

TUMOR PROGRESSION AND PHARMACOLOGICAL INTERVENTION: MODELING IMMUNOTHERAPEUTIC AND CHEMOTHERAPY STRATEGIES IN NEUROBLASTOMA

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Abstract. Neuroblastoma, the most common solid tumor causing cancer in infants, remains a leading cause of childhood cancer-related mortality. Despite advances in treatment, there is an ongoing need for more effective mathematical models and therapies to improve outcomes across neuroblastoma-specific patient populations. Immunotherapy and chemotherapy, particularly the use of Interleukin-2 (IL-2) and Cyclophosphamide, have shown promising therapeutic effects by enhancing immune responses and targeting cancer cells. Therefore, this study developed a coupled, nonlinear system of first-order differential equations to model the immune-cellular dynamics of neuroblastoma progression. The mathematical model captured the interactions between tumor cells, natural killer cells (NK), and cytotoxic T lymphocytes (CTLs), while exploring how IL-2 and Cyclophosphamide influenced these cell populations. The model investigated tumor population dynamics across various patient profiles, assessing the therapeutic impact of IL-2 and Cyclophosphamide. This study's approach supports the optimization of immunotherapy and chemotherapy strategies, providing actionable insights on how to improve clinical outcomes in neuroblastoma treatment.

1. Introduction. Cancer is a complex disease marked by the uncontrolled proliferation of abnormal cells that can invade and disrupt surrounding healthy tissue. Its development is driven by a combination of genetic mutations, environmental exposures, and lifestyle-related factors, making it a multifaceted challenge in modern medicine [15]. Neuroblastoma, the most common solid tumor in children under the age of four, holds a distinctive place in pediatric oncology due to its highly variable clinical behavior. It typically arises in infants within their first year of life and may present as either localized or widespread metastatic disease [16]. Neuroblastoma patients are classified into three risk categories: low, intermediate, and high, based on the International Neuroblastoma Risk Group (INRG) staging system (Table 1), which considers factors such as age, tumor stage, histology, and genetic features. For low risk patients, who have an estimated survival rate above 98%, observation or surgical resection is typically sufficient. Intermediate-risk patients, with survival rates exceeding 90%, often receive chemotherapy in combination with surgery. In contrast, high-risk patients undergo an intensive multimodal regimen that includes multiple cycles of combination chemotherapy, surgical resection, stem cell transplantation, local radiation, immunotherapy, and differentiation therapy [2]. This standardized risk-adapted patient classification system aims to enhance survival outcomes by providing a clinical framework to optimize treatment strategies in neuroblastoma, while minimizing the long-term adverse effects of treatment. Given the increasing use of immunotherapies in treatment regimens, a deeper understanding of the immune system's role in tumor control has become essential [1].

The immune response to cancer involves both the innate and adaptive immune systems, each contributing uniquely to tumor recognition and elimination. In this study, NK cells were modeled in association with the innate immune system, representing a rapid, nonspecific response to abnormal or stressed cells. CTLs, by contrast, are components of the adaptive immune system and mount antigen-specific responses following activation and clonal expansion [8]. This distinction is central to the development of any immunotherapeutic modeling framework, as it reflects differences in activation timing, memory formation, and therapeutic targeting. By incorporating both NK cells and CTLs into the objective model, we capture the complementary roles of innate and adaptive immunity in shaping tumor-immune dynamics under various treatment conditions. These mechanistic differences form the foundation for simulating differential immune responses across patient risk categories and treatment regimens.

Historically, mathematical modeling has played a pivotal role in cancer research, bridging the gap between theoretical biology and clinical application [3-5,7,10,13,17]. As the biological understanding of cancer has grown increasingly complex, mathematical and computational models have become essential tools for integrating diverse data types and biological processes into coherent frameworks capable of simulating tumor dynamics and predicting treatment outcomes [13]. In the context of neuroblastoma, a highly heterogeneous disease characterized by intricate interactions across molecular, cellular, and tissue-level scales, models such as the one presented offer valuable insights into tumor progression, therapeutic response, and disease evolution. They support a wide range of clinical applications, including the optimization of chemotherapy scheduling, immunotherapy planning, and personalized treatment strategies. Furthermore, they enable the formulation of testable hypotheses and the incorporation of experimental and clinical data into predictive simulations [13]. However, despite their promise, oncological modeling is challenged by the inherent complexity of biological systems, limited availability of high-

resolution data, and the technical demands of model validation, verification, and multiscale integration.

2. Methods. Building on a previously established framework by Song [17], this study modeled the dynamic interactions between tumor cells, NK cells, and CTLs, with modifications introduced to incorporate the therapeutic effects of two common drugs used for the treatment of neuroblastoma. The framework is formulated as a set of coupled, first-order ordinary differential equations to represent immune–tumor population dynamics under various pharmacological states.

2.1. Therapeutic agent selection. Two therapeutic agents were selected for the modeling of neuroblastoma treatment: Cyclophosphamide and IL-2. These drugs were chosen for their distinct yet complementary mechanisms. Cyclophosphamide acts primarily through direct tumor cell cytotoxicity, while IL-2 enhances immune system function. By incorporating both agents into our mathematical model, we aimed to analyze how chemotherapy-induced tumor cell death and immune-mediated tumor suppression operate independently and synergistically. This dual approach allowed us to explore the balance between direct cytotoxic effects and immune system activation in shaping tumor progression across different stages of disease.

Cyclophosphamide, a chemotherapy drug, directly targets tumor cells by slowing their proliferation and inducing apoptosis. It alkylates DNA, leading to the formation of crosslinks that interfere with replication and trigger cell death, particularly in rapidly dividing cells. Beyond its direct cytotoxicity, Cyclophosphamide can also modulate the tumor microenvironment by suppressing immune responses and altering inflammation dynamics [6]. Despite its immunosuppressive effects, its potent ability to reduce tumor burden makes it a cornerstone in neuroblastoma treatment in modern medicine.

IL-2, an immune-modulating cytokine, plays a critical role in activating NK cells, which are essential for the innate immune response against tumors. IL-2 binds to receptors on NK cells, promoting their proliferation, activation, and cytotoxicity. Activated NK cells can directly eliminate tumor cells by releasing perforin and granzymes, inducing apoptosis [14]. IL-2 also enhances the expression of activating receptors on NK cells, improving their ability to recognize and target tumor cells. In neuroblastoma treatment, this immune activation supports a shift toward a more robust, tumor-targeting immune environment [14].

2.2. Objective pharmacology model. The objective pharmacological model developed in this study captures the immune–tumor dynamics of neuroblastoma progression and evaluates the therapeutic effects of immunotherapy and chemotherapy treatments. The model (Equation 2.1) integrates key biological processes including tumor growth, immune activation, and drug-induced modulation of immune responses. By simulating tumor progression across low-, intermediate-, and high-risk patient profiles, this framework offered insights into optimizing treatment strategies and informing personalized therapeutic interventions.

$$(2.1) \quad \begin{cases} N'(t) = a_1 N(t)(1 - bN(t)) - a_2 N(t) - \alpha_1 N(t)T(t) + k_i I(t) \\ L'(t) = r_1 N(t)T(t) - \mu L(t) - \beta_1 L(t)T(t) \\ T'(t) = cT(t)(1 - dT(t)) - \alpha_2 N(t)T(t) - \beta_2 L(t)T(t) - k_c C(t) \\ I'(t) = -\frac{\log(2)}{h_i} 2^{-\frac{t}{h_i}} I(0) \\ C'(t) = -\frac{\log(2)}{h_c} 2^{-\frac{t}{h_c}} C(0) \end{cases}$$

Let $N(t)$, $L(t)$, and $T(t)$ represent the populations of NK cells, CTLs, and tumor cells, while $I(t)$ and $C(t)$ denote the concentrations of IL-2 and Cyclophosphamide.

2.2.1. Scaling and nondimensionalization. To reduce model complexity and highlight biological mechanisms, the system was nondimensionalization (Equation 2.2) using biologically relevant scaling factors. This approach reformulates the equations in terms of dimensionless variables and parameters, allowing for a more straightforward interpretation and comparison across treatment groups.

$$(2.2) \quad \begin{cases} N'(t) = p_1 N(t)(1 - qN(t)) - p_2 N(t) - N(t)T(t) + k_i I(t) \\ L'(t) = N(t)T(t) + rD(t) - L(t) - sL(t)T(t) \\ T'(t) = uT(t)(1 - vT(t)) - N(t)T(t) - \delta L(t)T(t) - k_c C(t) \\ I'(t) = -\frac{\log(2)}{h_i} 2^{-\frac{t}{h_i}} I(0) \\ C'(t) = -\frac{\log(2)}{h_c} 2^{-\frac{t}{h_c}} C(0) \end{cases}$$

The transformation introduces parameters $p_1 = \frac{a_1}{\mu}$ and $p_2 = \frac{a_2}{\mu}$, which normalize the NK cell proliferation and natural death rates relative to the CTL death rate μ . The parameter $q = \frac{b}{\mu\alpha_2}$ represents the NK cell carrying capacity scaled by the NK-induced tumor cell death rate. The term $r = \frac{T(0)}{\alpha_1\alpha_2} \cdot \frac{r_1}{\mu}$ accounts for CTL activation resulting from tumor cell debris generated by NK-mediated cytotoxicity, scaled by the initial tumor burden. The parameter $s = \frac{\beta_1}{\alpha_1}$ expresses the relative rates at which CTLs and NK cells are lost through interactions with tumor cells. The tumor growth rate is scaled as $u = \frac{c}{\mu}$, and the term $v = \frac{du}{\alpha_1}$ captures the effects of tumor carrying capacity modulated by NK activity. Finally, $\delta = \frac{\beta_2 r_1}{\alpha_1\alpha_2}$ characterizes the CTL-induced tumor cell death rate relative to that of NK cells. Together, these nondimensionalized parameters (Table X) highlight the dominant biological mechanisms governing tumor-immune dynamics and enable more generalized analysis across treatment and patient disease profiles.

2.2.2. Parameter selection. The proposed initial conditions and parameters were informed by the interactions among tumor progression, drug concentration, and patient population, and were tailored to disease stage, with modifications adapted from published literature [5]. This modeling framework optimized treatment planning by simulating a range of clinical scenarios and predicting treatment efficacy for specific patient groups. Our approach to modeling the immunotherapeutic dynamics of neuroblastoma is grounded in the International Neuroblastoma Risk Group (INRG) staging system [9], which significantly enhances the ability to compare patient populations in the context of therapeutic interventions.

Table 1: Neuroblastoma disease stages defined by the International Neuroblastoma Risk Group.

Disease Stage	Description
Low Risk	Patients with L1 (localized tumors in one area) or MS (asymptomatic with favorable biology and metastases limited to skin, liver, or bone marrow) are considered low risk. These patients typically require observation, with surgery or chemotherapy only if symptoms arise.
Intermediate Risk	L2 (regional tumors with IDRFs) and MS with unfavorable biology (e.g., diploidy) are classified as intermediate risk. These tumors may need chemotherapy, with surgery recommended if possible.
High Risk	M (distant metastases), MS with MYCN amplification, or L2 in patients over 18 months with unfavorable features are high risk. These patients require aggressive treatment including chemotherapy, surgery, and stem cell therapy.

In this study, we employ the INRG staging system to stratify patient populations into low, intermediate, and high-risk groups based on tumor stage and biological markers (Table 1). This classification supports comparative analyses across clinical trials and informs the initial conditions of our mathematical model. By aligning with an internationally accepted risk framework, we enhance the clinical relevance and reproducibility of our simulations.

For each risk group, we estimated the relative initial abundances of tumor cells, CTLs, and NK cells, whilst paying particular attention to capturing relative population sizes (Table 2). These stratified immune profiles enabled more accurate simulation of treatment outcomes under varying immunological baselines and allowed us to explore how immune composition influences therapeutic response.

Table 2: Initial cell populations by neuroblastoma risk group.

Cell Population	Low Risk	Intermediate Risk	High Risk
$N(0)$	—	—	—
$L(0)$	—	—	—
$T(0)$	—	—	—

The low-risk population was characterized by a relatively low tumor cell count and a robust immune response, where NK cells, part of the innate immune system, offer immediate defense. While CTLs, which belong to the adaptive immune response, provide a more targeted and long-term defense, their abundance is lower compared to NK cells. In the intermediate-risk population, the tumor cell count is higher, prompting a more significant role for CTLs in the immune response. Though NK cells still serve as the first line of defense, the increased tumor burden

necessitates a more coordinated immune response, with CTLs becoming increasingly critical for targeting and eliminating the growing tumor cells. In the high-risk population, the tumor cell count is further elevated, and the immune system faces greater challenges. While NK cells provided an early line of defense and gradually declined over time, CTLs proved essential for long-term tumor control. Their ability to recognize specific antigens and undergo clonal expansion enabled a more sustained immune response against the rapidly proliferating tumor cells.

Table 3: Pharmacology model parameters.

Parameter	Description	Units	Value
a_1	NK cell growth rate	$\text{cell} \cdot \text{day}^{-1}$	0.111
a_2	NK cell death rate due to natural death	day^{-1}	0.0412
b	Carrying capacity coefficient for NK cell population	cell^{-1}	1.02e-09
c	Natural tumor cell growth rate	day^{-1}	0.514
d	Carrying capacity coefficient for tumor cell population	cell^{-1}	1.02e-09
α_1	Rate of NK cell death due to tumor interaction	$\text{cell}^{-1} \cdot \text{day}^{-1}$	1e-07
α_2	Rate of NK-induced tumor death	$\text{cell}^{-1} \cdot \text{day}^{-1}$	3.23e-07
β_1	Rate of CTL-cell death due to tumor interaction	$\text{cell}^{-1} \cdot \text{day}^{-1}$	3.422e-10
β_2	Rate of CTL-induced tumor death	$\text{cell}^{-1} \cdot \text{day}^{-1}$	0.01245
μ	CTL cell death rate due to natural death	day^{-1}	0.02
r_1	Rate of NK-lysed tumor cell debris activation of CTLs	$\text{cell}^{-1} \cdot \text{day}^{-1}$	2.908e-11
k_c	Rate constant of Cyclophosphamide-mediated tumor death	$\text{mg}^{-1} \cdot \text{day}^{-1} \cdot \text{cell}$	0.9
k_i	Rate constant of IL-2-mediated stimulation	$\text{mg}^{-1} \cdot \text{day}^{-1} \cdot \text{cell}$	5e+04
h_i	Half-life of IL-2	day	–
h_c	Half-life of Cyclophosphamide	day	–
I_0	Dose of IL-2	mg	–
C_0	Dose of Cyclophosphamide	mg	–

Model parameters (Table 3) were selected to reflect the underlying biological processes driving neuroblastoma progression, immune system interactions, and the therapeutic effects of IL-2 and Cyclophosphamide. NK cell populations were regulated by intrinsic growth (a_1), death (a_2), and a carrying capacity constraint (b), while tumor-induced cytotoxicity was governed by the interaction rate (α_1). CTL dynamics were shaped by activation through NK-lysed tumor debris (r_1), natural cell death (μ), and tumor-induced depletion (β_1). Tumor proliferation was defined by the growth rate (c) and the carrying capacity (d), with immune-mediated reduction captured by NK and CTL-mediated lysis (α_2 , β_2).

Drug-related parameters include the rate of IL-2-mediated stimulation of NK cells (k_i) and the rate of Cyclophosphamide induced tumor reduction (k_c), both of which play important roles in modulating immune response and tumor dynamics in neuroblastoma. Their concentrations are modeled using first-order exponential decay based on pharmacokinetic half-lives (h_i , h_c), capturing the transient nature of these agents in systemic circulation. Initial dosages of IL-2 (I_0) and Cyclophosphamide (C_0) define the administration schedule for treatment simulations (Table 3).

2.2.3. Pharmacological schedules. Dosing schedules for Cyclophosphamide and Interleukin-2 (IL-2) were differentiated by treatment intensity (low-dose and high-dose) and divided into initial and recurring administrations. For Cyclophosphamide, low-dose treatment involved an initial dose of 2.5 mg/kg followed by recurring doses of 2 mg/kg every 24 hours. High-dose treatment began with an initial dose of 30 mg/kg, with recurring doses of 25 mg/kg administered at 24-hour intervals [6]. IL-2 was administered on a fixed 24-hour cycle. Low-dose schedules involved an initial and recurring dose of 3×10^6 units, while high-dose schedules used 6×10^6 units per dose on the same interval [12].

2.3. Caputo fractional order derivative framework. To enhance the biological realism of our neuroblastoma model, we incorporated the Caputo fractional-order derivative to capture memory-dependent immune and tumor dynamics. This framework will only be applied to three of the differential equations of CTL, NK, and Tumor cells, excluding the drug/treatment variables. The Caputo Operator has been shown to improve the accuracy of tumor growth modeling by accounting for historical system behavior, as demonstrated in recent studies [10]. By applying this approach to our model, we refined the characterization of tumor-immune interactions and treatment efficacy across neuroblastoma patient groups.

Table 4: Dosing schedules for Cyclophosphamide and Interleukin-2.

Drug	Schedule	Initial Dose	Recurring Dose
Cyclophosphamide	Low-dose	2.5 mg/kg	2 mg/kg
Cyclophosphamide	High-dose	30 mg/kg	25 mg/kg
IL-2	Low-dose	3×10^6 units	3×10^6 units
IL-2	High-dose	6×10^6 units	6×10^6 units

Tumor cells, CTLs, and NK cells are denoted by T, L, and N respectively. All other parameters are defined in Table 3.

Definition 1 Consider the following function $\varphi(t)$, when $t > 0$, and the Riemann-Liouville Integral (RLI) operator of a function $\varphi(t)$ is defined as follows:

$$(2.3) \quad I^\alpha \varphi(t) = \int_0^t \frac{(t-\tau)^{\alpha-1}}{\Gamma(\alpha)} \varphi(\tau) d\tau$$

$\alpha > 0$ is the order derivative and $x(t)$, $y(t)$, and $z(t)$ represent the respective population of NK, CTLs, and Tumor cells. The fractional derivative operator is denoted D_0^α and $\alpha > 0$ defines the fractional order allowing to model memory and hereditary effects better than the classical integer order derivatives when $\alpha > 0$ lies between the integer values and the gamma function are the generalization of the factorial function to continuous values, and $(t-\tau)^{\alpha-1}$ is the kernel function that is being integrated and gives the fractional derivative its memory property, where τ is a past time point on the interval $[0, t]$.

The fractional-order derivative of function $\varphi(t)$ in [equation 1] is defined by the following:

$$(2.4) \quad D^\alpha \varphi(t) = I^{n-\alpha} D^{(n)} \varphi(t)$$

where $D = d/dt$

Definition 2 Consider the function $\varphi(t)$ when $t > 0$, the Caputo fractional derivative of order α when $\alpha > 0$ is given by the following:

$$(2.5) \quad D^\alpha \varphi(t) = \frac{1}{\Gamma(n-\alpha)} \int_0^t (t-\tau)^{n-\alpha-1} \varphi^{(n)}(\tau) d\tau$$

where n is the n th derivative, α belongs to $(n-1, n)$ and $D^\alpha \varphi(t)$ is the Caputo fractional operator of the function $\varphi(t)$.

Theorem 1 Consider a system of fractional order equations in the form:

$$(2.6) \quad D_0^\alpha \varphi(t) = \varphi(t, Y(t)), Y(t_0) = Y_0$$

The following statements will be true when $J(Y^*)$ is the Jacobian Matrix:

- The equilibrium point is asymptotically stable only if all eigenvalues of the Jacobian Matrix satisfy $\arg \lambda_i > a\pi/2$ from 2.21 and 2.22
- The equilibrium point is unstable only if all eigenvalues of the Jacobian Matrix such that $\arg \lambda_i < a\pi/2$ from 2.21 and 2.22

Here we generalize an integer-order tumor interaction model, given by the following equations (2.7)–(2.9) is a set that is a continuous nonlinear ordinary differential equation:

$$(2.7) \quad N'(t) = \alpha_1 N(t)(1 - bN(t)) - \alpha_2 N(t) - \alpha_1 N(t)T(t)$$

$$(2.8) \quad L'(t) = r_1 N(t)T(t) + r_2 D(t) - \mu L(t) - \beta_1 L(t)T(t)$$

$$(2.9) \quad T'(t) = cT(t)(1 - dT(t)) - \alpha_2 N(t)T(t) - \beta_2 L(t)T(t)$$

where N , L , and T represent the populations of the natural killer cells, CTL cells, and tumor cells respectively. Furthermore α_1 , α_2 , b , r_1 , r_2 , μ , β_1 , β_2 , and c are all parameters from Table 3.

After non-dimensionalizing equations (2.7)–(2.9), we get the following equations:

$$(2.10) \quad N'(t) = p_1 N(t)(1 - qN(t)) - p_2 N(t) - N(t)T(t)$$

$$(2.11) \quad L'(t) = N(t)T(t) + rD(t) - L(t) - sL(t)T(t)$$

$$(2.12) \quad T'(t) = uT(t)(1 - vT(t)) - N(t)T(t) - (\delta)L(t)T(t)$$

where p_1, p_2, q, r, s, u, v , and δ are the nondimensional parameters. Now the proposed dimensionless model is put into Caputo fractional order derivative form with the following equations:

$$(2.13) \quad D_0^\alpha x(t) = p_1 x(t)(1 - qx(t)) - p_2 x(t)z(t)$$

$$(2.14) \quad D_0^\alpha y(t) = x(t)z(t) + rd(t) - y(t) - sy(t)z(t)$$

$$(2.15) \quad D_0^\alpha z(t) = uz(t)(1 - vz(t)) - x(t)z(t) - \delta y(t)z(t)$$

when $\alpha > 0$ is the order derivative and $x(t)$, $y(t)$, and $z(t)$ represents the respective cell population of the natural killer (NK) cells, the cytotoxic t lymphocytes (CTL) and the tumor (T).

2.4. Existence of Unique Solutions. In this section, the existence of a unique solution of the fractional order tumor model will be proved with the help of a lemma and definitions.

Lemma 1. Consider the system of equations defined by Caputo fractional-order derivatives:

$$(2.16) \quad D^a x(t) = p_1 x(1 - qx) - p_2 xz$$

$$(2.17) \quad D^a y(t) = xz + rd - y - syz$$

$$(2.18) \quad D^a z(t) = uz(1 - vz) - xz - \delta yz$$

where $0 < a \leq 1$. Then the system admits a unique solution under appropriate conditions, ensuring that disturbances in initial conditions do not lead to non-deterministic behaviors. This reinforces the stability of the fractional-order system.

The initial conditions of the fractional order derivatives can be written as $x(t_0) = x_0, y(t_0) = t_0$, and $z(t_0) = z_0$. Equations (2.13)–(2.15) can be written in the form:

$$(2.19) \quad D^a Y(t) = R_1 Y(t) + x(t)R_2 Y(t), Y(t_0) = Y_0$$

where Y_0 are initial conditions of the function $Y(t)$ which is the column vector of the equations $x(t)$, $y(t)$, and $z(t)$ are the respective population equations of natural killer cells, cytotoxic t-lymphocyte cells, and tumor cells

$$(2.20) \quad Y(t) = \begin{bmatrix} x(t) \\ y(t) \\ z(t) \end{bmatrix}$$

$$(2.21) \quad R_1 = \begin{bmatrix} 0 & 0 & 0 \\ 0 & -1 & 0 \\ u & 0 & v \end{bmatrix}$$

$$(2.22) \quad R_2 = \begin{bmatrix} p_1(1-q) & 0 & -p_2 \\ 1 & 0 & 0 \\ -1 & -\delta & -1 \end{bmatrix}$$

The following definitions are required for the existence and uniqueness of solutions for equation 2.19 .

Definition 3 Consider $C[0, \theta]$ to belong to a continuous vector $Y(t)$ with the components of functions of $x(t)$, $y(t)$, and $z(t)$

Definition 4 $Y(t)$ is a column vector that satisfies equation (2.22) which belongs to $C[0, \theta]$.

Theorem 2 The system of equations given by equation (2.22) has a unique solution $Y(t)$ that belongs to $C[0, \theta]$

Proof of Lemma 1. The system of fractional order differential equations (2.16)-(2.18) can be written as follows:

$$(2.23) \quad I^{1-a} \frac{d}{dt} Y(t) = R_1 Y(t) + x(t) R_2 Y(t)$$

where

$$(2.24) \quad D_\alpha[Y] = I^{1-a} \frac{d}{dt} Y(t)$$

$R_1 Y(t)$ indicates that $Y(t)$ evolves with a rate proportional to itself (logistic/ exponential growth/decay)

$x(t) R_2 Y(t)$ introduces the interaction between $y(t)$ and $x(t)$ indicating that $x(t)$ influences rate of change $Y(t)$.

Apply the Riemann Louiville Integral to operate I^a to both sides of the equation

$$(2.25) \quad I^a [D_\alpha[Y]] = I^a (R_1 Y(t) + x(t) R_2 Y(t))$$

Here we solve the fractional integral for Y

$$(2.26) \quad I = \int_0^\tau Y(\tau) d\tau = Y(t) - Y(0)$$

Substitute $Y(t) - Y(0)$ for I for the integral

$$(2.27) \quad Y(t) - Y(0) = I^a (R_1 Y(t) + x(t) R_2 Y(t))$$

Isolate $Y(t)$ to get the initial conditions

$$(2.28) \quad Y(t) = Y(0) + I^a (R_1 Y(t) + x(t) R_2 Y(t))$$

Define operator $G[Y(t)]$ which also belongs on the continuous function $C[0, \theta]$

$$(2.29) \quad G[Y(t)] = Y(0) + I^a (R_1 Y(t) + x(t) R_2 Y(t))$$

The solution of $Y(t)$ is a fixed point on the operator G , this satisfies certain properties like:

- Mapping into the space: $C[0, \theta]$ so that it operates within the continuous function and since $Y(0)$ and $I^a (R_1 Y(t) + x(t) R_2 Y(t))$ are continuous, the fractional integral I^a preserves continuity
- Contraction mapping: The operator G is a contraction under certain conditions meaning $\|G[Y_1(t)] - G[Y_2(t)]\| \leq L \|Y_1(t) - Y_2(t)\|$, with $L < 1$, which guarantees a unique solution

where I^a represents the Riemann–Liouville fractional integral.

Consider two solutions $Y(t)$ and $Z(t)$ to analyze the difference between two trajectories:

$$(2.30) \quad G[Y(t)] - G[Z(t)] = I^a [R_1 (Y(t) - Z(t)) + R_2 (Y(t) - Z(t))]$$

Here we introduce the exponential decay factor and multiply both sides of the equation by e^{-nt} :

$$(2.31) \quad e^{-nt} [G(Y(t)) - G(Z(t))] = e^{-nt} I^a [R_1 (Y(t) - Z(t)) + R_2 (Y(t) - Z(t))]$$

Expand the fractional integral using the definition of the Riemann–Liouville fractional integral to replace I^α :

(2.32)

$$I^\alpha [R_1(Y(t) - Z(t)) + R_2(Y(t) - Z(t))] = \frac{1}{\Gamma(\alpha)} \int_0^t (t-c)^{\alpha-1} [R_1(Y(c) - Z(c)) + R_2(Y(c) - Z(c))] dc$$

This formulation ensures that past values $f(c)$ contribute to the present state $f(t)$, weighted by $(t-c)^{\alpha-1}$, which scales historical influence.

Next, apply exponential decay within the integral multiplying by $e^{-n(t-c)}$:

(2.33)

$$\frac{1}{\Gamma(\alpha)} \int_0^t (t-c)^{\alpha-1} e^{-n(t-c)} [Y(c) - Z(c)] e^{-nc} [R_1 + uR_2] dc$$

Now introduce norm bound, it ensures that differences between solutions remain controlled over time

(2.34)

$$\|G[Y(t)] - G[Z(t)]\| \leq \frac{1}{\Gamma(\alpha)} \int_0^t (t-c)^{\alpha-1} e^{-n(t-c)} \|Y(t) - Z(t)\| [R_1 + uR_2] dc$$

Since norm properties allow a unique solution that depend on continuous initial conditions:

(2.35)

$$\|Y(c) - Z(c)\| \leq \|Y(t) - Z(t)\|,$$

when applying inequality (2.35) to inequality (2.34), we then factor $\|Y(t) - Z(t)\|$ out of the integral

(2.36)

$$\|G[Y(t)] - G[Z(t)]\| \leq (R_1 + uR_2) \|Y(t) - Z(t)\| \frac{1}{\Gamma(\alpha)} \int_0^t (t-c)^{\alpha-1} e^{-n(t-c)} dc$$

Now the integral evaluates to $\frac{\Gamma(\alpha)}{n^\alpha}$, we can substitute:

(2.37)

$$\|G[Y(t)] - G[Z(t)]\| \leq (R_1 + uR_2) \frac{1}{n^\alpha} \|Y(t) - Z(t)\|$$

so we can conclude:

(2.38)

$$\|G[Y(t)] - G[Z(t)]\| \leq (R_1 + uR_2) \frac{1}{n^\alpha} \|Y(t) - Z(t)\| \int_0^t \frac{\alpha-1}{\Gamma(\alpha)} dc$$

This bound ensures stability and controls deviations between trajectories.

Substituting the integral back into our expression because it is the definite integral of a constant independent of c integrating from $[0, t]$:

(2.39)

$$\|G[Y(t)] - G[Z(t)]\| \leq (R_1 + uR_2) \frac{1}{n^\alpha} \|Y(t) - Z(t)\| \frac{\alpha-1}{\Gamma(\alpha)} t$$

This introduces a bounded scaling factor, which ensures a contraction effect.

Now we establish the contraction property and are observing the structure of the term:

(2.40)

$$\|G[Y(t)] - G[Z(t)]\| \leq (R_1 + uR_2) \frac{t}{n^\alpha \Gamma(\alpha)} \|Y(t) - Z(t)\|$$

Since the coefficient $\frac{t}{n^\alpha \Gamma(\alpha)}$ acts as a damping factor, it ensures:

(2.41)

$$\|G[Y(t)] - G[Z(t)]\| < \|Y(t) - Z(t)\|$$

The integral term accumulates past influences but remains bounded. The contraction property ensures that the operator G smooths out deviations over time. This proves that G satisfies a stability condition, meaning perturbations diminish rather than grow.

Since the operator $G[Y(t)]$ satisfies a contraction property, we guarantee the existence of a unique fixed solution, meaning:

(2.42)

$$G[Y(t)] = Y(t)$$

Thus, $Y(t)$ must satisfy the corresponding integral equation.

2.5. Integration of Y(t) using RLI. Using fractional calculus, the solution is expressed in terms of the initial condition $Y(0)$ and the fractional integral I^α :

$$(2.43) \quad Y(t) = Y(0) + I^\alpha(R_1 Y(t) + x(t)R_2 Y(t))$$

where I^α represents memory-dependent contributions.

Expanding the solution form using fractional integral properties:

$$(2.44) \quad Y(t) = Y(0) + \frac{t^\alpha}{\Gamma(\alpha+1)}[R_1 Y(0) + x(0)R_2 Y(0)] + I^{\alpha+1}[R_1 Y'(t) + x'(t)R_2 Y(t) + x(t)R_2 Y'(t)]$$

- The first term $Y(0)$ captures the initial state
- The second term introduces memory scaling using Gamma function properties
- The third term accumulates past interactions via the fractional integral $I^{\alpha+1}$, ensuring long-term dependencies

Thus, the existence of a fixed point leads directly to the solution formulation

Operating equation (2.44) to the initial fractional order derivatives stated in equations (2.13)–(2.15):

$$(2.45) \quad x(t) = x(0) + \frac{t^\alpha}{\Gamma(\alpha+1)}[p_1 x(0)(1 - qx(0)) - p_2 x(0)z(0)] + I^{\alpha+1}[p_1(1 - 2qx(t))x'(t) - p_2(z(t)x'(t) + x(t)z'(t))]$$

$$(2.46) \quad y(t) = y(0) + \frac{t^\alpha}{\Gamma(\alpha+1)}[x(0)z(0) + rd(t) - y(0) - sy(0)z(0)] + I^{\alpha+1}[x'(t)z(t) + x(t)z'(t) - y'(t) - sy'(t)z(t)]$$

$$(2.47) \quad z(t) = z(0) + \frac{t^\alpha}{\Gamma(\alpha+1)}[u(1 - vz(0)) - x(0)z(0) - \delta y(0)z(0)] + I^{\alpha+1}[-vz'(t) - x'(t)z(t) - x(t)z'(t)]$$

Each population (N, L, T) now follows fractional-order memory dynamics, meaning past interactions influence current behavior. The Gamma function scaling ensures appropriate historical weighting, while the fractional integral term $I^{\alpha+1}$ allows for persistent effects in tumor-immune interactions. The system accounts for biological delays, making the model more realistic than classical differential equations.

2.6. Stability Analysis. Using the nondimensionalized model, we can solve for critical points and find $N_0 = L_0 = T_0 = 0$ for the trivial solution, and for non-zero values we have

$$(2.48) \quad N_i^* = \frac{p_1 - p_2 \pm \sqrt{4k_n p_1 q D(t) + p_1^2 - 2p_1 p_2 - 2p_1 T(t) + p_2^2 + 2p_2 T(t) + T^2(t)} - T(t)}{2p_1 q}$$

$$(2.49) \quad L_i^* = \frac{rD(t) + N(t)T(t)}{sT(t) + 1}$$

$$(2.50) \quad T_i^* = \frac{-\delta L(t) + u \pm \sqrt{\delta^2 L^2(t) - 2\delta u L(t) + 2\delta L(t)N(t) - 4k_t uv D(t) + u^2 - 2uN(t) + N^2(t)} - N(t)}{2uv}$$

and the Jacobian of the non-dimensionalized model is

$$J = \begin{bmatrix} -2p_1 q N(t) + p_1 - p_2 - T(t) & 0 & -N(t) & k_n \\ T(t) & -sT(t) - 1 & -sL(t) + N(t) & r \\ -T(t) & -\delta T(t) & -\delta L(t) - 2uvT(t) + u - N(t) & -k_t \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

for the trivial case, the Jacobian becomes

$$J = \begin{bmatrix} p_1 - p_2 & 0 & 0 & k_n \\ 0 & -1 & 0 & r \\ 0 & 0 & u & -k_t \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

This gives us the eigenvalues 0, $p_1 - p_2$, -1 , and u . Since u has a positive sign, -1 has a negative sign, and $p_1 - p_2$ could be positive or negative, we can conclude that the trivial case is a saddle point. For the case $L_0 = T_0 = D_0 = 0$, $N_0 = \frac{p_1 - p_2 + \sqrt{p_1^2 - 2p_1p_2 + p_2^2}}{2p_1q} = \frac{1}{q}$

$$J = \begin{bmatrix} -p_1 - p_2 & 0 & -\frac{1}{q} & k_n \\ 0 & -1 & \frac{1}{q} & r \\ 0 & 0 & u - \frac{1}{q} & -k_t \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

This gives us the eigenvalues $-p_1 - p_2$ and -1 , which are negative, and $u - \frac{1}{q}$ which could be negative or positive. Since u and q are positive, $u - \frac{1}{q}$ will only be negative when $u < \frac{1}{q}$ or when $q < \frac{1}{u}$. So this set of initial conditions is a saddle point when $q > \frac{1}{u}$ (which corresponds with a NK population cap less than that of the tumor growth rate), and a stable sink when $0 < q < \frac{1}{u}$ (which corresponds with a NK population cap greater than that of the tumor growth rate).

—c—c—c— Parameters Range Eigenvalue Stability p_1 $(0, p_2)$ $p_2 - p_1 > 0$ unstable p_1 (p_2, ∞) $p_2 - p_1 < 0$ saddle point p_2 (p_1, ∞) $u + \frac{1}{q} \left(\frac{p_2}{p_1} - 1 \right) > 0$ unstable q, p_2 $q \in \left(0, \frac{1}{u} \left(1 - \frac{p_2}{p_1} \right) \right)$, $p_2 \in (0, p_1)$ $u + \frac{1}{q} \left(\frac{p_2}{p_1} - 1 \right) < 0$???

For $N = \frac{p_1 - p_2 - T(t)}{p_1q}$, $L = \frac{N(t)T(t)}{sT(t)+1}$, $T = \frac{u - N(t) - \delta L(t)}{uv}$, $D = 0$,

$$J = \begin{bmatrix} -p_1 + p_2 + \frac{z}{uv} & 0 & -\frac{p_1 - p_2 - \frac{z}{uv}}{p_1q} & k_n \\ \frac{z}{uv} & -\frac{sz}{uv} - 1 & -\frac{sz(p_1 - p_2 - \frac{z}{uv})}{p_1quv(\frac{sz}{uv} + 1)} + \frac{p_1 - p_2 - \frac{z}{uv}}{p_1q} & r \\ -\frac{z}{uv} & -\frac{\delta z}{uv} & 2\delta L(t) - \frac{\delta z(p_1 - p_2 - \frac{z}{uv})}{p_1quv(\frac{sz}{uv} + 1)} - u + 2N(t) - \frac{p_1 - p_2 - \frac{z}{uv}}{p_1q} & -k_t \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

where $z = u - \delta L(t)$

3. Results. Our simulations produced a series of graphs that illustrated key aspects of immune cell dynamics and neuroblastoma tumor progression under various treatment conditions. These visualizations revealed critical trends, including temporal changes in tumor burden and immune cell populations, and demonstrate the relative efficacy of Cyclophosphamide and IL-2 compared to control groups. Notably, combined therapeutic strategies consistently outperformed single-agent interventions, highlighting the potential benefit of multi-modal treatment approaches in high-risk cases.

3.1. Numerical simulation. Numerical simulations were performed in Python using the NumPy and SciPy libraries. Parameter values were adapted from existing literature (Table 3), while initial immune and tumor cell counts were determined based on relative proportions characteristic of each neuroblastoma risk group (Table 2). Simulations were run across the three patient-risk categories to assess immune response dynamics and treatment effectiveness under varying clinical conditions.

3.1.1. Low-risk neuroblastoma. Low-risk simulations began with relatively small tumor populations and a partially functional immune system. The model evaluated ..

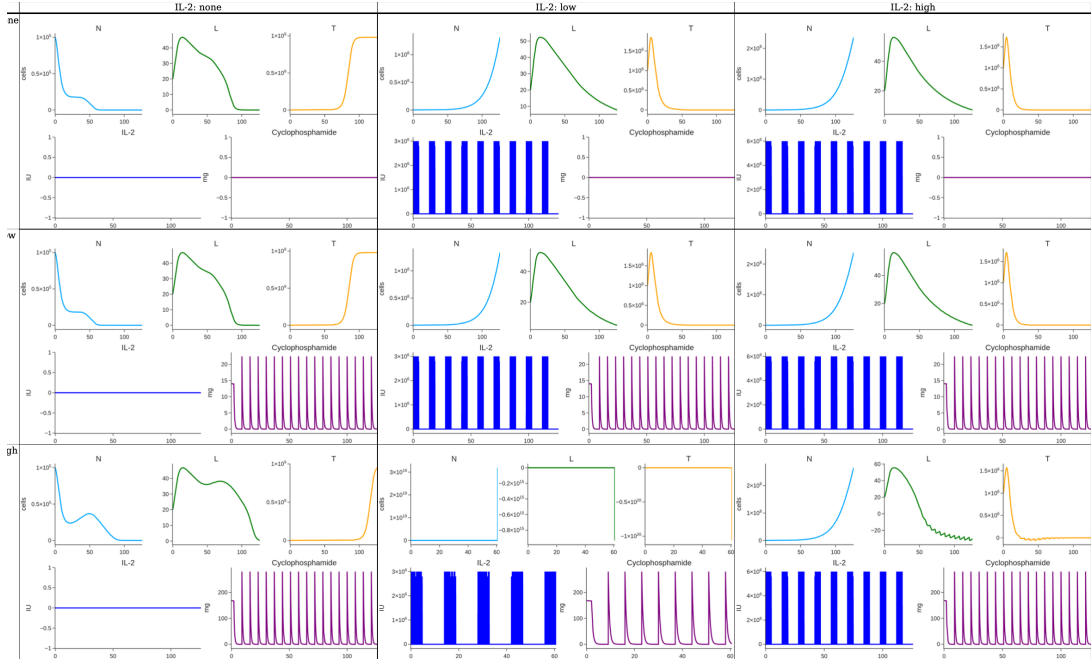


Fig. 1: Low-risk tumor progression under control, IL-2, Cyclophosphamide, and combination treatment.

3.1.2. Intermediate-risk neuroblastoma. Intermediate-risk simulations were initialized with a higher tumor burden and a moderately suppressed immune response ..

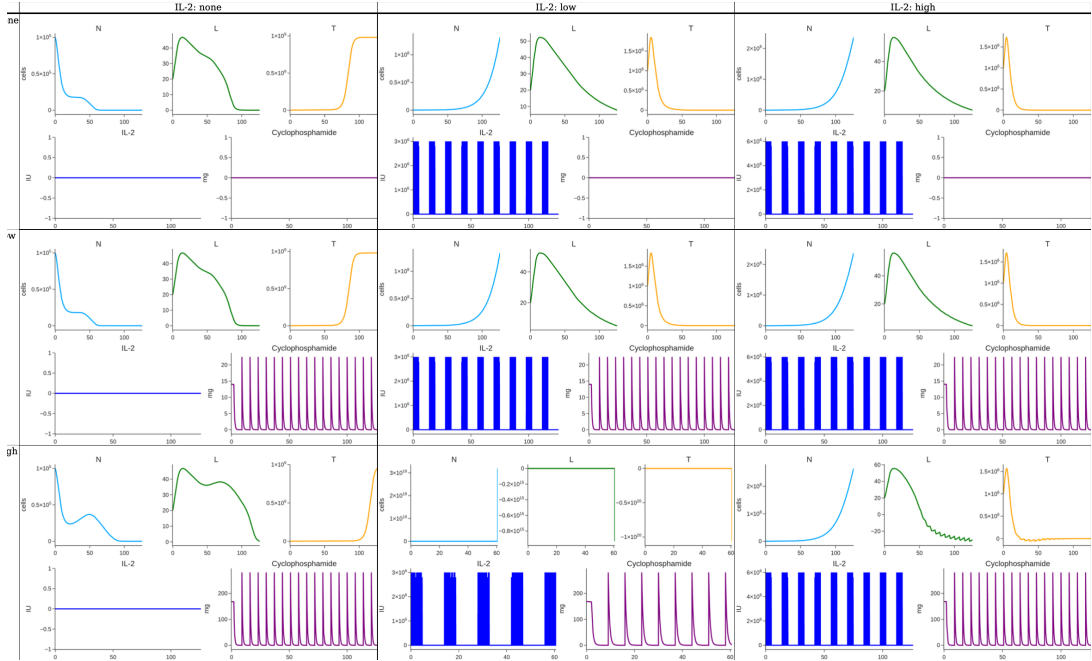


Fig. 2: Intermediate-risk tumor progression under control, IL-2, Cyclophosphamide, and combination treatment.

The simulations for the intermediate-risk group illustrated how ..

3.1.3. High-risk neuroblastoma. High-risk simulations were characterized by aggressive tumor growth and severely compromised immune cell populations.

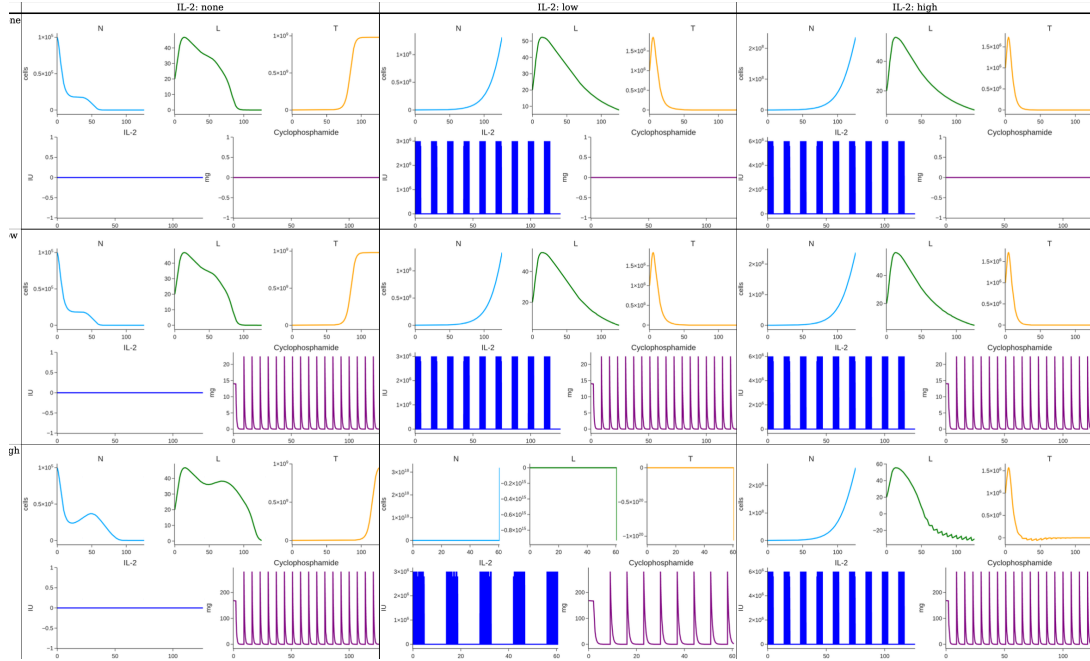


Fig. 3: High-risk tumor progression under control, IL-2, Cyclophosphamide, and combination treatment.

Findings from the high-risk simulations revealed ..

4. Discussion. This study examined the dynamic interactions between tumor cells, immune responses, and therapeutic agents in neuroblastoma using a mathematical modeling framework. Our results emphasized the crucial role of NK cells and CTLs in tumor suppression and demonstrated that both Interleukin-2 (IL-2) and Cyclophosphamide significantly enhanced immune-mediated tumor elimination. IL-2 constrained tumor growth by promoting NK cell proliferation and cytotoxic activity, while Cyclophosphamide exerted both direct tumor-killing effects and immune-stimulating properties. Simulations revealed that each treatment reduced tumor burden through distinct, complementary mechanisms.

By integrating immunotherapeutic and chemotherapeutic effects, our model highlighted the synergistic potential of combined therapies. This predictive framework provides valuable insights for treatment optimization and underscores the role of mathematical models in guiding cancer therapy design and clinical decision-making.

Data availability. All data and code used in this study are available on GitHub at: <https://github.com/JGarza189/neuroblastoma-2025>.

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