of T-cells into the body will suppress cancer at greater rates than drug treatment alone. This research has significant importance as it provides an integrated theoretical understanding of both chemotherapy and cellular-immunotherapy, as well as shows the potential of comparative models to direct the development of optimal methods of treating leukemia.

II. MODEL FORMULATION

The interactions between tumor cells, the immune effector cells and drug concentrations are modeled as a nonlinear system of ODE's where the variables, denoted by $T(t), E(t)$ and $C(t)$, represent the tumor cell population, the number of immune effector cells and the concentration of chemotherapeutic drugs at time t. The tumor population is assumed to grow logistically in the absence of immune response and chemotherapy, with intrinsic growth rate rrr and carrying capacity K. The immune system attacks tumor cells through a saturating functional response, reflecting the biological fact that immune killing cannot increase indefinitely as tumor burden rises. Chemotherapy is assumed to reduce tumor cells directly, with the strength of drug-induced cytotoxicity proportional to both the drug concentration and the tumor population. At the same time, the immune effector cells are recruited at a constant basal rate and are additionally stimulated in the presence of tumor cells, since the immune system responds to tumor-associated antigens. However, immune cells also experience natural death, suppression due to tumor-induced exhaustion, and toxicity caused by chemotherapy. Finally, the chemotherapeutic drug concentration is modeled by a balance between constant drug infusion and natural clearance from the body. Based on these assumptions, the governing system is written as

$$\frac{dT}{dt} = rT\left(1 - \frac{T}{K}\right) - \frac{pET}{a+T} - qCT \tag{1}$$

$$\frac{dE}{dt} = s + \frac{cET}{g+T} - mET - dE - \eta CE \tag{2}$$

$$\frac{dC}{dt} = u - \lambda C \tag{3}$$

Here, $rT\left(1 - \frac{T}{K}\right)$ represents logistic tumor growth, $\frac{pET}{a+T}$ describes immune-mediated killing of tumor cells with saturation effect, and qCT is the chemotherapy-induced tumor cell death term. In the immune equation, sss denotes the constant influx of immune effector cells, $\frac{cET}{g+T}$ models tumor-stimulated immune proliferation, mET represents immune exhaustion or inactivation caused by persistent tumor burden, dE is the natural death of immune cells, and ηCE captures the suppressive effect of chemotherapy on immune function. In the drug equation, uuu is the rate of administration of chemotherapy and λ is the drug clearance rate. All parameters are assumed to be positive constants, and the initial conditions are taken as $T(0) \geq 0, E(0) \geq 0$ and $(0) \geq 0$, ensuring biological feasibility of the model. This formulation provides a mathematically tractable but biologically meaningful framework for studying how tumor progression, immune surveillance, and chemotherapy interact to produce different dynamical outcomes such as tumor persistence, immune control, oscillatory relapse, or complete tumor elimination.

Table 1: Nomenclature of variables and parameters

Symbol	Meaning
$T(t)$	Tumor cell population at time (t)
$E(t)$	Immune effector cell population at time (t)
$C(t)$	Chemotherapeutic drug concentration at time (t)
r	Intrinsic growth rate of tumor cells
K	Carrying capacity of tumor population
p	Maximum immune killing rate
a	Half-saturation constant for immune killing
q	Drug-induced tumor cell kill rate
s	Constant source rate of immune cells
c	Tumor-stimulated immune proliferation rate
g	Half-saturation constant for immune stimulation
m	Tumor-induced immune exhaustion rate
d	Natural death rate of immune cells
η	Chemotherapy-induced immune suppression rate
u	Drug infusion/input rate
λ	Drug clearance rate

III. BOUNDEDNESS, AND INVARIANT REGION

For the biological relevance of the proposed tumor–immune–chemotherapy system, it is necessary to show that its solutions remain nonnegative and bounded for all future time whenever the initial populations and drug concentration are nonnegative. Consider the system (1)-(3) with initial conditions:

$$T(0) \geq 0, E(0) \geq 0 \text{ and } C(0) \geq 0 \tag{4}$$

To establish positivity, we observe that on the boundary planes of the nonnegative octant, the vector field does not point outward. Indeed, when $T = 0$, we have $\frac{dT}{dt} = 0$

so the tumor population cannot become negative. When $E = 0$

$$\frac{dE}{dt} = s \geq 0 \tag{5}$$

which shows that the immune cell population is pushed back into the nonnegative region. Similarly, when $C = 0$

$$\frac{dC}{dt} = u \geq 0 \tag{6}$$

and thus the drug concentration also remains nonnegative. Therefore, the nonnegative orthant

$$\mathbb{R}_+^3 = \{(T, E, C) \in \mathbb{R}^3 : T(0) \geq 0, E(0) \geq 0, C(0) \geq 0\} \tag{7}$$

is positively invariant, meaning that every solution starting in this region remains there for all $t \geq 0$.

Next, we show boundedness of solutions. From the tumor equation, since the immune-killing term and chemotherapy term are nonnegative, it follows that

$$\frac{dT}{dt} \leq rT\left(1 - \frac{T}{K}\right) \tag{8}$$

By comparison with the logistic equation, we obtain

$$0 \leq T(t) \leq max\{T(0), K\} \text{ for all } t \geq 0 \tag{9}$$

Hence the tumor population is bounded above by the carrying capacity level or the initial value, whichever is larger.

For the drug concentration, equation (3) is linear and has the explicit solution

$$C(t) = C(0)e^{-\lambda t} + \frac{u}{\lambda}\left(1 - e^{-\lambda t}\right) \tag{10}$$

Therefore, $0 \leq C(t) \leq max\left\{C(0), \frac{u}{\lambda}\right\}$ for all $t \geq 0$

so the drug concentration is also bounded.

To obtain boundedness of the immune population, note that since $T(t)$ is bounded, say

$T(t) \leq M_T$ and $C(t) \geq 0$, we have

$$\frac{dE}{dt} = s + \frac{cET}{g+T} - mET - dE - \eta CE \leq s + \frac{cET}{g+T} - dE \tag{11}$$

Because $\frac{T}{g+T} \leq 1$, it follows that

$$\frac{dE}{dt} \leq s + (c-d)E \tag{12}$$

This already shows that the immune population cannot blow up in finite time. A sharper bound can be obtained by using the fact that the negative term $-mET$ dominates for sufficiently large EEE whenever $T \geq 0$, while if T is small then the growth contribution $\frac{cET}{g+T}$ is also small. Thus, in all biologically feasible cases, $E(t)$ remains bounded for all ≥ 0 . Alternatively, since both $T(t)$ and $C(t)$ are bounded, the immune equation is a linear differential inequality in , and standard comparison arguments guarantee the existence of a constant $M_E > 0$ such that

$$0 \leq E(t) \leq M_E \text{for all } t \geq 0 \tag{13}$$

Hence there exist positive constants M_T, M_E and M_C such that every solution of the system eventually enters and remains in the bounded set

$$\Omega = \{(T,E,C) \in \mathbb{R}_+^3 : 0 \leq T \leq M_E, 0 \leq E \leq M_E, 0 \leq C \leq M_C\} \tag{14}$$

This set Ω is called a positively invariant absorbing region of the system. Biologically, this means that the tumor cell population, immune response, and drug concentration remain meaningful and finite for all time, which confirms that the model is well posed and suitable for further equilibrium, stability, and bifurcation analysis.

Thus, for every nonnegative initial condition, the solution $T(t), E(t), C(t)$ of the proposed model remains nonnegative and bounded for all $t \geq 0$ and the nonnegative bounded region $\Omega \subset \mathbb{R}_+^3$ forms an invariant region for the system. This guarantees the biological admissibility of the model and provides the mathematical foundation for subsequent qualitative analysis.

4. Equilibrium analysis: the equilibrium points of the tumor–immune–chemotherapy system are obtained by setting the right-hand sides of the governing equations equal to zero. thus, for the system (1)-(3), an equilibrium point (T^*, E^*, C^*) satisfies

$$rT^*\left(1-\frac{T^*}{K}\right) - \frac{pE^*T^*}{a+T^*} - qC^*T^* = 0 \tag{15}$$

$$s + \frac{cE^*T^*}{g+T^*} - mE^*T^* - dE^* - \eta C^*E^* = 0 \tag{16}$$

$$u - \lambda C^* = 0 \tag{17}$$

From equation (17), the equilibrium drug concentration is immediately obtained as $C^* = \frac{u}{\lambda}$

Hence every equilibrium of the full three-dimensional system must lie on the plane

$C = \frac{u}{\lambda}$, and the analysis reduces to solving the first two algebraic equations in T^* and E^*.

The first biologically important equilibrium is the tumor-free equilibrium. Setting T^* =0 in equation (15), the equation is automatically satisfied. Substituting T^* =0 into equation (16), we obtain

$$s - dE^* - \eta C^*E^* = 0 \tag{18}$$

Using $C^* = \frac{u}{\lambda}$, this gives

$$E_0{}^* = \frac{s}{d+\frac{\eta u}{\lambda}} \tag{19}$$

Therefore, the tumor-free equilibrium is

$$\epsilon_0 = \left(0, \frac{s}{d+\frac{\eta u}{\lambda}}, \frac{u}{\lambda}\right) \tag{20}$$

This equilibrium always exists for positive parameter values and represents a state in which the tumor has been eliminated, while the immune population is maintained by basal recruitment and is reduced according to the level of chemotherapy toxicity.

Next, we determine the positive or coexistence equilibrium, where tumor cells, immune cells, and chemotherapy concentration are all present. Assume $T^* > 0$. Then equation (15) may be divided by T^*, yielding

$$r\left(1-\frac{T^*}{K}\right)-\frac{pE^*}{a+T^*}-qC^*=0$$

Solving for E^*, we obtain $E^*=\frac{a+T^*}{p}\left[r\left(1-\frac{T^*}{K}\right)-qC^*\right]$ (21)

Substituting $C^*=\frac{u}{\lambda}$, this becomes

$$E^*=\frac{a+T^*}{p}\left[r\left(1-\frac{T^*}{K}\right)-q\frac{u}{\lambda}\right] \tag{22}$$

Similarly, from equation (16), by factoring out E^* from the terms involving immune dynamics, we get

$$s+E^*\left(\frac{cT^*}{g+T^*}-mT^*-d-\eta C^*\right)=0$$

Therefore, $E^*=-\frac{s}{\frac{cT^*}{g+T^*}-mT^*-d-\eta C^*}$ (23)

Using $C^*=\frac{u}{\lambda}$, we obtain

$$E^*=-\frac{s}{\frac{cT^*}{g+T^*}-mT^*-d-\eta\frac{u}{\lambda}} \tag{24}$$

Equating expressions (22) and (24) gives a nonlinear algebraic equation in T^*:

$$\frac{a+T^*}{p}\left[r\left(1-\frac{T^*}{K}\right)-qC^*\right]=-\frac{s}{\frac{cT^*}{g+T^*}-mT^*-d-\eta\frac{u}{\lambda}}$$

This equation generally cannot be solved explicitly in a simple closed form, so numerical methods are usually employed to determine the positive equilibrium values. Once a positive root T^* is obtained, the corresponding immune equilibrium E^* follows directly from either equation (22) or equation (24), and the chemotherapy component is given by $C^*=\frac{u}{\lambda}$. Thus, the coexistence equilibrium may be written as

$$\epsilon_1=\left(T^*,E^*,\frac{u}{\lambda}\right) \tag{25}$$

where $T^*>0$ and $E^*>0$ satisfy the above relations.

For the coexistence equilibrium to be biologically feasible, the values T^* and E^* must be positive. From equation (22), positivity of E^*requires

$$r\left(1-\frac{T^*}{K}\right)-q\frac{u}{\lambda}>0 \tag{26}$$

which implies $T^*<K\left(1-\frac{qu}{r\lambda}\right)$, provided $\frac{qu}{r\lambda}<1$

This shows that excessively large chemotherapy input may destroy the coexistence state by suppressing tumor persistence altogether. On the other hand, equation (24) requires that

$$\frac{cT^*}{g+T^*}-mT^*-d-\eta\frac{u}{\lambda}<0 \tag{27}$$

In order for $E^* > 0$. Hence the existence of a biologically meaningful coexistence equilibrium depends on a balance among tumor stimulation of immunity, immune exhaustion, natural immune death, and the toxic effect of chemotherapy on immune cells.

Therefore, the system admits two principal types of equilibria: the tumor-free equilibrium ϵ_0 which always exists, and the positive coexistence equilibrium ϵ_1 , which exists only when the model parameters satisfy suitable positivity conditions. Biologically, the tumor-free equilibrium corresponds to successful therapeutic control or eradication of the tumor, while the coexistence equilibrium represents a persistent but controlled tumor burden maintained by the balance between tumor growth, immune response, and chemotherapy. These equilibrium points form the basis for the next stage of analysis, namely local stability and bifurcation investigation, through which one can determine under what conditions each state is stable and how changes in treatment or biological parameters may shift the system from one regime to another.

IV. LOCAL STABILITY OF TUMOR-FREE AND COEXISTENCE STATES

To determine the local behavior of the tumor–immune–chemotherapy system near its equilibrium points, we analyze the Jacobian matrix of the nonlinear system (1)-(3)

$$f_1(T,E,C) = rT\left(1-\frac{T}{K}\right) - \frac{pET}{a+T} - qCT \tag{28}$$

$$f_2(T,E,C) = s + \frac{cET}{g+T} - mET - dE - \eta CE \tag{29}$$

$$f_3(T,E,C) = u - \lambda C \tag{30}$$

Then the Jacobian matrix of the system is given by

$$J(T,E,C) = \begin{bmatrix} r\left(1-\frac{2T}{K}\right) - \frac{paE}{(a+T)^2} - qC & -\frac{pT}{a+T} & -qT \\ \frac{cgE}{(g+T)^2} - mE & \frac{cT}{g+T} - mT - d - \eta C & -\eta E \\ 0 & 0 & -\lambda \end{bmatrix} \tag{31}$$

Since the third equation is linear and independent of T and E, one eigenvalue is always

$$\mu_3 = -\lambda < 0 \tag{32}$$

Therefore, the local stability of each equilibrium is determined by the remaining two Eigen values associated with the upper-left 2×2 block of the Jacobian.

4.1. Local stability of the tumor-free equilibrium:

The tumor-free equilibrium is

$$\epsilon_0 = \left(0, \frac{s}{d+\frac{\eta u}{\lambda}}, \frac{u}{\lambda}\right)$$

Substituting $T = 0, E = \frac{s}{d+\frac{\eta u}{\lambda}}, C = \frac{u}{\lambda}$ λu into the Jacobian matrix (31), we obtain

$$J(\epsilon_0) = \begin{bmatrix} r - \frac{pE_0}{a} - q\frac{u}{\lambda} & 0 & 0 \\ \frac{cE_0}{g} - mE_0 & -d - \eta\frac{u}{\lambda} & -\eta E_0 \\ 0 & 0 & -\lambda \end{bmatrix} \tag{33}$$

Where $E_0 = \frac{s}{d+\frac{\eta u}{\lambda}}$

Since this matrix is triangular in structure, its eigenvalues are

$$\mu_1 = r - \frac{pE_0}{a} - q\frac{u}{\lambda}, \mu_2 = -d - \eta\frac{u}{\lambda}, \mu_3 = -\lambda \tag{34}$$

Clearly, $\mu_2 < 0, \mu_3 < 0$. Thus the local stability of the tumor-free equilibrium depends only on the sign of μ_1.

Substituting $E_0 = \frac{s}{d+\frac{\eta u}{\lambda}}$, we obtain

$$\mu_1 = r - \frac{p}{a}\frac{s}{d+\frac{\eta u}{\lambda}} - q\frac{u}{\lambda}$$

Therefore, the tumor-free equilibrium E_0 is locally asymptotically stable if

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$r < \frac{p}{a}\frac{s}{d+\frac{\eta u}{\lambda}} + q\frac{u}{\lambda}$

and unstable if $r > \frac{p}{a}\frac{s}{d+\frac{\eta u}{\lambda}} + q\frac{u}{\lambda}$

This condition has a clear biological interpretation: the intrinsic growth ability of the tumor must be weaker than the combined suppressive effect of immune surveillance and chemotherapy. If this inequality holds, small perturbations around the tumor-free state decay over time, implying successful elimination of the tumor. If it fails, tumor cells can regrow from small residual populations, making the tumor-free state unstable.

For convenience, one may define the threshold quantity $\mathcal{R}_0 = \frac{r}{\frac{p}{a}\frac{s}{d+\frac{\eta u}{\lambda}}+q\frac{u}{\lambda}}$ (35)

Then the tumor-free equilibrium is locally asymptotically stable when $\mathcal{R}_0 < 1$ and unstable when $\mathcal{R}_0 > 1$.

4.2. Local stability of the coexistence equilibrium: Let $\epsilon_1 = (T^*, E^*, C^*) = \left(T^*, E^*, \frac{u}{\lambda}\right)$ be a biologically feasible coexistence equilibrium with $T^* > 0$ and $E^* > 0$. Evaluating the Jacobian matrix at ϵ_1, we obtain

$$J(\epsilon_1) = \begin{bmatrix} A & B & -qT^* \\ D & F & -\eta E^* \\ 0 & 0 & -\lambda \end{bmatrix}$$

$$A = r\left(1 - \frac{2T^*}{K}\right) - \frac{paE^*}{(a+T^*)^2} - qC^*$$

$$B = -\frac{pT^*}{a+T^*}$$

$$D = \frac{cgE^*}{(g+T)^2} - mE^*$$

$$F = \frac{cT^*}{g+T^*} - mT^* - d - \eta\frac{u}{\lambda}$$

Again, one eigenvalue is $-\lambda < 0$, and the remaining two eigenvalues are determined by the reduced matrix

$$J_2 = \begin{bmatrix} A & B \\ D & F \end{bmatrix}$$

The characteristic equation of this 2×2 block is

$$\mu^2 - tr(J_2)\mu + det(J_2) = 0$$

Where $tr(J_2) = A + F$

And $det(J_2) = AF - BD$

According to the Routh–Hurwitz criterion for a second-order polynomial, the coexistence equilibrium ϵ_1 is locally asymptotically stable if and only if

$tr(J_2) < 0$ and $det(J_2) > 0$ (36)

If either of these conditions fails, then the coexistence equilibrium becomes unstable. In particular, if

$tr(J_2) = 0$ and $det(J_2) > 0$ (37)

Then the system may undergo a Hopf bifurcation, leading to sustained oscillations in tumor and immune populations. Biologically, this corresponds to periodic remission and relapse behavior under chemotherapy.

Thus, the coexistence equilibrium is locally asymptotically stable whenever the combined damping effects in the tumor–immune subsystem dominate the destabilizing interactions. The trace condition ensures that the average feedback in the system is dissipative, while the determinant condition guarantees that the equilibrium is not a saddle point. These criteria provide the mathematical basis for studying how parameters such as chemotherapy dose u, immune killing rate p, drug toxicity η, and tumor growth rate rrr influence the qualitative behavior of the system.

Table 2: Summary table

Equilibrium state	**Stability condition**	**Biological meaning**
Tumor-free equilibrium (ϵ_0)	$r < \frac{p}{a}\frac{s}{d+\frac{\eta u}{\lambda}} + q\frac{u}{\lambda}$	tumor elimination is maintained
Coexistence equilibrium (ϵ_1)	$tr(J_2) < 0, \det(J_2) > 0$	stable persistence of tumor with immune control

Coexistence equilibrium at critical point	$tr(J_2) = 0, \det(J_2) > 0$	onset of oscillatory dynamics via Hopf bifurcation

V. BIFURCATION ANALYSIS WITH CHEMOTHERAPY AS CONTROL PARAMETER

In order to understand how chemotherapy influences the qualitative dynamics of the tumor–immune interaction system, we now treat the chemotherapy input rate u as the principal bifurcation parameter. Since the equilibrium drug concentration is given by $C^* = \frac{u}{\lambda}$, variation in u directly changes the tumor growth suppression term and the immune toxicity term. Consequently, changes in chemotherapy intensity may alter the number, type, and stability of equilibrium states, producing transitions between tumor persistence, tumor control, and tumor eradication. Such qualitative transitions are mathematically described through bifurcation analysis.

Consider again the system (1)-(3), we get

At equilibrium, $C^* = \frac{u}{\lambda}$, so the tumor-free equilibrium is

$$\epsilon_0 = \left(0, \frac{s}{d + \frac{\eta u}{\lambda}}, \frac{u}{\lambda}\right)$$

From the local stability analysis, the eigenvalue governing tumor invasion near the tumor-free state is

$$\mu_1(u) = r - \frac{p}{a}\frac{s}{d + \frac{\eta u}{\lambda}} - q\frac{u}{\lambda}$$

The sign of $\mu_1(u)$ determines whether the tumor-free equilibrium is stable or unstable. The critical chemotherapy level at which stability changes is obtained by solving

$$r - \frac{p}{a}\frac{s}{d + \frac{\eta u}{\lambda}} - q\frac{u}{\lambda} = 0 \qquad (38)$$

Let $u = u_c$ denote a root of this equation. Then u_c represents the threshold chemotherapy input at which the tumor-free state changes its stability. If $< u_c$, then $\mu_1(u) > 0$, so the tumor-free equilibrium is unstable and small tumor populations can invade. If $> u_c$, then $\mu_1(u) < 0$, so the tumor-free equilibrium becomes locally asymptotically stable and the tumor tends to be eliminated. Therefore, equation (38) defines a biologically meaningful treatment threshold, and the system undergoes a transcritical-type bifurcation at $= u_c$, where the tumor-free equilibrium exchanges stability with a positive coexistence equilibrium.

As u varies, the entries A and F change explicitly because they contain the term u/λ, and they also change implicitly because the equilibrium values T^* and E^* depend on u. Hence chemotherapy can alter the sign of the trace and determinant of the Jacobian, causing changes in local stability. In particular, if for some critical value $u = u_H$

$$tr(J_2) = 0, \det(J_2) > 0$$

There exists a Hopf-bifurcation where the coexistence-equilibrium will lose its stability. As an alternative, the existence of a family of small amplitude periodic solution near the coexistence-equilibrium can be possible. From biological point of view, these periodically varying populations of tumors and immune cells may induce recurrent cycles of remission and relapse during chemotherapy. These oscillating patterns are particularly interesting in cancer modeling, as treatments do not always have fixed effects; rather their impacts depend upon the complex interactions among tumor burden, immune response and treatment regimen over time. The model has therefore two significant chemotherapy-induced bifurcations. First, there is a transcritical bifurcation with respect to tumor free state, which represents the boundary line between eradication or persistence of the tumor. Second, there is a Hopf bifurcation with respect to the coexistence states, which corresponds to the beginning of sustainable oscillations in both tumor and immune populations. Finally, according to some values of parameters, the non-linear equations of equilibrium for T^* can admit more than one root. Consequently, two coexisting steady states could collapse and disappear when changing the value of uuu by making use of a saddle-node bifurcation. It is biologically significant because it shows that the treatment result depends not only on the drug dosage but also on the initial tumor load and the patient's immunological status.

Numerically analyzing a bifurcation diagram involves selecting values of the parameter u over a range of biological relevance and calculating the equilibrium tumor burdens (T^*) that correspond to each value. The resulting bifurcation diagrams are plots of these equilibrium tumor burdens versus the selected parameter. Stable branches typically have solid lines and unstable branches are represented with dashed lines. At low levels of u there will generally be a coexisting equilibrium representing a tumor burden that remains greater than zero; however, as u increases toward its critical value (u_c) , the tumor burden decreases and when it reaches u_c, the tumor free equilibrium has become stable. If either of two other possible Hopf points occur before or after this point, then a new type of solution (oscillations) may arise during the "intermediate" chemotherapy treatment regimen. Thus, the bifurcation diagram provides a simple graphical representation of how changes in chemotherapy dose affect transitions from persistent tumor through controlled coexistence to oscillatory relapse to complete tumor eradication. From a clinical standpoint, the bifurcation analysis illustrates that chemotherapy represents a dynamic, controllable variable as opposed to simply being a toxic input. There is a minimum concentration of chemotherapeutic agent required to eliminate a tumor and if the concentration is too high, it can suppress both the growth rate of cancerous cells and kill healthy immune cells thereby reducing the body's ability to fight future infections. Since this reduction in immune function could lead to additional complex behavior (transient or oscillatory), the threshold concentrations of chemotherapeutic agents defined in the bifurcation analysis (i.e., u_c and u_H) represent useful measures for developing treatment strategies that maintain sufficient suppression of tumors while maintaining some degree of immunity.

Table 3: Summary table of chemotherapy-induced bifurcations

Bifurcation type	**Mathematical condition**	**Biological interpretation**
Transcritical bifurcation	$r < \frac{p}{a}\frac{s}{d+\frac{\eta u}{\lambda}} - q\frac{u}{\lambda} = 0$	threshold between tumor persistence and tumor eradication
Hopf bifurcation	$tr(J_2) = 0, \det(J_2) > 0$	onset of remission–relapse oscillations
Saddle-node bifurcation	multiple positive equilibria merge and disappear	bistability and treatment dependence on initial condition

VI. NUMERICAL CASE STUDY AND SIMULATIONS

To illustrate the analytical results of the tumor–immune–chemotherapy model, we now consider a numerical case study based on a biologically reasonable set of positive parameter values. The aim of this section is to examine how variation in chemotherapy input affects the long-term behavior of the system, to verify the theoretical stability conditions, and to demonstrate the occurrence of threshold behavior predicted by the bifurcation analysis. For the numerical simulations, let the parameter values be chosen as
$r = 0.5, K = 1000, p = 1.0, a = 50, q = 0.2, s = 3.0, c = 2.0, g = 80, m = 0.0005$
$d = 0.3, \eta = 0.05, \lambda = 1.0$
The initial conditions are taken as $T(0) = 80, E(0) = 12, C(0) = 0$
which represent an initially established tumor, an active but limited immune response, and absence of drug concentration before treatment begins. Under these assumptions, the equilibrium drug concentration is $C^* = \frac{u}{\lambda}$, and therefore the chemotherapy input rate u becomes the main control parameter governing the numerical behavior of the system.
To determine the critical chemotherapy threshold at which the tumor-free equilibrium changes stability, we use the condition

$$r - \frac{p}{a}\frac{s}{d+\frac{\eta u}{\lambda}} - q\frac{u}{\lambda} = 0$$

Substituting the above parameter values gives
$u_c \approx 1.723$

This result implies that when the chemotherapy input is below 1.723 , the tumor-free equilibrium is unstable and the tumor cannot be completely eradicated, whereas when the chemotherapy input exceeds this threshold, the tumor-free equilibrium becomes locally asymptotically stable and complete elimination of the tumor becomes possible. Thus, u_c acts as a treatment threshold separating persistent-tumor and eradication regimes.

For simulation purposes, we consider three representative chemotherapy levels: a low-dose case $u = 0.5$, an intermediate-dose case $u = 1.0$ and a high-dose case $u = 2.0$. In the low-dose case $u = 0.5$, the numerical solution shows that the tumor population decreases initially due to both immune action and chemotherapy, but it does not vanish completely. Instead, it approaches a positive coexistence equilibrium, indicating that the treatment is insufficient to eliminate the tumor. The immune population initially rises in response to tumor stimulation and then settles to a moderate positive level, while the drug concentration approaches its steady-state value $C^* = 0.5$. In the intermediate-dose case $u = 1.0$, the tumor burden is reduced further and the equilibrium tumor size becomes smaller than in the previous case, yet the system still converges to a coexistence state rather than to a tumor-free state.

High dose chemotherapy can reduce the tumor size down to near-zero but will likely be unable to eradicate it completely. High dose chemotherapy $(u = 2.0)$ is greater than the u_c (critical) value and thus will eventually cause the tumor population to decay to nearly zero. The immune cells however, will remain at a lower population size due to the effects of chemotherapy on the immune system caused by the parameter η, and the drugs concentration will approach its steady-state value of $C^* = 2.0$. Thus, these numerical results demonstrate that chemotherapy acts as an effective bifurcation parameter causing the transition from a persistent tumor to an eradicated tumor. Table 4 lists some of the calculated approximate equilibrium values for each of the three chemotherapy levels using the selected parameters. As shown in this table, the tumor burden decreases progressively with increasing intensities of chemotherapy. For both low and medium-doses of chemotherapy, the coexistence equilibrium is stable; for sufficiently strong chemotherapy, the tumor-free equilibrium is stable. Additionally, although higher intensities of chemotherapy tend to produce larger populations of immune cells, they also damage immune cells. The interaction between killing tumors and suppressing the immune system is one of the key dynamics within the model.

This means that moderate chemotherapy improves tumor suppression but remains below the eradication threshold. In the high-dose case $u = 2.0$, which lies above the critical value u_c, the tumor population decays toward zero and the system approaches the tumor-free equilibrium. The immune population stabilizes at a reduced but positive level because chemotherapy suppresses immune cells through the parameter η, and the drug concentration tends to $C^* = 2.0$. Therefore, the numerical results clearly confirm the theoretical prediction that chemotherapy acts as a bifurcation parameter capable of shifting the system from tumor persistence to tumor eradication.

Using the chosen parameter values, approximate equilibrium values for the three chemotherapy levels are listed in Table 4. These values demonstrate the gradual decrease in tumor burden as chemotherapy intensity increases. For low and intermediate doses, the coexistence equilibrium is stable, whereas for sufficiently high chemotherapy the tumor-free state becomes stable. The calculations also show that the immune cell population does not necessarily increase with stronger treatment, because chemotherapy simultaneously damages immune cells. This competition between tumor kill and immune suppression is one of the most important dynamical features of the model.

Table 4: Numerical equilibrium values for different chemotherapy levels

Chemotherapy input (u)	**Drug equilibrium $C^* = u$**	**Tumor equilibrium (T^*)**	**Immune equilibrium (E^*)**	**Dynamical outcome**
0.5	0.5	8.93	23.31	stable coexistence
1	1	7.85	17.13	stable coexistence
2	2	0	7.5	tumor-free stable state

A basic sensitivity study may be run to better understand how changes in parameters affect the behavior of the system; this is accomplished by changing one parameter at a time while holding all other parameters constant. The results from these studies suggest that increasing the immune killing parameter p will lower the chemotherapy threshold (u_c) required for eliminating a tumor as increased effectiveness of an immune response reduces the required dose of chemotherapy necessary to kill the tumor cells. Increasing the drug induced death rate of the tumor cells (q), increases the effectiveness of treatment allowing for reduced doses of chemotherapy to be used for successful elimination of the tumor. Conversely, increasing the rate at which tumors grow (r) increases the threshold value of chemotherapy (u_c) indicating that a higher dose or more aggressive chemotherapy is required to treat and successfully remove tumors. Finally, increasing the immune toxicity parameter (η), reduces overall treatment efficacy through decreased immune function capability and could require increased doses of chemotherapy to achieve successful removal of tumors.

Table 5: Qualitative sensitivity of the critical chemotherapy threshold

Parameter	**Effect on (u_c) when parameter increases**	**Biological interpretation**
p	decreases	stronger immune killing reduces required chemotherapy
q	decreases	more effective drug action improves tumor suppression

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r	increases	faster tumor growth requires stronger treatment
η	increases	stronger immune toxicity weakens therapeutic benefit

The numerical findings are summarized below for the sake of completeness. When chemotherapy is weak, the tumor will remain at a stable equilibrium (coexistence) with its environment. However, when chemotherapy is moderately strong, additional reductions to the tumor burden occur although the tumor still has a positive size. Finally, when chemotherapy is sufficiently strong it will pass through a "critical" point where the previously unstable tumor free steady state becomes stable. At this point, there will exist an eradicated tumor steady state. The above stated simulation results agree completely with the local stability and bifurcation analysis performed in previous sections. Additionally, these simulation results add support to the primary conclusion of this study, which was that chemotherapy acts as a dynamic control parameter whose effectiveness is dependent upon two mechanisms: i) cytotoxic effects directly against cancer cells, ii) immune system suppression indirectly acting against cancer cells.

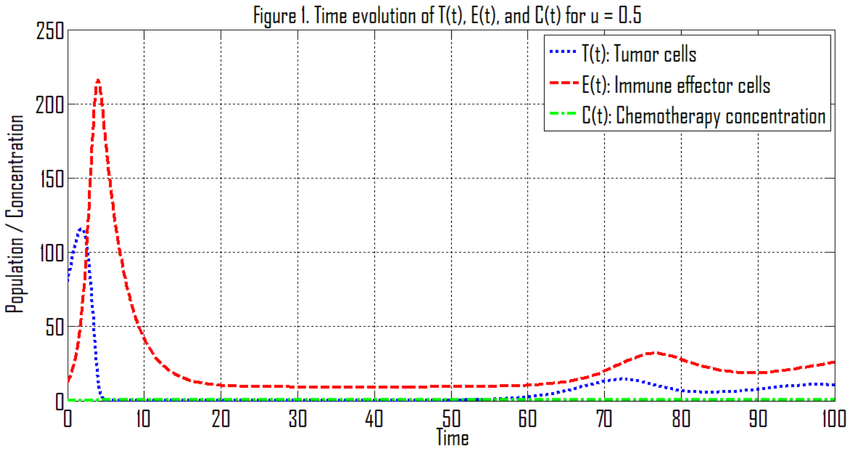


Figure 1. Time evolution of T(t), E(t), and C(t) for u = 0.5

Temporal dynamics of the populations for tumor cells (T), immune effector cells (E) and chemo-therapy concentration (C) with a constant, low chemotherapy input level $(u = 0.5)$ are shown in figure 1. At first, due to action of both chemotherapy and immune system on tumor cells, T decreases. However, the intensity of this therapeutic approach does not allow complete eradication of tumors. During this transient time, the tumour cell population size reaches a new steady value slightly above zero, indicating converging to an unstable co-existence equilibrium. The size of the effector population $E(t)$ adapts during transient time and reaches a positive size as well. This indicates that the immune system will stay active but is incapable of eliminating the tumor entirely. The drug concentration $C(t)$ starts from its initial value and has a monotonic trend toward $C^* = 5.0$. Therefore, as shown in figure 1, low levels of chemotherapy are capable of reducing tumor burden but do not lead to a complete disappearance of tumor, resulting in long-lasting, immunologically controlled tumor persistence.

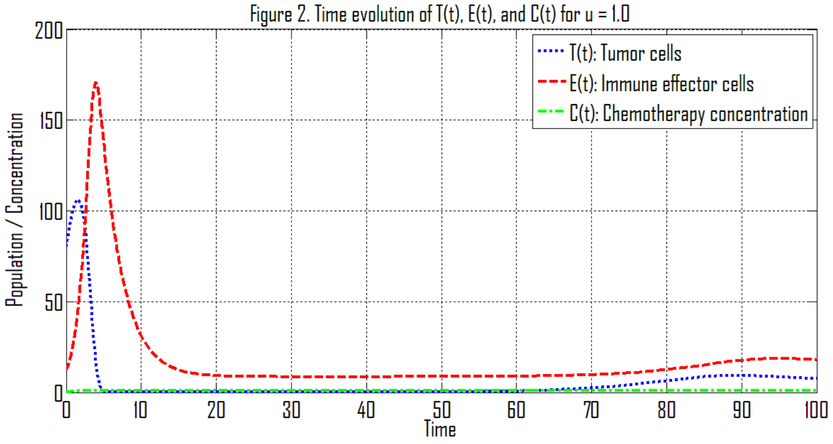


Figure 2. Time evolution of T(t), E(t), and C(t) for u = 1.0

The system dynamic behavior for the middle strength chemotherapy is illustrated by Figure 2. As compared to the dynamics shown in Figure 1, the tumour grows to a much lower positive equilibrium point and declines at a faster rate, demonstrating clearly that an increase in the strength of chemotherapy will result in better tumour suppression. The tumour growth however does remain positive, therefore the tumour will always grow over time and never completely disappears; thus the system will be driven towards a coexistence equilibrium (where both tumours and healthy cells coexist) but never reach a tumour free equilibrium. Likewise, the number of immune cells eventually levels off at a positive constant (a lower level then in the case where less effective chemotherapy was used), due primarily to the cytotoxic effect that chemotherapy has on immune cells. The drug concentration ultimately approaches the steady state concentration $C^* = 1.0$, consistent with analytical predictions. Thus, as can be seen from the results presented in figure 2, application of moderate amounts of chemotherapy is superior to application of small amounts of chemotherapy in reducing tumour size, yet neither condition meets the critical threshold for removal of all tumour.

Figure 3. Time evolution of T(t), E(t), and C(t) for u = 2.0

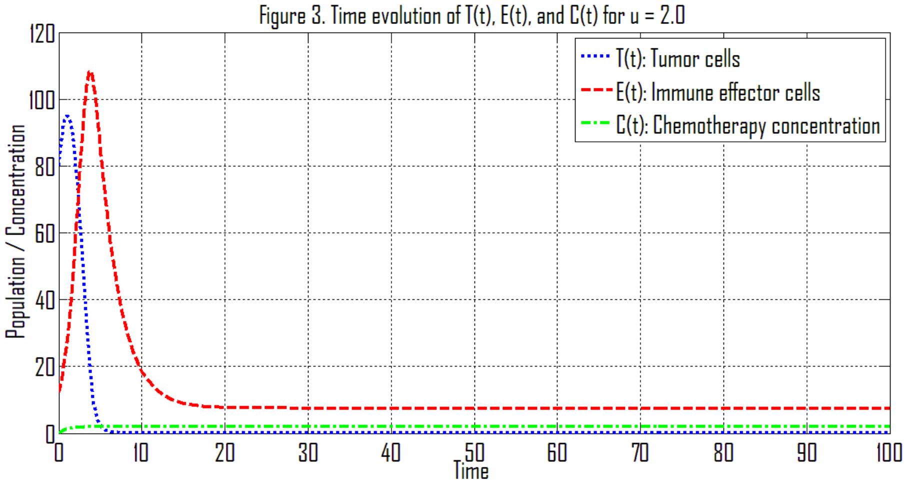
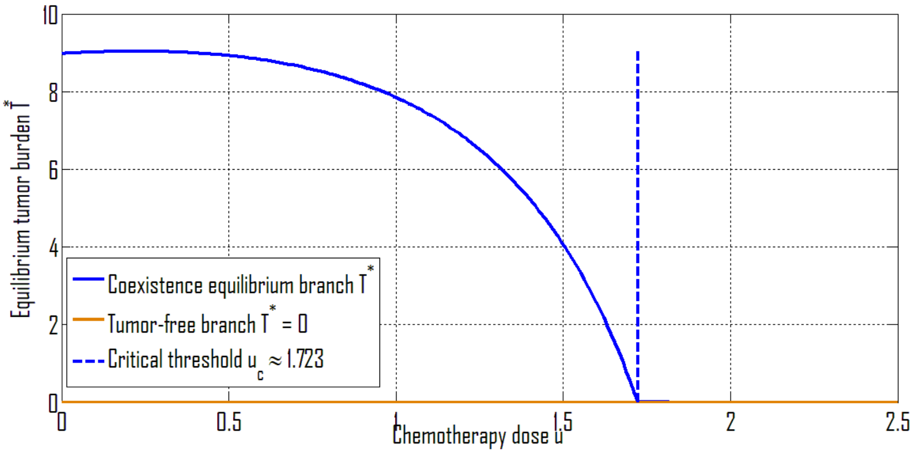


Figure 3 shows how the system behaves in terms of time when we increase the chemotherapy input to $u = 2.0$, which is greater than the critical value for the chemotherapy input ($u_c \approx 1.723$). It clearly illustrates that the tumor population $T(t)$ will continue to decrease until it reaches zero. Therefore, as expected theoretically, there exists a sufficient dose of chemotherapy that will change the system's behavior from one where the tumor persists, to one where the tumor is eradicated. The population of immune cells is still present after chemotherapy; however, its size is decreased since chemotherapy kills both tumor cells and immune effector cells. Additionally, $C(t)$, i.e., the drug concentration, will converge to the constant value $C^* = 2.0$

Figure 4. Bifurcation diagram of T^* versus chemotherapy dose u



The bifurcation diagram of the model is generated using numerical methods. The model is run in continuous time, with the equilibrium value of tumor burden (T^*) plotted against the chemotherapy parameter (u). The resulting plot depicts a positive stable branch of co-existence equilibriums for u_c, the tumor free branch of equilibriums becomes stable. Figure (4) represents a concise representation of the behavior of the tumor burden over time under various conditions and clearly shows the type of transition identified in the analytical solution. By adjusting parameters such that both the determinant and trace of the reduced Jacobian matrix are equal to zero while its determinant remains positive, an additional form of solution may emerge through a Hopf bifurcation. These oscillatory solutions represent periodic relapses of tumors. However, in the current example, no evidence was found of a Hopf bifurcation.

The equilibrium tumor burden changes with chemotherapy dose u as shown in Fig. 4. Below lower values for u, the diagram illustrates a positive stable branch of co-existence equilibria which means that there will be a Tumor (of some size) present, even when treatment is being given. Increasing the value of u as described results in decreasing the Equilibrium Tumor Burden continuously, showing an increasing antitumor effect from the chemotherapy. The co-existence branch and the tumor-free branch meet at the critical point $u_c \approx 1.723$. This represents the bifurcation threshold. Above the threshold value, the tumor-free equilibrium becomes stable while the equilibrium tumor burden becomes zero. Because this figure captures the qualitative change in system dynamics caused by chemotherapy (persistence vs eradication), it is an important graph to understand the effects of chemotherapy acting as a control parameter.

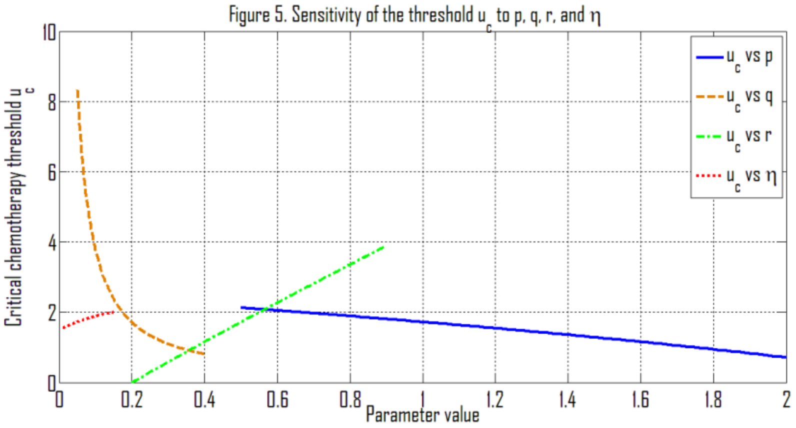


Figure 5. Sensitivity of the threshold u_c to p, q, r, and η

Figure 5 illustrates how the chemotherapeutic threshold for tumor eradication (u_c) is affected by variations in the biological variables p, q, r and η . For example, as the level of immunological killing increases (p), so does the relative level of u_c. Therefore, an increased ability of the body's immune system to kill cancer cells results in a lower amount of chemotherapy required for complete tumor destruction. Similarly, increasing the effectiveness of chemotherapy (q) will result in a decrease in the relative level of u_c, indicating that higher doses of chemotherapy may be able to completely destroy all remaining cancerous cells. On the other hand, if the intrinsic rate of tumor growth (r) increases then this would increase the relative level of u_c. This implies that more rapidly growing tumors would require higher levels of chemotherapy to eradicate them. Finally, as the degree to which chemotherapy suppresses the host's natural immunity (η) increases so too will the relative level of u_c. This is due to the fact that increased toxicity of the drugs used in chemotherapy can weaken the host's own ability to defend against cancer and therefore make it more difficult to eliminate all cancerous cells.

Together, Figures 1 to 5 illustrate the predictions made by the mathematical model using experimental data and help establish a clear biological basis for chemotherapy's impact on interactions between tumors and immune systems. The three images (Figures 1 to 3) clearly show that increasing chemotherapy intensity leads to the long term outcome changing from coexistence to eradication of all cancer cells. The fourth figure provides an example of when such a phase shift will occur. The fifth illustrates how various properties of the basic model can influence where that threshold exists. Finally these four pictures support the fact that chemotherapy functions as a type of bifurcation parameter. In addition they highlight two very important aspects of how effective chemotherapy will be; first it kills cancer cells directly and secondly it preserves some degree of host immunity.

VII. BIOLOGICAL INTERPRETATION

Cancer development (tumor) is not solely based on the intrinsic growth rate of cancer cells. Rather, the rate of tumor growth is influenced by a dynamic interaction among the tumor's inherent proliferation rate, the host's immune response against the tumor, and the effect of chemotherapy. If chemotherapy is insufficiently potent, the tumor will grow despite the presence of immune-effector cells capable of slowing down its expansion. However, these immune-effector cells are usually unable to completely eliminate tumors. This illustrates a real-world scenario in which an immune response recognizes and attacks tumor cells. Yet, due to the highly proliferative nature of cancer cells, their tendency to evade the immune response, and/or their ability to exhaust the immune response, these tumor cells continue to exist. As a result, the co-existence equilibria found in models represent clinically-relevant scenarios in which tumors remain active but in a dormant or controlled manner. Chemotherapy can play two roles in the treatment of cancer. Chemotherapy kills proliferating malignant cells resulting in a decrease in tumor mass and subsequently reducing the tumor's capacity to grow. Chemotherapy can also inhibit the host's immune cells responsible for antitumoral defense. Therefore, an increase in chemotherapy dosing may have a positive effect on tumor kill but also negatively affect the host's ability to defend itself against future tumors. From a clinical standpoint, this illustrates one of the primary shortcomings of chemotherapy, i.e., aggressive treatment can impair normal host immune function and ultimately limit the host's capability to effectively manage subsequent tumors. Accordingly, the model provides a quantitative representation of the established clinical relationship between chemotherapy intensity and immune preservation. One of the most significant biological insights presented through the modeling efforts was the identification of a "threshold" level of chemotherapy. Below this threshold level of chemotherapy, although tumor size may be reduced as a result of treatment, tumors are typically not eliminated. Consequently, a steady-state coexistence exists for all three species. Conversely, above this threshold, the model predicts that both chemotherapy and host-immune surveillance acting in combination can lead to tumor eradication. The existence of such a "threshold" level of chemotherapy indicates that successful cancer therapy necessitates more than merely administering some amount of drug. Instead, there is a minimum intensity of chemotherapy necessary to convert a biological system with persistent disease into one with eradicated disease. In practical terms, suboptimal levels of chemotherapy may never successfully eliminate disease regardless of whether they temporarily reduce tumor burden; however, optimal therapy can provide long-term elimination of tumors. Bifurcations in systems describe qualitatively different behaviors as system parameters vary. Specifically, when chemotherapy is considered as a control parameter, small variations in chemotherapy dosage can result in large qualitative differences in outcomes. For instance, chemotherapy can induce either tumor eradication or sustained control of tumor burden. Bifurcations can also occur in systems involving chemotherapeutic agents leading to periodic phenomena including relapse/remission cycles that are commonly observed in numerous types of cancers treated with chemotherapy. These cycles occur when treatment initially results in partial or complete remission but then leads to regrowth of residual tumor cells. Relapse/Remission cycles can occur as a consequence of impaired or delayed host-antitumoral immune responses; inefficient drug activity; and/or adaptation mechanisms developed by the tumor. Therefore, bifurcation theory provides explanations for why treatments for cancer are typically unpredictable; patients often recover and then experience recurrence. Finally, another meaningful biological implication of the model is that treatment efficacy does not rely exclusively on chemotherapy dosage. Other factors include: increased rates of killing by host antitumoral immune mechanisms; increased rates of tumor growth; decreased levels of cytotoxicity induced by chemotherapy toward host antitumoral immune mechanisms; etc. This view demonstrates that cancer treatment should be viewed as a multi-factorial process involving balancing the aggressiveness of the tumor; the competency of host antitumoral immune responses; and the adverse effects associated with treatment. The model indicates that the best clinical approach is to find a balance between reducing the number of tumors enough and retaining enough of an immune system response. This fits with a biological view of “optimal” or “personalized” therapy, where the amount and timing of chemo drugs are tailored to each patient's level of immune function and the characteristics of their tumors. Therefore, the model provides a theoretical basis for understanding in a general sense, how non-linear interplay among tumor cells, immune response and chemotherapeutic agents will determine if the disease remains, oscillates or is completely eliminated, and also provide some guidance on designing new treatments for cancer that are more "balanced" and based on biology.

VIII. CONCLUDING REMARKS

In summary, the tumor-Immune-Chemotherapy (TIC) model represents a comprehensive mathematical approach to studying the dynamic interactions among three critical factors affecting cancer progression: Tumor Proliferation; Immune Response; and Therapeutic Control. This study illustrates that the system is mathematically "biologically well posed" in terms of positivity, boundedness and Existence of Invariant Region(s), and that the model exhibits either tumor free equilibrium (TFE) or co-existence equilibrium (CE) depending upon the value of its parameters. Moreover, local stability analysis demonstrates that the TFE becomes stable once the cumulative suppressive effect of immune surveillance and chemotherapy exceeds the inherent growth characteristics of the Tumor. On the other hand, CE remains significant as long as treatment fails to completely eradicate the Tumor. Furthermore, bifurcation analysis applied to chemotherapy as a control parameter identifies threshold behavior distinguishing tumor persistence from elimination, while illustrating the possibility of oscillatory remission-rlapse dynamics via hopf-bifurcations. Finally, numerical case studies support these theoretical findings by demonstrating that low to intermediate chemotherapy doses result in stable co-existence, whereas sufficiently high chemotherapy dosage will drive the system towards the tfe. Sensitivity results provide additional evidence supporting that success of cancer therapy relies not only on intensity of chemotherapy, but also efficiency of killing by immune response, rate of growth of the tumor, and toxicity induced to immune response by drugs. Therefore, these findings clearly illustrate that successful cancer therapy requires balancing direct suppression of tumors with preservation of immune competency, and highlight the importance of optimized/personalized treatment strategies involving administration of chemotherapy at levels sufficient to achieve tumor control without compromising host defense.

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