



Equilibrium Dynamics and Threshold Conditions in Tumor–Immune Models with Chemotherapy

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Abstract: This research presents a non-linear tumor-immune-chemotherapy model that distinguishes drug sensitive from drug resistant tumors with respect to chemotherapy dynamics and immune response. The model includes Gompertzian tumor growth, immune mediated killing, differential drug sensitivity, treatment induced drug resistance, immune suppression, and drug clearance. Biologically feasible equilibrium states were established by analytical investigation along with biological conditions of threshold for invasion by sensitive or resistant tumor cell types. Chemotherapy is demonstrated to have a double-edged sword effect in this model; increasing treatment intensity will be effective at suppressing sensitive tumor cells, however it also promotes the relative proportion of resistant tumor cells. Numerically simulated results demonstrate that local stability remains around positive equilibria and resistant tumor cells can remain present within the model despite an increase in chemotherapy. Further sensitivity analysis was conducted to identify factors that influence the models behavior including tumor growth rate, immune killing rates, chemotherapy efficacy, selective pressure on resistance development, degree of immune suppression and drug clearance. Ultimately the data supports that reduction in sensitive tumor population through chemotherapy does not eliminate all cancer (resistant cells), nor prevent recurrence due to continued presence of resistant cells.

Keywords: Tumor–immune dynamics, chemotherapy, drug resistance, mathematical modeling, equilibrium analysis, threshold conditions, Gompertz growth, resistance invasion

I. INTRODUCTION

Cancer is a complex disease which includes uncontrolled cell growth (proliferation) as well as dynamic interactions between cancerous cells, the body's immune response, and treatments applied to the patient. Although chemotherapy has been shown to be effective in treating many patients with cancer, it has limitations. These include differences in the tumor population and effects of chemotherapy on the immune response as well as development of drug resistance among some cancer cells. A specific example of this effect of chemotherapy is when chemotherapy is used at high enough doses to kill sensitive populations of tumor cells but also creates conditions where resistant tumor populations are allowed to continue growing or develop further. One possible method to investigate such nonlinear relationships in cancer treatment models is through mathematical models. The purpose of this investigation was to examine nonlinear interactions using a mathematical model of the relationship between tumors, the immune response, and chemotherapy. This was accomplished through developing a mathematical model of tumor-immune-chemotherapy interactions based upon distinguishing between sensitive and resistant populations of tumor cells and through examining the role of chemotherapeutic agents' ability to induce killing within tumor cells as well as induction of resistance to chemotherapy. Additionally, equilibrium and stability analyses were performed along with a numerical analysis to assess how both chemotherapy dosage levels and the degree of selective pressure due to chemotherapy would impact long term patterns of tumor behavior and outcomes from treatment.

Ledzewicz *et al.* (2015) introduced a 3compartment mathematical model which described heterogeneous tumour populations; the compartments represented tumour cells based upon how they responded to treatments. The authors studied how chemotherapy affects heterogeneous cancer populations. They indicated that the heterogeneity within the tumour can have significant implications regarding the overall treatment process. Additionally, they illustrated the use of compartmental modelling as a tool for studying chemotherapy. Yuan *et al.* (2017) presented a review article discussing drug resistance as one of the primary challenges associated with the use of chemotherapy for treating cancer. They discussed the use of natural products as possible tools to overcome drug resistance. Additionally, they identified drug efflux inhibition and alternative cell death pathways as additional strategies that could be used to combat drug resistance. The authors emphasized that drug resistance can significantly decrease the efficacy of chemotherapy. Therefore, it is essential to include resistant tumour populations when developing models for chemotherapy treatment.



Pedersen *et al.* (2018) performed a pilot study examining whether tumour-infiltrating lymphocytes, i.e. immunocompetent cells reactive against tumours, can be utilized therapeutically in patients diagnosed with metastatic ovarian cancer through adoptive cell therapy. The study supported the idea that cellular immunity plays an important role in cancer treatment. The results from this pilot study provided evidence supporting the inclusion of immune-effector populations in tumour models. **Rejhová *et al.* (2018)** examined both individual natural compounds and combinations of these compounds as potential treatments for colorectal cancer. In addition to identifying several mechanisms that potentially contribute to antitumour activity including inhibiting tumour-cell proliferation and inducing apoptosis, they also proposed combination treatments as a method to minimize side effects. Rejhová *et al.* (2018), suggested that combination strategies may represent a useful mechanism to combat drug resistance. Overall, the study indicates that combination strategies can provide greater therapeutic options by incorporating multiple mechanisms of action to treat colorectal cancer. **Das *et al.* (2019)** used Michaelis-Menten type kinetic equations to develop a model describing non-linear interactions between tumours and the immune system. Das *et al.* (2019) stated that their focus on non-linear interactions was critical because they believe that non-linearity is necessary to capture the complexity inherent in tumour-immune systems. They also noted that while their model assumed that immune killing rates follow Michaelis-Menten type kinetics, such assumptions are consistent with biological observations where there exists limitations to what extent an immune system can kill tumour cells. **Zhou *et al.* (2019)** studied how chemotherapy induces immunogenic cell death which has been shown to be an effective method for activating antitumor immunity. Chemotherapy induced damage associated molecular patterns have been shown to activate dendritic-cells through antigen presentation. This process promotes the activation of an immune response against the tumor. The study showed that chemotherapy not only affects the tumor itself but it also impacts the body's immune system and therefore this effect should be included when modeling chemotherapy and immunity simultaneously. **Shi *et al.* (2020)** investigated whether or not tumor-infiltrating lymphocytes play a role in osteosarcoma patients who had a poor response to neoadjuvant chemotherapy. They found that tumor-infiltrating lymphocytes could potentially serve as an adjuvant immunotherapeutic agent. Additionally, they noted that when the chemotherapy response was poor, there appeared to be significant immune activity. Therefore, the interaction between the tumor and the immune system is still very relevant. Furthermore, Shi *et al.* motivated researchers to consider simultaneously chemotherapy and the mechanisms by which the immune system controls tumors. **Dehingia *et al.* (2021)** introduced an optimal-control framework including immunotherapy, chemotherapy and gene therapy. They viewed cancer therapy as a dynamic optimization problem where multiple mechanisms of action are taken into account at once. Using optimal-control methods, they investigated different treatment strategies. Overall, their research demonstrated that optimal-control theory can assist in balancing competing objectives to achieve optimal therapeutic outcomes. Moreover, their study provided a foundation for expanding existing models of cancer growth to include non-linear treatments.

Al-Shamma *et al.* (2023) concentrated on aldehyde dehydrogenase as an essential factor contributing to chemotherapy resistant cancers. They documented that these enzymes are highly expressed in chemoresistant cancer cells. Consequently, these enzyme activities will decrease the amount of chemotherapy-induced oxidative stress thereby allowing cancer cells to survive longer. They described using combinations of targeted therapies and chemotherapy/immunotherapy to address the biological complexity of acquiring multi-drug resistance. **Bao *et al.* (2024)** presented a mathematical model examining the combined treatment of drug-resistant tumors. Their framework analyzed both the impact of tumor resistance and numerous types of therapeutic actions together. Bao *et al.* assessed the stability characteristics of their model and utilized numerical simulations to analyze their model. The results from Bao *et al.* indicated that utilizing a combination of chemotherapy and immunotherapy can result in greater tumor control than monotherapy alone. In addition, sensitivity analyses were conducted to identify key factors affecting model behavior. **Maleki *et al.* (2024)** identified how cancer cells can exist within multiple cell cycles. These differences create variability in treatment response, while the ability of these cells to persist through treatments creates heterogeneity. Therefore, the authors' examination identifies a significant biologic basis for the creation of tumor heterogeneity. Additionally, this biologic basis provides a clear rationale for mathematically distinguishing among tumor populations based upon their inherent treatment susceptibilities. **Omer and Mambili-Mamboundou (2024)** modeled the interaction between oncolytic virotherapy and immunotherapy. They established a mathematical model that analyzed the interactions between virus-infected tumor cells, uninfected tumor cells, immune systems, and the role of transforming growth factors (TGF- β). Their research found evidence supporting the concept of treatment synergy; additionally, they provided evidence illustrating how mathematical models could provide a rational comparison of alternative combination approaches for treating patients with solid tumors. In addition to developing a model of the combined treatment of solid tumors, Omer and **Mambili-Mamboundou (2024)** established a mathematical framework for optimizing combined treatments by maximizing tumor reductions while minimizing side effects. The model consisted of three groups of cells tumor cells, normal cells, and immune cells and TGF- β . Persistence and extinction were determined for each group of cells. Equilibrium stability or instability was determined. Finally, an optimal-control problem was defined using Pontryagin's Maximum Principle. The objectives included reducing tumor size and limiting



toxicities associated with treatments. In conclusion, this study clearly illustrated the importance of both analyzing equilibriums and optimizing treatments when evaluating cancer treatments. The second study conducted by Omer and **Mambili-Mamboundou (2025)** addressed heterogeneity of tumor cells and drug resistance by defining two subpopulations of tumor cells—chemosensitive and chemoresistant. Treatment protocols consisting of chemotherapy and/or immunotherapy were evaluated for their synergistic effectiveness in controlling the subpopulation of tumor cells exhibiting resistance to treatment. The significance of this study lies in its demonstration of why one cannot always assume that all tumor cells will respond similarly to the same chemotherapy protocol. **Gholami et al. (2026)** examined parameter-sensitivity analyses of mathematical models representing breast cancer. While focusing primarily on the influences of treatment and immune mechanisms on the behavior of tumor cells over time, the researchers also evaluated the sensitivities of model outputs relative to various input parameters. Parameter-sensitivity analysis is critical to establishing which biological processes have the greatest impact on output from a mathematical model representing a complex biological system such as a living organism. Therefore, this research is illustrative of the increasing reliance on parameter-based mathematical modeling to evaluate the dynamics of cancer treatment.

The remaining part of this paper will be structured in a way that follows: In section 2 the nonlinear model of tumor – immune – chemotherapeutic effects from drug-sensitive tumor cells (DSTC), drug-resistant tumor cells (DRTC) cytotoxic T-cells (CTL) and the concentration of drugs used as chemotherapies are formulated. In Section 3 the qualitative properties of the model are investigated by establishing the boundedness, non-negativity, and biologically valid equilibrium states. Section 4 provides an investigation into the sensitivity of equilibria to stable invasion of DSTC and DRCT, along with derivation of threshold conditions for both types of invasions. Section 5 studies the transition from one type of equilibrium to another through chemotherapy input and resistance selection as primary controls. Section 6 shows some examples of how to use simulation and experimental computation to examine how treatments can cause changes in the dynamics of tumors. Section 7 describes the main theoretical results of the work presented here, while highlighting which have biological relevance particularly regarding suppressive effect of drug-sensitive cells and persistent resistant cells. In addition, Section 8 gives a summary of the most important results, limitations and potential areas for future research.

Figure 1. Schematic interaction diagram of the proposed sensitive–resistant tumor–immune–chemotherapy model.

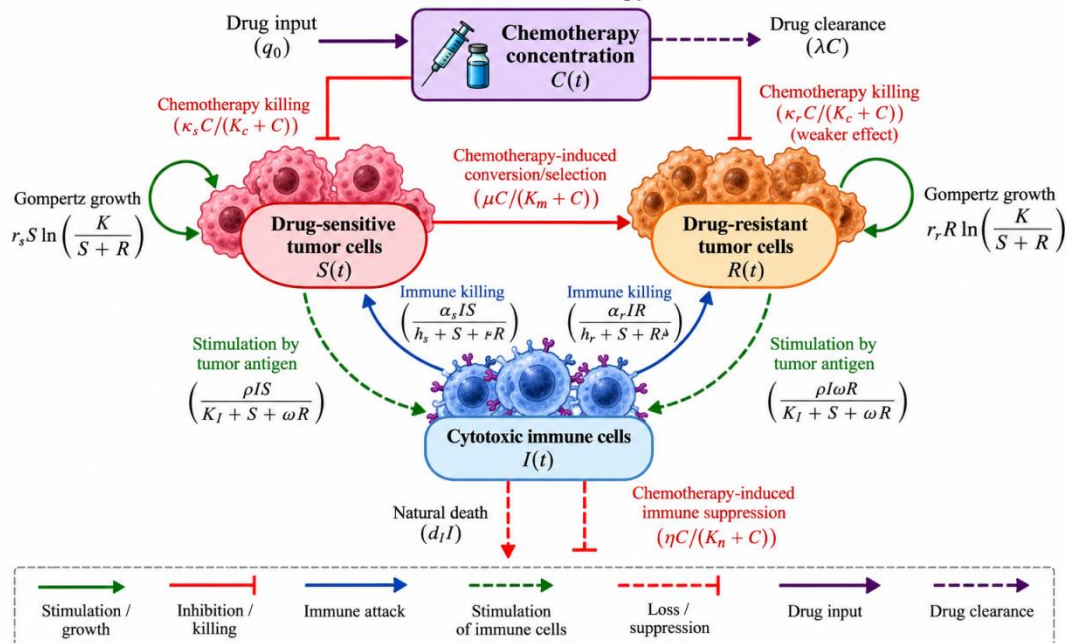


Figure 1 presents the interaction structure of the proposed sensitive–resistant tumor–immune–chemotherapy model, in which the tumor population is divided into drug-sensitive cells $S(t)$ and drug-resistant cells $R(t)$, while $I(t)$ represents cytotoxic immune cells and $C(t)$ denotes chemotherapy concentration. Both tumor phenotypes undergo Gompertz growth, $r_s S \ln(\frac{K}{S+R})$ and $r_r R \ln(\frac{K}{S+R})$, respectively. Chemotherapy enters the system at rate q_0 and is removed through clearance λC ; it exerts a stronger cytotoxic effect on sensitive cells, $\frac{\kappa_s C}{K_c + C}$, and a weaker effect on resistant cells, $\frac{\kappa_r C}{K_c + C}$.



$\frac{\kappa_r C}{K_c + C}$, reflecting differential drug susceptibility. In addition, chemotherapy promotes the conversion or selection of sensitive cells toward the resistant phenotype through the saturating term $\frac{\mu C}{K_m + C}$. Cytotoxic immune cells attack both tumor populations through saturating immune-killing mechanisms governed by α_s and α_r , whereas tumor-associated antigens stimulate immune activity through the term involving ρ , with ω representing the relative antigenic contribution of resistant cells. The immune population is simultaneously reduced by natural death $d_I I$ and chemotherapy-induced suppression $\frac{\eta C}{K_\eta + C}$. Thus, the diagram highlights the competing mechanisms of tumor proliferation, immune-mediated destruction, chemotherapy cytotoxicity, treatment-induced resistance, immune stimulation, and treatment-related immunosuppression that collectively determine whether the system evolves toward tumor persistence, resistant-cell dominance, controlled disease, or tumor elimination.

II. MATHEMATICAL MODEL FORMULATION

Introduce four state variables:

$S(t)$: Drug-sensitive tumor cells

$R(t)$: Drug-resistant tumor cells

$I(t)$: Cytotoxic immune-effector population

$C(t)$: Effective chemotherapy concentration

A suitable new model is

$$\frac{dS}{dt} = r_s S \ln \left(\frac{K}{S+R} \right) - \frac{\alpha_s I S}{h_s + S+R} - \frac{\kappa_s C}{K_c + C} S - \frac{\mu C}{K_m + C} S \quad (1)$$

$$\frac{dR}{dt} = r_r R \ln \left(\frac{K}{S+R} \right) - \frac{\alpha_r I R}{h_r + S+R} - \frac{\kappa_r C}{K_c + C} R - \frac{\mu C}{K_m + C} S \quad (2)$$

$$\frac{dI}{dt} = s_I + \frac{\rho I(S+\omega R)}{K_I + S+\omega R} - d_I I - \xi I(S+R) - \frac{\eta C}{K_\eta + C} I \quad (3)$$

$$\frac{dC}{dt} = q(t) - \lambda C - \gamma C(S+R) \quad (4)$$

Here:

$r_j X_j \ln \left(\frac{K}{S+R} \right)$ represents Gompertzian competitive tumor growth.

$\frac{\mu C}{K_m + C} S$ represents chemotherapy-associated conversion/selection from sensitive to resistant phenotype.

$\frac{\kappa_j C}{K_c + C} S$ gives saturating pharmacodynamic tumor killing.

And $-\gamma C(S+R)$ allows tumor burden to alter effective drug availability.

An important modeling restriction is $0 \leq \kappa_r < \kappa_s$, so resistant cells are less susceptible to chemotherapy.

For constant chemotherapy, $q(t) = q_0$

Table 1. State variables, model parameters, biological interpretations, units, and baseline numerical values				
Symbol	Type	Biological interpretation	Unit*	Baseline value
$S(t)$	State variable	Drug-sensitive tumor-cell population at time t	normalized population	$S(0) = 0.7$
$R(t)$	State variable	Drug-resistant tumor-cell population at time t	normalized population	$R(0) = 0.02$
$I(t)$	State variable	Cytotoxic immune-effector-cell population	normalized population	$I(0) = 0.2$
$C(t)$	State variable	Effective chemotherapy concentration	normalized concentration	$C(0) = 0$
r_s	Parameter	Maximum intrinsic growth rate of drug-sensitive tumor cells	day^{-1}	0.3



r_r	Parameter	Maximum intrinsic growth rate of drug-resistant tumor cells	day^{-1}	0.22
K	Parameter	Effective tumor carrying-scale parameter in the Gompertz growth law	normalized population	1.5
α_s	Parameter	Immune-mediated killing coefficient for sensitive tumor cells	day^{-1}	0.45
α_r	Parameter	Immune-mediated killing coefficient for resistant tumor cells	day^{-1}	0.32
h_s	Parameter	Half-saturation constant for immune killing of sensitive cells	normalized population	0.3
h_r	Parameter	Half-saturation constant for immune killing of resistant cells	normalized population	0.35
κ_s	Parameter	Maximum chemotherapy-induced killing rate of sensitive tumor cells	day^{-1}	0.65
κ_r	Parameter	Maximum chemotherapy-induced killing rate of resistant tumor cells	day^{-1}	0.12
K_c	Parameter	Half-saturation chemotherapy concentration for drug-induced tumor killing	normalized concentration	0.4
μ	Parameter	Maximum chemotherapy-induced sensitive-to-resistant conversion/selection rate	day^{-1}	0.2
K_m	Parameter	Half-saturation concentration governing chemotherapy-induced resistance selection	normalized concentration	0.5
s_I	Parameter	Basal source/recruitment rate of cytotoxic immune cells	Population ⁻¹ day^{-1}	0.04
ρ	Parameter	Maximum tumor-antigen-mediated immune stimulation rate	day^{-1}	0.35



K_I	Parameter	Half-saturation constant for tumor-induced immune stimulation	normalized population	0.5
ω	Parameter	Relative antigenic contribution of resistant cells to immune stimulation	dimensionless	0.7
d_I	Parameter	Natural death rate of cytotoxic immune cells	day^{-1}	0.1
ξ	Parameter	Tumor-burden-induced immune exhaustion/suppression coefficient	$Population^{-1} day^{-1}$	0.08
η	Parameter	Maximum chemotherapy-induced immune-suppression rate	day^{-1}	0.18
K_η	Parameter	Half-saturation concentration for chemotherapy-induced immune suppression	normalized concentration	0.45
q_0	Control parameter	Constant chemotherapy input rate	concentration day^{-1}	variable: 0 – 3.0
λ	Parameter	Natural chemotherapy clearance rate	day^{-1}	0.8
γ	Parameter	Tumor-dependent chemotherapy depletion/uptake coefficient	$Population^{-1} day^{-1}$	0.15
ϵ	Parameter	Small regularization constant used for tumor-free Gompertz threshold analysis	normalized population	10^{-4}

III. MATHEMATICAL PROPERTIES AND ANALYTICAL SOLUTION

In this section we will establish nonnegativity and boundedness before equilibrium analysis.

For $S(0), R(0), I(0), C(0) \geq 0$

the boundary conditions satisfy

$$\left. \frac{dS}{dt} \right|_{S=0} = 0, \left. \frac{dR}{dt} \right|_{R=0} = \frac{\mu C}{K_m + C} S \geq 0, \left. \frac{dI}{dt} \right|_{I=0} = s_I > 0, \left. \frac{dC}{dt} \right|_{C=0} = q_0 \geq 0$$

Hence $\mathbb{R}_+^4$ is positively invariant.

The chemotherapy equation also gives the useful inequality $\frac{dC}{dt} \leq q_0 - \lambda C$

and therefore

$$C(t) \leq C(0)e^{-\lambda t} + \frac{q_0}{\lambda}(1 - e^{-\lambda t}) \quad (5)$$

$$\text{so that } \lim_{t \rightarrow \infty} C(t) \leq \frac{q_0}{\lambda} \quad (6)$$



At a tumor-free state, $S^* = R^* = 0$

$$\text{and consequently } C_0 = \frac{q_0}{\lambda} \quad (7)$$

Equation (3) then gives

$$I_0 = \frac{\frac{S_I}{d_I + \frac{\eta C_0}{K\eta + C_0}}}{\frac{\eta C_0}{K\eta + C_0}} \quad (8)$$

Thus,

$$E_0 = \left[0, 0, \frac{\frac{S_I}{d_I + \frac{\eta C_0}{K\eta + C_0}}}{\frac{\eta C_0}{K\eta + C_0}}, \frac{q_0}{\lambda} \right] \quad (9)$$

For positive equilibria, define $N^* = S^* + R^*$

$$\text{From the drug equation, } C^* = \frac{q_0}{\lambda + \gamma N^*} \quad (10)$$

From the immune equation,

$$I^* = \frac{\frac{S_I}{d_I + \xi N^* + \frac{\eta C^*}{K\eta + C^*}}}{\frac{\eta C^*}{K\eta + C^*} + \frac{\rho(S^* + \omega R^*)}{K_I + S^* + \omega R^*}} \quad (11)$$

Equations (10)–(11) reduce the four-dimensional equilibrium problem to two nonlinear algebraic equations in S^* and R^* .

Table 2. Existence and biological feasibility conditions for tumor-free, sensitive-dominant, resistant-dominant, and mixed coexistence equilibria

Equilibrium state	Equilibrium representation	Existence condition	Biological feasibility condition	Biological interpretation
Tumor-free equilibrium E_0	$E_0 = [0, 0, I_0, C_0]$ Where $C_0 = \frac{q_0}{\lambda}$ $I_0 = \frac{\frac{S_I}{d_I + \frac{\eta C_0}{K\eta + C_0}}}{\frac{\eta C_0}{K\eta + C_0}}$	Exists for $q_0 \geq 0, \lambda > 0, S_I > 0, d_I > 0$	$C_0 \geq 0, I_0 > 0$. For resistance to small tumor invasion, additionally require $\tau_S < 1$ and $\tau_R < 1$	Complete absence of both sensitive and resistant tumor populations while immunity and chemotherapy remain present.



Sensitive-dominant equilibrium E_S	$E_S = (S_S^*, 0, I_S^*, C_S^*), S_S^* > 0$	A positive solution S_S^* must satisfy the sensitive-cell equilibrium equation together with $C_S^* = \frac{q_0}{\lambda + \gamma S_S^*}$ and the corresponding immune equilibrium relation.	$S_S^* > 0, I_S^* > 0, C_S^* > 0$. Strictly, when $\mu > 0$ and $C_S^* > 0$, the term $\frac{\mu C_S}{K_m + C_S}$ continuously generates R , so an exact $R^* = 0$ equilibrium requires $\mu = 0, C_S^* = 0$ or $S_S^* = 0$. Otherwise E_S is interpreted as a boundary/reference state for resistance-invasion analysis.	Tumor burden is predominantly chemotherapy-sensitive; useful as the reference state for determining whether resistant cells can invade.
Resistant-dominant equilibrium E_R	$E_R = (0, R_R^*, I_R^*, C_R^*)$	A positive root R_R^* satisfies $r_r \ln\left(\frac{K}{R_R^*}\right) - \frac{\alpha_r I_R^*}{h_r + I_R^*} - \frac{\kappa_r C_R^*}{K_c + C_R^*} = 0$ with $C_R^* = \frac{q_0}{\lambda + \gamma R_R^*}$	$R_R^* > 0, I_R^* > 0, C_R^* \geq 0$ requiring $d_I + \xi R_R^* + \frac{\eta R_R^*}{K_\eta + C_R^*} - \frac{\rho \omega R_R^*}{K_I + \omega R_R^*} > 0$	Persistent tumor composed entirely or predominantly of chemotherapy-resistant cells.
Mixed coexistence equilibrium E_M	$E_M = (S_M^*, R_M^*, I_M^*, C_M^*)$	The complete nonlinear equilibrium system must admit a simultaneous positive solution with $S_M^* > 0$ and $R_M^* > 0$.	$S_M^* > 0, R_M^* > 0, I_M^* > 0, C_M^* > 0$, together with a positive immune denominator and satisfaction of both tumor balance equations.	Long-term coexistence of sensitive and resistant malignant phenotypes under immune pressure and chemotherapy.

IV. EQUILIBRIUM STABILITY AND THRESHOLD CONDITIONS

Write $\dot{X} = F(X), X = (S, R, I, C)^T$ with Jacobian

$$J = \begin{pmatrix} F_{1S} & F_{1R} & F_{1I} & F_{1C} \\ F_{2S} & F_{2R} & F_{2I} & F_{2C} \\ F_{3S} & F_{3R} & F_{3I} & F_{3C} \\ F_{4S} & F_{4R} & F_{4I} & F_{4C} \end{pmatrix} \quad (12)$$

Because the Gompertz law has a logarithmic singularity exactly at zero, the rigorous tumor-free invasion analysis should use a small-cell regularization such as

$$\ln\left(\frac{K+\epsilon}{S+R+\epsilon}\right), \epsilon > 0 \quad (13)$$



for local threshold calculations. This avoids claiming an ordinary Jacobian linearization at a point where the unregularized vector field is not differentiable.

Define the effective sensitive-tumor invasion exponent

$$\Lambda_S = r_s \ln \left(\frac{K+\epsilon}{\epsilon} \right) - \frac{\alpha_s I_0}{h_s} - \frac{\kappa_s C_0}{K_c + C_0} - \frac{\mu C_0}{K_m + C_0} \quad (14)$$

Then introduce the dimensionless threshold

$$\tau_S = \frac{r_s \ln \left(\frac{K+\epsilon}{\epsilon} \right)}{\frac{\alpha_s I_0}{h_s} + \frac{\kappa_s C_0}{K_c + C_0} + \frac{\mu C_0}{K_m + C_0}} \quad (15)$$

Hence, $\tau_S < 1$ corresponds to suppression of invasion by sensitive tumor cells, while $\tau_S > 1$ permits their initial expansion.

$$\text{For resistant cells, } \Lambda_R = r_r \ln \left(\frac{K+\epsilon}{\epsilon} \right) - \frac{\alpha_r I_0}{h_r} - \frac{\kappa_r C_0}{K_c + C_0} \quad (16)$$

Giving

$$\tau_R = \frac{r_r \ln \left(\frac{K+\epsilon}{\epsilon} \right)}{\frac{\alpha_r I_0}{h_r} + \frac{\kappa_r C_0}{K_c + C_0}} \quad (17)$$

A particularly interesting contribution is the resistance-invasion threshold calculated around a sensitive-dominant equilibrium

$$E_S = (S_S^*, 0, I_S^*, C_S^*)$$

For a rare resistant clone,

$$\Lambda_{R|S} = r_r \ln \left(\frac{K}{S_S^*} \right) - \frac{\alpha_r I_S^*}{h_r + S_S^*} + \frac{\kappa_r C_S^*}{K_c + C_S^*} \quad (18)$$

Thus

$$\Lambda_{R|S} = 0 \quad (19)$$

defines the critical boundary separating resistance exclusion from resistance invasion.

Figure 2. Threshold map in the (q_0, μ) -plane showing regions of tumor persistence, sensitive-tumor suppression, and resistant-tumor invasion.

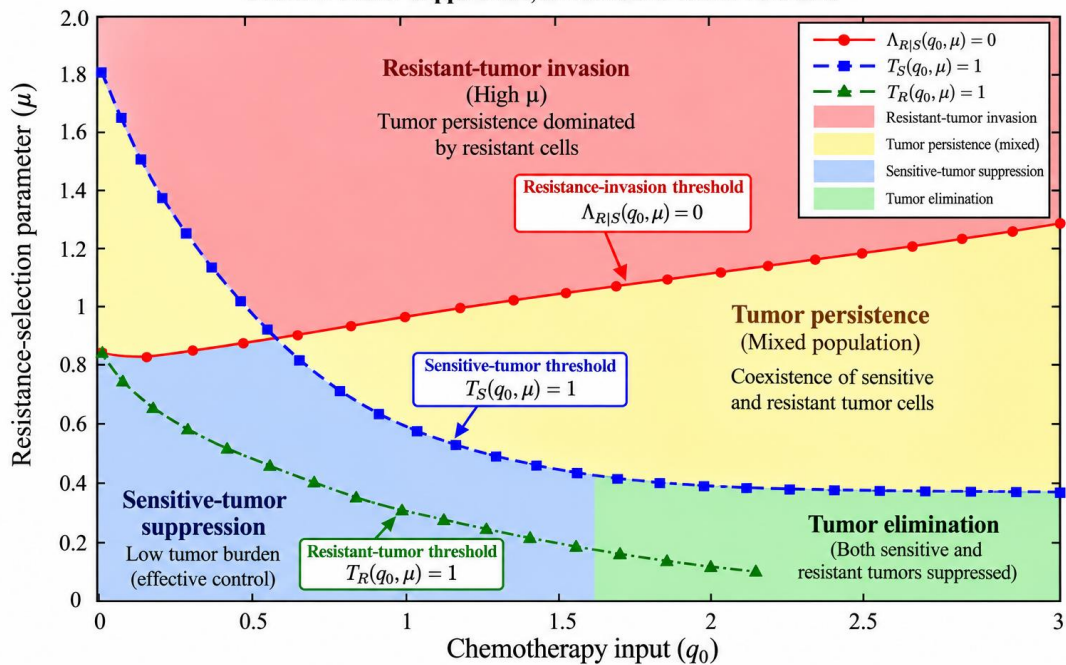




Figure 2 depicts how the long term dynamics of the tumor/immune system will respond to changes in the amount of chemotherapy administered q_0 and the rate of selection for tumor cell resistance (μ). There are three curves, each representing a different “threshold” and together they define boundaries within the (q_0, μ) plane of parameters that determine the type of dynamic response of the system. The red curve shows the boundary of the “resistance-invasion” threshold $\Lambda_{R|S}(q_0, \mu)$; any points above this boundary result in the invasion and subsequent domination of resistant tumor cells, especially if there is a significant degree of resistance selection. The blue dashed curve, $T_S(q_0, \mu) = 1$, defines the “suppression-threshold” for drug sensitive tumor cells and the green dash-dotted curve, $T_S(q_0, \mu) = 1$ defines the “suppression-threshold” for resistant tumor cells. When chemotherapy dosing q_0 is relatively small and resistance selection is moderate, then in the lower right region of the blue area of the graph, there is an indication that drug sensitive tumor cells have been effectively suppressed resulting in a smaller tumor burden. The yellow region in the center of the graph is indicative of a state of persistent mixed disease where both drug sensitive and resistant tumor cell populations exist. Finally, as shown in the upper left green area of the graph, when either sufficient amounts of chemotherapy are administered or when resistance selection is minimal, then the immune system is able to eliminate both drug sensitive and resistant tumor cells. Therefore overall, this graph shows that treatment outcomes depend on both chemotherapy intensity q_0 and the rate of tumor cell resistance selection (μ): administering enough chemotherapy may help to suppress tumors, however, administering too much chemotherapy with insufficiently high rates of resistance selection can lead to resistant tumor cell persistence; therefore it should be recognized that the suppression of sensitive tumor cells does not always equate to the eradication of all tumor cells.

V. CHEMOTHERAPY-MEDIATED EQUILIBRIUM TRANSITIONS

Treat chemotherapy input q_0 and resistance-selection coefficient μ as the two principal control parameters. Critical curves are defined by

$$\tau_S(q_0, \mu) = 1 \quad (20)$$

$$\tau_R(q_0) = 1 \quad (21)$$

$$\Lambda_{R|S}(q_0, \mu) = 0 \quad (22)$$

These curves divide parameter space into qualitatively different regimes.

One especially publishable hypothesis is a non-monotonic chemotherapy effect: increasing q_0 initially reduces total tumor burden, but sufficiently strong treatment can increase the resistant fraction

$$\phi_R = \frac{R}{S+R} \quad (23)$$

because sensitive cells experience stronger chemotherapy mortality and chemotherapy contributes to the $S \rightarrow R$ pathway.



Figure 3. Equilibrium bifurcation diagram of S^* , R^* , and total tumor burden $N^* = S^* + R^*$ versus chemotherapy input (q_0).

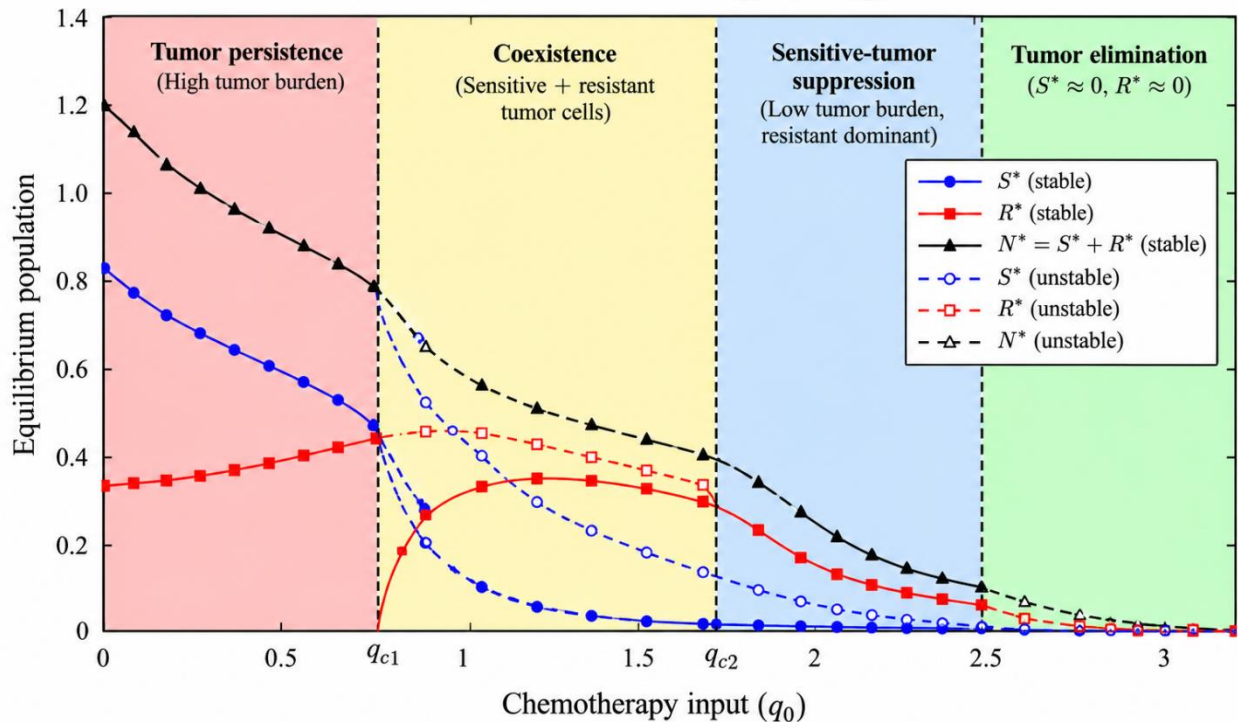


Figure 3 illustrates how the equilibrium populations of drug-sensitive tumor cells S^* , drug-resistant tumor cells R^* , and the total tumor burden $N^* = S^* + R^*$ change as the chemotherapy input q_0 is increased. At low chemotherapy levels, the system lies in the tumor-persistence region, where S^* , R^* , and consequently N^* remain appreciably positive, indicating a high equilibrium tumor burden. As q_0 approaches the first critical value q_{c1} , the sensitive-cell population decreases substantially, while the resistant component remains important, marking a transition toward coexistence of the two tumor phenotypes. Between q_{c1} and q_{c2} , the diagram shows a coexistence regime in which chemotherapy progressively suppresses the sensitive population, but resistant cells continue to maintain a positive tumor burden. Beyond q_{c2} , the system enters the sensitive-tumor-suppression region: S^* is nearly zero and R^* constitutes most of the remaining tumor population, illustrating treatment-driven resistant-cell dominance. With a further increase in chemotherapy input, both R^* and the total burden N^* decrease and eventually approach zero in the tumor-elimination region. The solid and dotted lines in the diagram show the difference between a stable and an unstable solution of equilibrium. This shows how the nature of tumor growth equilibrium (magnitude) is changed by alterations to chemotherapeutic treatments. The diagram also illustrates how sequential transitions occur as the level of chemotherapy increases with respect to sequential transitions from high levels of tumor persistence through coexistence with both persistent and resistant strains of cancer cells prior to achieving the tumor-free state when chemotherapy levels are sufficient.

VI. NUMERICAL SIMULATION AND COMPUTATIONAL EXPERIMENTS

Use MATLAB ode45 for nonstiff regimes and verify difficult parameter sets with ode15s. Equilibria can be computed with fsolve, while the eigenvalues of the numerical Jacobian can be used to confirm analytical stability conditions.

A representative nondimensional baseline could be initialized as

$$S(0) = 0.70, R(0) = 0.02, I(0) = 0.20, C(0) = 0 \quad (24)$$

The simulations should examine at least four regimes:

$$q_0 < q_{c1}, q_{c1} < q_0 < q_{c2}, q_0 \approx q_{c2}, q_0 > q_{c2}$$

Numerically solve



$$\frac{dX}{dt} = F(t, X), X(0) = X_0 \quad (25)$$

and define the terminal tumor burden

$$N_{\infty}(q_0) = S(t_f; q_0) + R(t_f; q_0) \quad (26)$$

Also calculate

$$\phi_R(t_f) = \frac{R(t_f)}{S(t_f) + R(t_f)} \quad (27)$$

This allows chemotherapy to be evaluated in terms of both tumor burden and phenotypic composition.

Figure 4. Time evolution of sensitive tumor cells, resistant tumor cells, immune cells, and chemotherapy concentration under low, intermediate, and high chemotherapy inputs.

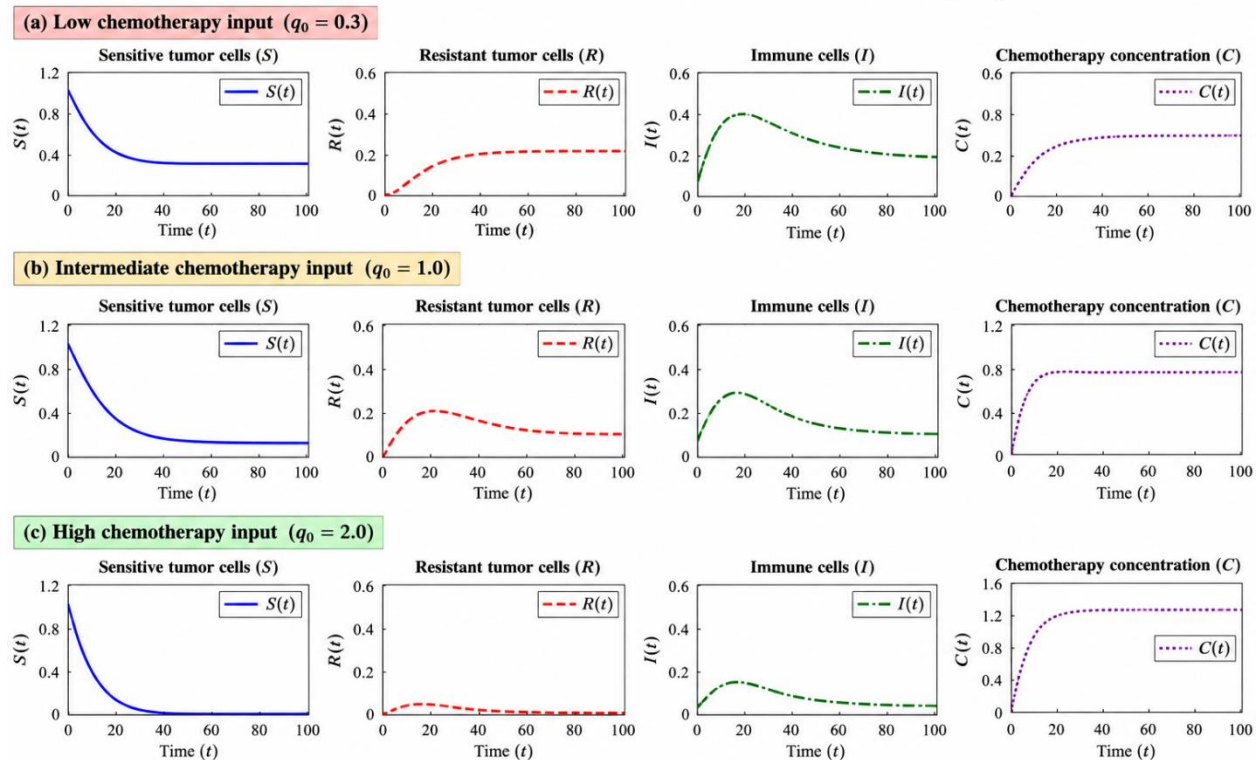


Figure 4 illustrates in time for the parameters $S(t)$ for drug-sensitive tumor cells, $R(t)$ for drug-resistant tumor cells, $I(t)$ for cytotoxic immune cells and $C(t)$ for chemotherapy concentration at three different levels of chemotherapy input q_0 the transient and stable behavior of the system as a function of increased chemotherapy input. For low chemotherapy input ($q_0 = 0.3$), we observe that $S(t)$ first falls rapidly, then converges to a positive level. In contrast, $R(t)$ grows slowly towards a long term equilibrium. The immune cell population shows an initial increase, after which it converges to a positive value. Finally, $C(t)$ is a relative small steady state concentration. With the medium input ($q_0 = 0.1$), drug-sensitive tumor cells are more strongly suppressed than with low input. However, drug-resistant cells first grow, reach a transient maximum and then fall back to a smaller but non-zero level. This indicates that there is partial control over the tumor, but also a residue of drug-resistant tumors. The immune response also shows a transient peak followed by a gradual decrease, consistent with the combined effects of reduced tumor stimulation and chemotherapy-induced immune suppression, while the drug concentration rapidly approaches a higher plateau. Under **high chemotherapy input** ($q_0 = 0.2$), $S(t)$, rapidly approaches zero and $R(t)$ displays only a small transient increase before becoming strongly suppressed; however, the immune-cell population is also markedly reduced as chemotherapy concentration reaches its highest steady level. Taken together, the simulations demonstrate a clear treatment-intensity-dependent transition from persistent mixed tumor burden at low chemotherapy, through enhanced tumor control at intermediate treatment, to near-complete suppression of both tumor phenotypes at high chemotherapy, while also highlighting the trade-off between improved tumor killing and increased chemotherapy-induced suppression of the antitumor immune response.



Figure 5. Two-parameter numerical response surface/heat map of long-term total tumor burden N_∞ and resistant fraction ϕ_R against chemotherapy input (q_0) and resistance-selection parameter (μ).

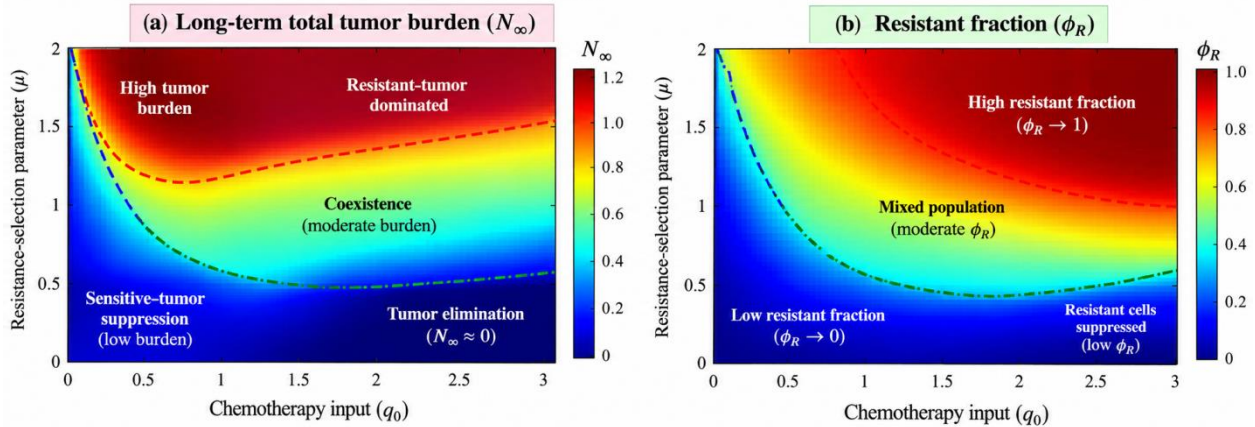


Figure 5 presents a two-parameter numerical characterization of the long-term tumor response as a function of chemotherapy input q_0 and the resistance-selection parameter μ . Panel (a) shows the asymptotic total tumor burden N_∞ , where warmer colors indicate larger residual tumor populations and cooler colors represent stronger tumor control. At low chemotherapy input and/or high resistance selection, the model predicts a high tumor burden or a resistant-tumor-dominated state, whereas intermediate combinations of q_0 and μ produce coexistence with a moderate residual burden. Increasing chemotherapy while maintaining relatively low resistance selection moves the system toward sensitive-tumor suppression and ultimately the tumor-elimination region, characterized by $N_\infty \approx 0$. Panel (b) shows the corresponding resistant fraction ϕ_R , with values approaching unity in the upper region indicating that resistant cells constitute nearly the entire surviving tumor population. In contrast, low values of μ are associated with a small resistant fraction, while intermediate parameter combinations generate mixed sensitive-resistant populations. The curved boundaries separating these regimes demonstrate that chemotherapy efficacy depends strongly on the magnitude of resistance selection rather than on q_0 alone. In particular, increasing chemotherapy can reduce the overall tumor burden while simultaneously increasing the relative importance of resistant cells when μ is sufficiently large. Thus, the two panels together reveal an important distinction between **reducing total tumor burden** and **preventing resistant-cell dominance**, highlighting the need to consider both N_∞ and ϕ_R when evaluating the long-term dynamics of chemotherapy in the proposed model.

Table 3. Numerical equilibrium values, dominant Eigen value, threshold status, resistant fraction, and long-term dynamical outcome for representative chemotherapy regimes

Chemotherapy regime	q_0	S^*	R^*	I^*	C^*	Dominant eigen value $\max \Re(\lambda)$	τ_S	τ_R	Resistant fraction on ϕ_R^*	Threshold/stability status	Long-term outcome
Low	0.3	≈ 0	0.463	$0.5/2$	0.345	-0.0891	3.95	8.161	≈ 1	$\tau_S > 1, \tau_R > 1$ stable positive equilibrium	Resistant-tumor persistence



Intermediate	1	≈ 0	0.593	$\frac{0.3}{4}$	1.125	-0.1305	$\frac{3.22}{9}$	8.52	≈ 1	$\tau_s > 1, \tau_R > 1$ stable resistant equilibrium	Sensitive cells suppressed; resistant tumor persists
High	2	≈ 0	0.607	$\frac{0.2}{9}$	2.244	-0.1469	$\frac{2.99}{1}$	8.521	≈ 1	$\tau_s > 1, \tau_R > 1$ stable positive equilibrium	Strong sensitive-cell suppression but resistant-tumor dominance

Here, $\phi_R^* = \frac{R^*}{S^* + R^*}$ and the dominant eigenvalue is defined as

$$\lambda_{dom} = \max\{Re(\lambda_i)\}$$

Thus, $\lambda_{dom} < 0$ for all three numerical cases, indicating local asymptotic stability of the computed positive equilibrium.

For example, at $q_0 = 0.30$, the Jacobian eigenvalues are approximately

$$\lambda_1 = -0.8731, \lambda_2 = 0.3343$$

$$\lambda_{3,4} = -0.0891 \pm 0.1002i \text{ so that } \lambda_{dom} = -0.0891$$

At $q_0 = 1.00$, $\lambda_{dom} \approx -0.1305$ while at $q_0 = 2.00$, $\lambda_{dom} \approx -0.1469$

The numerical results reveal an important feature of the proposed model: increasing chemotherapy intensity strongly suppresses the drug-sensitive phenotype, but with the Table 1 baseline parameters it does not eliminate the resistant phenotype. Instead,

$S^* \rightarrow 0$ while $R^* > 0$ giving $\phi_R^* \rightarrow 1$ Consequently, increasing chemotherapy from

$q_0 = 0.30 \rightarrow 1.00 \rightarrow 2.00$ does not produce a transition to the tumor-free equilibrium for this particular parameter set. The long-term state instead becomes increasingly dominated by resistant tumor cells. The computed values $\tau_s > 1, \tau_R > 1$ are consistent with the tumor-free state failing the proposed local invasion-threshold criterion.

This result is scientifically useful because it illustrates the main conceptual distinction of the new model:

suppression of sensitive tumor cells $\Rightarrow$ eradication of the total tumor

It also demonstrates why explicitly including $R(t)$ changes the conclusions obtained from a single-tumor-population chemotherapy model. With

$\kappa_r = 0.12 \ll \kappa_s = 0.65$ chemotherapy exerts much weaker direct cytotoxic pressure on resistant cells, while the conversion term $\frac{\mu C}{K_m + C} S$ feeds the resistant compartment during treatment.

VII. RESULTS AND BIOLOGICAL INTERPRETATION

The analytical and numerical results demonstrate that the long-term behavior of the proposed tumor-immune-chemotherapy system is determined by the balance between intrinsic tumor proliferation and the combined suppressive effects of immune activity, chemotherapy, and treatment-induced phenotypic conversion. For sensitive tumor cells, growth is opposed by immune-mediated killing and direct chemotherapy cytotoxicity, whereas the conversion term



additionally removes cells from the sensitive compartment and contributes to the resistant population. Consequently, tumor control is governed not only by the magnitude of chemotherapy input q_0 , but also by the relative susceptibility of the sensitive and resistant phenotypes and the strength of the immune response.

A particularly important result is the dual effect of chemotherapy. Increasing q_0 , raises chemotherapy exposure and therefore enhances killing of sensitive tumor cells,

$$q_0 \uparrow \Rightarrow S \downarrow \quad (28)$$

However, because resistant cells are less susceptible to treatment and chemotherapy contributes to sensitive-to-resistant selection/conversion, stronger treatment can increase the relative resistant fraction,

$$q_0 \uparrow \Rightarrow \phi_R = \frac{R}{S+R} \uparrow \quad (29)$$

over relevant parameter regimes. Thus, a reduction in total or sensitive tumor burden does not necessarily imply successful control of drug resistance.

This behavior is evident across the analytical and numerical results. Figure 2 provides the analytical threshold landscape in the (q_0, μ) -plane and separates sensitive-tumor suppression, mixed persistence, resistant invasion, and tumor-control regimes. Figure 3 illustrates the corresponding equilibrium transitions as chemotherapy increases, showing the progressive reduction of S^* , changes in R^* , and the resulting variation in total tumor burden $N^* = S^* + R^*$. Figure 4 provides transient confirmation of these mechanisms: stronger chemotherapy produces faster sensitive-cell suppression, while resistant cells may exhibit a transient increase or persist after the sensitive population has declined. Figure 5 extends these findings over the two-parameter space and demonstrates that regions of low total tumor burden N_∞ do not necessarily coincide with regions of low resistant fraction ϕ_R .

The results therefore distinguish tumor eradication from resistance prevention. Suppression of sensitive cells may be associated with

$$\tau_S < 1 \quad (30)$$

but this condition alone does not ensure that resistant cells cannot invade. Resistance prevention additionally requires

$$\Lambda_{R|S} < 0 \quad (31)$$

Hence, an intensity in chemotherapy capable of suppressing S will allow R to grow. The model's central mathematical implications are these three distinctions among the sensitive-tumor control (to eliminate tumors), resistance control (to stop growth of resistant cells) and total tumor elimination.

$$\gamma_p^\tau = \frac{\partial \tau}{\partial p} \frac{p}{\tau} \quad (32)$$

For

$$p \in \{r_s, r_r, \alpha_s, \alpha_r, \kappa_s, \kappa_r, \mu, \eta, \rho, \lambda\} \quad (33)$$

Positive sensitivity indices are those which indicate an increase in a parameter increases the invasion threshold for that particular parameter, and thus positive sensitivity indicates a parameter that supports persistent invasive cell populations. Conversely, Negative sensitivity indicators represent those which indicate a decrease of a parameter decreases the invasion threshold for that particular parameter, and thus Negative Sensitivity Indicates Parameters That Support Suppression Of Tumor Growth. Generally speaking, the increased growth rates of tumors r_s and r_r favor the presence of invasive cells; while the increased ability to kill by the Immune System (α_s, α_r) and Chemotherapy (κ_s, κ_r) would be expected to suppress tumor growth. The resistance selection parameter (μ) , however has a dual function. While it reduces the number of sensitive cells available for chemotherapy or immune-mediated killing at any



given time, It also promotes the generation of additional resistant-cells. Similarly, the functions regulated by η, ρ and λ , all have indirect effects on treatment outcome via suppression of the immune response, activation of the immune response, and clearance of Chemotherapy from circulation respectively.

The overall results therefore define how these model components relate to one another.

sensitive – tumor suppression $\neq$ resistance prevention $\neq$ complete tumor eradication

The threshold values derived in this study represent hypothetical model-based criteria that were established using both the proposed equations and chosen parameter values. As such they may serve to provide a model theoretic indication of where and when transition might occur dynamically within the system but cannot be used for clinical use (i.e. setting actual chemotherapy dosages or treatment protocols). Clinical application of these results would need to include either empirical estimates of the parameters from patients and/or other independent confirmation.

VIII. CONCLUSION

The proposed nonlinear model for the interaction of a tumor with its host's immune system and chemotherapy has demonstrated that the effectiveness of chemotherapy is dependent upon the interaction of the strength of the chemotherapy, the level of immune activity in the body and the degree of drug resistance within the tumor. The analysis described here distinguishes between "sensitive" and "resistant" types of tumor cells; as such it indicates that strong enough chemotherapy will be able to suppress sensitive populations while resistant populations may survive or even become predominant due to their reduced sensitivity to drugs as well as selective pressures imposed by the treatment itself. Additionally, equilibrium, threshold and numerical studies suggest that tumor persistence (with either a mix of both cell populations or one type predominating), sensitive-population suppression, resistant-population domination and effective tumor control can all result from different combinations of chemotherapy input and resistance pressure. In addition, these studies indicate that sensitive-tumor suppression, resistance prevention and complete tumor eradication are three separate mathematical states, indicating that suppressing sensitive tumor cells does not guarantee preventing an invasion by resistant-type tumor cells. Therefore, the model suggests that consideration needs to be given to both the total number of tumor cells present at the time of initiation of therapy and the proportion of those cells which are drug-resistant. The results of this study are theoretically based model derived predictions and do not constitute clinical dosing advice. Future work is needed in order to validate experimentally the predictive capability of this model, estimate parameters for individual patients, quantify uncertainty associated with predictions made using this model, determine optimal schedules for administration of treatments and develop methods for determining optimal controls for treatment application.

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