

The Theoretical Limits of Cancer Immunotherapy: A Stability Analysis of Checkpoint Inhibitor Dynamics

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Abstract—While immune checkpoint inhibitors have revolutionized cancer treatment, predicting which patients will be cured and which will relapse remains a clinical challenge. The tumor microenvironment is a chaotic, evolving battleground where cancer cells and immune cells constantly fight for dominance. To decode this complexity, we built a mathematical model using non-linear differential equations to track this biological tug-of-war, treating the immunotherapy dose as a control “dial” that restores the killing power of exhausted T-cells. Rather than relying solely on empirical trial-and-error, we used rigorous stability analysis to pinpoint the exact mathematical tipping point of the system. We derived a strict, quantifiable threshold proving that a cure is analytically guaranteed only when the drug dose successfully overcomes the ratio of the tumor’s intrinsic growth rate to the patient’s baseline immune strength. Ultimately, this framework provides a theoretical blueprint for the microenvironment, offering a foundation for calculating the exact personalized doses needed to force a tumor into complete, irreversible collapse.

Index Terms—Cancer Immunotherapy, Immune Checkpoint Inhibitors, Mathematical Oncology, Non-linear Dynamics, Ordinary Differential Equations, Stability Analysis, Phase Space.

I. INTRODUCTION

The immune system’s capacity to identify and eradicate malignant cells is the cornerstone of cancer immunotherapy. While traditional treatments such as chemotherapy and radiation target tumor proliferation directly, immunotherapy leverages the host’s endogenous defenses. Among the most significant advancements in this field is the development of Immune Checkpoint Inhibitors (ICIs) [1]. Tumors frequently exploit immune checkpoint pathways, such as the Programmed Death-1 (PD-1) and its ligand (PD-L1) axis, to induce effector T-cell exhaustion and evade immune surveillance [2]. ICIs operate by blocking these inhibitory pathways, thereby restoring the cytotoxic functionality of T-cells within the tumor microenvironment (TME).

Despite the profound clinical success of ICIs in certain malignancies, a substantial proportion of patients exhibit primary or acquired resistance. The TME is a dynamically evolving ecosystem characterized by non-linear interactions between proliferating tumor cells, recruited immune cells, and therapeutic agents. Consequently, predicting the outcome of immunotherapy based solely on biological intuition or *in*

vitro experimentation is insufficient, necessitating the use of advanced computational and mathematical frameworks [7].

Theoretical biology and mathematical oncology provide critical tools for decoding this complexity. By representing cellular interactions through deterministic mathematical models, we can isolate the fundamental dynamics driving tumor escape versus tumor eradication [5], [6]. Previous foundational models have successfully established the basis of tumor-immune interactions using standard ordinary differential equations (ODEs) and predator-prey dynamics [3], [4]. However, predicting the precise theoretical boundary at which an exogenously administered immunotherapy destabilizes tumor growth requires a highly targeted analytical approach.

In this study, we construct a deterministic mathematical model utilizing a system of first-order ODEs to simulate the continuous dynamics between a logistically growing tumor population and an active effector T-cell population. We introduce a novel control parameter representing the ICI concentration, which acts directly upon the interaction coefficient between the two populations.

The structure of this paper is as follows: Section II details the formulation of the mathematical model and outlines our core biological assumptions. Section III presents the analytical derivation of the system’s equilibria and establishes the Jacobian matrix. Section IV conducts a definitive stability analysis to prove the theoretical thresholds for complete tumor eradication. Finally, Section V discusses the translation of these mathematical inequalities into potential clinical insights for immunotherapy scheduling.

II. MATHEMATICAL MODEL

To analyze the efficacy of ICIs, we construct a two-dimensional system of non-linear ODEs tracking the temporal evolution of the tumor cell population, $T(t)$, and the effector T-cell population, $E(t)$. Our model builds upon foundational tumor-immune mathematical frameworks [3], [4], modified specifically to account for checkpoint blockade dynamics.

A. Core Biological Assumptions

The mathematical formulation is grounded in the following validated biological assumptions:

- 1) *Logistic Tumor Proliferation*: In the absence of immune predation, the tumor expands logistically up to a maximum physical and nutrient-derived carrying capacity K .
- 2) *Michaelis-Menten Immune Recruitment*: Effector T-cell recruitment is stimulated by tumor antigens. To prevent biologically unrealistic infinite recruitment rates, we utilize a saturating Michaelis-Menten-like term, a standard practice in mathematical immunology [3].
- 3) *Tumor-Induced Immune Exhaustion*: Prolonged exposure to tumor antigens and the suppressive TME induces an exhausted phenotype in effector T-cells, characterized by diminished cytotoxic capacity [2]. We model this as an active depletion term driven by tumor density.
- 4) *Immunotherapy as a Killing Multiplier*: The checkpoint inhibitor I systematically removes immunosuppressive signals (e.g., PD-L1), effectively multiplying the baseline killing efficiency c of existing T-cells [1], rather than acting as a direct cytotoxic agent.

B. The Governing Equations

Based on the defined parameters and assumptions, the dynamics of the tumor-immune ecosystem are governed by the following system of non-linear differential equations:

$$\frac{dT}{dt} = rT \left(1 - \frac{T}{K}\right) - c(1 + I)ET \quad (1)$$

$$\frac{dE}{dt} = s + \frac{\rho TE}{g + T} - \mu E - dTE \quad (2)$$

In (1), r represents the intrinsic tumor growth rate, and the interaction term $c(1 + I)$ dictates the rate at which immune cells eliminate tumor cells, scaled directly by the exogenously administered immunotherapy concentration $I \geq 0$.

C. Parameter Estimation and Units

To ensure the mathematical framework reflects biological reality and to perform subsequent numerical simulations, the system parameters must be grounded in established clinical and experimental literature. The state variables $T(t)$ and $E(t)$ are quantified in terms of total cell count, while the temporal dimension t is measured in days.

Due to the high variability of tumor microenvironments across different malignancies and patients, we utilize a standard baseline parameter set derived from foundational mathematical oncology literature, notably the estimated rates from Kuznetsov et al. [3] and Kirschner and Panetta [4].

The baseline parameter values utilized for our stability thresholds and phase space visualizations are detailed in Table

II. The immunotherapy control parameter I is treated as a dimensionless multiplier ($I \geq 0$) that is systematically varied to observe system bifurcations.

In (2), s denotes the baseline influx of native T-cells from lymphoid organs, ρ is the maximum antigen-driven immune recruitment rate, and g is the steepness coefficient (the tumor population at which recruitment is half-maximal). The term μ is the natural apoptosis rate of immune cells. Finally, d represents the specific rate of tumor-induced T-cell exhaustion and deactivation within the TME [2].

TABLE I
BASELINE PARAMETER VALUES AND UNITS

Param.	Estimated Value	Units	Source
r	0.18	days ⁻¹	[3]
K	1×10^9	cells	[3]
c	2.5×10^{-9}	cells ⁻¹ days ⁻¹	Estimated
s	1.3×10^4	cells days ⁻¹	[4]
ρ	0.124	days ⁻¹	[3]
g	2.0×10^7	cells	[3]
μ	0.041	days ⁻¹	[3]
d	3.4×10^{-10}	cells ⁻¹ days ⁻¹	[4]

III. EQUILIBRIUM AND STABILITY ANALYSIS

To determine the long-term biological outcomes of the tumor-immune ecosystem, we evaluate the steady states of the system by setting the temporal derivatives in (1) and (2) to zero. The fundamental principles of non-linear dynamics dictate that the local asymptotic stability of these equilibria governs the clinical fate of the patient [6].

A. The Tumor-Free Equilibrium (TFE)

A critical state of interest in clinical oncology is the complete eradication of the malignancy, where the tumor population $T^* = 0$. Substituting $T = 0$ into the immune dynamics equation (2) yields the steady-state effector T-cell population:

$$0 = s + 0 - \mu E - 0 \Rightarrow E^* = \frac{s}{\mu} \quad (3)$$

Thus, the Tumor-Free Equilibrium (TFE) is mathematically defined as:

$$E_{TFE} = 0, \frac{s}{\mu} \quad (4)$$

Biologically, this state represents a scenario where the tumor is eradicated, and the immune system returns to its baseline equilibrium, maintained solely by the innate influx s and natural apoptosis μ .

B. Tumor Escape (Coexistence) Equilibrium

While the goal of immunotherapy is to reach E_{TFE} , the system may also exhibit a non-trivial coexistence equilibrium, $E_c = (T^*, E^*)$, representing tumor escape and chronic progression. Setting (1) to zero for $T \neq 0$ yields the tumor nullcline:

$$E = \frac{r}{c(1 + I)} \left(1 - \frac{T}{K}\right) \quad (5)$$

Substituting (5) into the immune nullcline derived from (2) results in a high-order polynomial in terms of T . The roots of this polynomial represent the physical tumor burden during immune evasion. The primary objective of the checkpoint inhibitor I is to destabilize this coexistence state.

C. Jacobian Matrix and Linearization

To determine whether a patient's system will naturally converge to the tumor-free state (i.e., local asymptotic stability), we linearize the non-linear system around E_{TFE} [5]. Let $f(T, E) = \frac{dT}{dt}$ and $g(T, E) = \frac{dE}{dt}$. The Jacobian matrix J is defined as:

$$J = \begin{bmatrix} \frac{\partial f}{\partial T} & \frac{\partial f}{\partial E} \\ \frac{\partial g}{\partial T} & \frac{\partial g}{\partial E} \end{bmatrix} \quad (6)$$

Calculating the partial derivatives and evaluating them specifically at the E_{TFE} coordinates $0, \frac{s}{\mu}$ yields:

$$J_{TFE} = \begin{bmatrix} r - \frac{cs(1+l)}{\mu} & 0 \\ \frac{s}{\mu} & \frac{\rho}{g} - d - \mu \end{bmatrix} \quad (7)$$

D. Eigenvalue Derivation and Therapeutic Threshold

The local stability of the TFE is dictated by the eigenvalues of J_{TFE} . Because J_{TFE} evaluated at the tumor-free state is a lower triangular matrix, its eigenvalues λ_1 and λ_2 are explicitly its diagonal entries:

$$\lambda_1 = r - \frac{cs(1+l)}{\mu} \quad (8)$$

$$\lambda_2 = -\mu \quad (9)$$

For the tumor-free state to be locally asymptotically stable, the real parts of all eigenvalues must be strictly negative. Since the natural death rate of immune cells $\mu > 0$, it follows that $\lambda_2 < 0$ is unconditionally satisfied. Therefore, system stability depends entirely on the condition $\lambda_1 < 0$:

$$r - \frac{cs(1+l)}{\mu} < 0 \quad (10)$$

Rearranging this inequality to solve for the immunotherapy control parameter l , we isolate the critical threshold required for tumor eradication:

$$1 + l > \frac{r\mu}{cs} \Rightarrow l > \frac{r\mu}{cs} - 1 \quad (11)$$

Equation (11) represents the theoretical limit of the immunotherapy. It analytically proves that the administered checkpoint inhibitor concentration l must exceed the ratio of the tumor's intrinsic growth potential ($r\mu$) to the immune system's baseline clearance capacity (cs). If l falls below this threshold, λ_1 becomes positive, a transcritical bifurcation occurs, the TFE becomes an unstable saddle point, and the tumor permanently escapes immune surveillance.

IV. PHASE SPACE DYNAMICS AND THERAPEUTIC BIFURCATIONS

While local stability analysis defines the theoretical limits of immunotherapy near specific equilibria, analyzing the global phase space provides a comprehensive visual understanding of the tumor-immune ecosystem. The phase plane, defined by the coordinates (T, E) , illustrates the dynamic trajectories of patient outcomes based on varying initial tumor burdens and immune states.

A. Nullcline Formulation

The phase space is geometrically partitioned by nullclines—the physical boundaries where the rate of change for a specific population is zero.

The tumor nullcline, derived by setting (1) to zero (for $T > 0$), forms a linear boundary with a negative slope:

$$E = \frac{r}{c(1+l)} - \frac{T}{K} \quad (12)$$

The y -intercept of this boundary is inversely proportional to the immunotherapy dose l .

The immune nullcline, derived by setting (2) to zero, yields a non-linear rational curve:

$$E = \frac{s(g+T)}{\mu(g+T) + dT(g+T) - \rho T} \quad (13)$$

The intersections of (12) and (13) dictate the location and existence of the system's coexistence (escape) equilibria.

B. Bistability and Basins of Attraction

In the absence of effective immunotherapy (where l is low or zero), the phase space exhibits bistability. The vector field is divided by a separatrix into two distinct basins of attraction: the Tumor-Free Basin and the Escape Basin.

If a patient's initial biological state—determined by their baseline tumor volume and native T-cell count—lies above the separatrix, their trajectory converges to E_{TFE} . Conversely, if the state lies below the separatrix, the immune system is overpowered by exhaustion, and the trajectory is pulled inevitably toward the tumor escape equilibrium E_C .

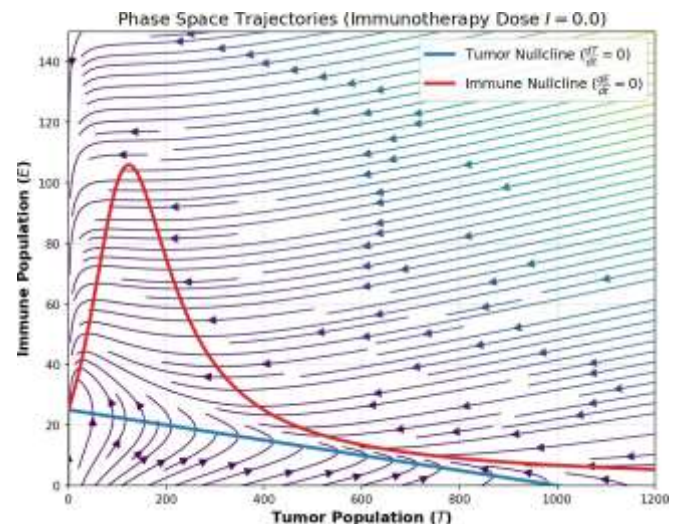


Fig. 1. Phase space trajectories of the tumor-immune system. The blue nullcline represents $\frac{dT}{dt} = 0$, and the red nullcline represents $\frac{dE}{dt} = 0$. The vector field demonstrates how increasing the immunotherapy parameter l shifts the separatrix, expanding the basin of attraction for the Tumor-Free Equilibrium.

C. The Immunotherapy-Induced Bifurcation

The clinical action of the checkpoint inhibitor I acts as a bifurcation parameter. Mathematically, increasing I structurally alters the phase space.

As I increases, the y -intercept of the tumor nullcline (12) decreases, effectively rotating the boundary downwards. When I surpasses the critical threshold defined in (11), a transcritical bifurcation occurs. The coexistence intersections physically vanish, and the escape valley is mathematically destroyed. Consequently, the separatrix disappears, and the entire phase space transforms into a single basin of attraction flowing globally toward the Tumor-Free Equilibrium, regardless of the initial tumor burden.

V. CONCLUSION AND CLINICAL INSIGHTS

In this study, we formulated a deterministic mathematical model of the tumor-immune microenvironment to investigate the non-linear dynamics of immune checkpoint blockade therapy. By utilizing a system of ordinary differential equations and treating the immunotherapy concentration as an exogenous control parameter, we moved beyond empirical observation to establish theoretical boundaries for therapeutic success.

A. Biological Interpretation of the Threshold

The central result of our stability analysis is the analytical derivation of the critical threshold for tumor eradication, defined as $I > \frac{\mu}{cs} - 1$. This inequality provides profound clinical insights by quantifying the exact balance of biological forces required for a cure.

Mathematically, it demonstrates that the necessary immunotherapy dose I is directly proportional to the tumor's intrinsic growth rate (r) and the natural death rate of effector T-cells (μ). Conversely, the required dose is inversely proportional to the baseline innate immune influx (s) and the baseline killing efficiency (c). Biologically, this implies that patients with highly aggressive tumors (high r) or weak innate immune recruitment (low s) will require non-linearly higher doses of checkpoint inhibitors to force the system into a stable cure state.

B. Therapeutic Bifurcation and Global Stability

Our phase space analysis visually confirms that immunotherapy does not merely reduce the tumor mass incrementally; rather, it fundamentally alters the physical landscape of the microenvironment. By crossing the derived bifurcation threshold, the therapy destroys the coexistence equilibrium. This shifts the system from a bistable state—where tumor escape is highly probable—into a globally stable state where the patient's own immune system is mathematically guaranteed to drive the tumor population toward the Tumor-Free Equilibrium (E_{TFE}).

C. Limitations and Future Directions

While this model provides a rigorous analytical foundation, it relies on the assumption of a well-mixed, spatially homogeneous microenvironment. Real solid tumors exhibit high spatial

heterogeneity and fractal-like stromal structures that impede T-cell diffusion. Future theoretical work should expand this model by incorporating spatial dynamics via partial differential equations (PDEs) or by applying fractional calculus to account for the "memory effects" and anomalous diffusion of exhausted T-cells navigating a dense tumor matrix.

Ultimately, bridging this theoretical framework with patient-specific genomic and immunological data could pave the way for highly personalized, mathematically optimized dosing schedules, reducing both therapeutic failure and immune-related adverse events.

REFERENCES

- [1] D. M. Pardoll, "The blockade of immune checkpoints in cancer immunotherapy," *Nature Reviews Cancer*, vol. 12, no. 4, pp. 252–264, 2012.
- [2] E. J. Wherry, "T cell exhaustion," *Nature Immunology*, vol. 12, no. 6, pp. 492–499, 2011.
- [3] V. A. Kuznetsov, I. A. Makalkin, M. A. Taylor, and A. S. Perelson, "Nonlinear dynamics of immunogenic tumors: parameter estimation and global bifurcation analysis," *Bulletin of Mathematical Biology*, vol. 56, no. 2, pp. 295–321, 1994.
- [4] D. Kirschner and J. C. Panetta, "Modeling immunotherapy of the tumor-immune interaction," *Journal of Mathematical Biology*, vol. 37, no. 3, pp. 235–252, 1998.
- [5] A. d'Onofrio, "A general framework for modeling tumor-immune system competition and immunotherapy: Mathematical analysis and biomedical inferences," *Physica D: Nonlinear Phenomena*, vol. 208, no. 3–4, pp. 220–235, 2005.
- [6] S. H. Strogatz, *Nonlinear Dynamics and Chaos: With Applications to Physics, Biology, Chemistry, and Engineering*. 2nd ed., CRC Press, 2015.
- [7] X. Lai and A. Friedman, "Combination therapy of melanoma with BRAF/MEK inhibitor and immune checkpoint inhibitor: a mathematical model," *BMC Systems Biology*, vol. 11, no. 1, p. 70, 2017.