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Mathematical Analysis of Growing Tumor and its Treatments with Chemotherapy and Immunotherapy

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ABSTRACT
The analysis of growing tumor cells and the interaction between the host immune system and tumor cells help to understand the dynamics of tumor growth cells. Such a system has various important methods of cancer therapy such as virotherapy, immunotherapy, chemotherapy, radiotherapy, drug and vaccine therapy such as chemotherapy, immunotherapy and many other scientific solutions to analyze the cancer cell dynamics. Therefore, we analyze a mathematical model involving an ordinary differential equation system to interact between the growing tumor cells and cells in the immune system, including cytotoxic CD8+ T cells combined with drug and vaccine intervention to these cells. This model of a control function represents the application of natural killer cells combined with CD8+ T cell treatment to the system. Further, the impact of additional CD8+ T cell regulation parameters with natural killer cell help to reduce the proliferation rate of tumor growth cell also observe. The obtained result will help to develop a control mechanism and to provide the dynamic interactions between the tumour cells, immune system, and drug response systems.

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INTRODUCTION

A technical system that uses mathematical concepts and physical techniques to solve real-world problems is known as mathematical modelling. In the field of biomathematics or mathematical oncology, applied mathematics is a very popular technique to analyze biological problems and with the computational method, it is investigating the efficiency of treatment. Mathematical Biology or Bio- bio-mathematics can solve several issues like blood flow problems, ecological problems, synovial joints issues, respiratory systems, and in oncology to reduce cancer. Mathematical modelling focuses on the theoretical principles and mathematical techniques to study cancer and analyzed the tumor growth rate and it also allows the efficiency of computing ability and controls the system. Application of mathematics in the biological field covers theoretical biology, mathematical biology, mathematical life science, etc. Mathematical biology is a vast area of research study where one can work in mathematical ecology, mathematical demography, mathematical bioeconomics, mathematical medical science, mathematical agriculture, and biofluid dynamics. Thomas Malthus developed a population growth mathematical model, which was also known as the exponential model [1], then Verhuslt proposed a logistic growth model [2] and Richard formulated a population growth model by solving Bernoulli differential equation[3]. Blumberg's study on the concept of growth modified the logistic growth model [4], then Torner also changed the logistic growth model known as the generic growth model [5]. Misra and Chakravarty present the dynamics of arterial wall tissues with the enzymatic action of DNA knots [7]. Buis generalized the logistic law of the growth model [8], while Tsoularis analyzed the logistic growth model [11]. Misra and Dravid were developed to identify transcription factor binding sites of genes [12]. Misra et al. to determine a human-sized heart's left ventricular wall stresses [15]. Recently Mallick et al. studied nanofluids in a porous microchannel [20]. Misra et al. designed a model on microfluidic tubes that bear promises of important applications in human microcirculatory systems [23]. Cancer is one of the most painful and harmful diseases in the present scenario. It is a non-infectious or non-communicable, acute, sub-acute, and chronic disease. The history of cancer started in Egypt and dates back to about 3000 BC. The Greek Physician Hippocrates (460-370 BC), the Father of Medicine, gave the words 'Cancer' The word cancer is derived from the ancient Greek word "carcinomas and carcinoma", which means Crab or Tumor. A tumor is an abnormal mass of tissue that is

formed when normal cells begin to change and grow uncontrollably. A basic definition of cancer can be given as a class of diseases characterized by uncontrolled growth of cells and invasion into the surrounding tissue. Tumors divide into two categories i) Benign Tumor, and ii) Malignant Tumors. In the body tissue, the cancer cell is present and develops rapidly. This rapid growth of cell is known as tumor growth and the rate of developing new cell define the tumor growth cell dynamics. A benign tumor means that the tumor can grow but does not proliferate to the other body parts. It will never affect the handy tissue or other body parts but it may be dangerous when it will occur in the brain and crowd the typical structure and required surgery to reduce it. A malignant tumor is a cancerous tumor that can also grow and proliferate to other body parts. The cancer cell is moved in the blood cell and lymph nodes, where it can spread to other tissue within the body and that is called metastasis. It will need strong treatment including surgery, radiation, chemotherapy, and immunotherapy medication. If a tumor grows in blood vessels and does not acquire proper oxygen in blood vessels then the angiogenic factor helps to create new blood vessels to grow the tumor is known as angiogenesis. George et al. formulated the population cell growth to measure the cell volume growth rate and probability per unit time of division [6]. Bajzer et al. analyzed the receptor-mediated regulation of growth and tested the auto-stimulation and competing populations functional model [9]. Bellomo et al. discussed tumor evolution ad its interaction with the immune system [10]. Pillis et al. proposed mixed immunotherapy and chemotherapy of tumors: modelling, application and biological interpretations [13]. Kumar et al. proposed a mathematical model of radioimmunotherapy for tumor treatment [14]. Dixit et al. discussed the chemotherapy of tumor growth with an aspect of biological stoichiometry [17]. Benzekry et al. introduced mathematical modelling with three theories which were competition, angiogenesis inhibition, and proliferation inhibition [18]. Wei introduced the mathematical modelling of tumor growth which was a stable model for analyzing the growth rate of tumors [19]. Unni et al. proposed new mathematical models that interacted between tumor cells and cells in the immune systems including natural killer cells, dendritic cells, and cytotoxic CD8+ T cells combined with the drug [21]. Owolabi et al. worked on a problem of a fitted operator method for a model arising in vascular tumor dynamics [24]. Bunonyo et.al proposed the modelling and application of chemo-immunotherapy and radiotherapy treatments [25]. Over the years, mathematical modelling helps to diagnose cancer and tumor growth cells, and during the last 50 years many mathematical models were developed that analyze the interaction between various cells such as tumor cells, dendritic cells, cytotoxic cells and natural killer cells. However, tumor dynamics and their interaction with the immune system are still not achieved at their level, and treatment procedure is still time-consuming and not more effective. This work tries to make a new formulation with the new computational method and use some drug therapy to prevent and control tumor growth. Additionally, a new parameter of cytotoxic cells and natural killer cells is proposed that helps to find a better and more accurate result in this field to detect tumor growth dynamics.

MATERIAL AND METHODS

This section focuses on a mathematical model that incorporates four different cell populations and their interactions to control tumor cell growth using drugs and vaccines. The main cell types involved are tumor, natural killer, dendritic, and cytotoxic CD8+ T cells. The model utilizes equations that consider cell dynamics, conservation of mass, and diffusion to describe the behaviour of these cells. The proliferation rates of the different cell types and the effects of drug intervention are included in the equations.

$$\frac{\partial[\cdot]}{\partial t} + \nabla \cdot (\vec{u}\,[\cdot]) - \delta_D \nabla^2[\cdot] = f(\cdot) - g(\cdot) - K_{[\cdot]} z(M) \qquad (1)$$

Here, the function $f(\cdot)$ and $g(\cdot)$ the proliferation rates of the natural (N) cell, tumor (T) cell, dendritic (D) cell, and cytotoxic CD8+T (L) cell and for the drug intervention are represented drug and vaccine terms. The term $z(M) = 1 - e^{-M}$ represents the impact of the doxorubicin drug on pharmacokinetics or the cell cycle. The parameter $K_{[\cdot]}$ represents the killing of cells, and when $K_{[\cdot]} = 0$ there is no effect of the drug on virus elimination.

Modelling of Tumor Cells

The tumor cell dynamics can be modeled using the logistic population growth model, where the proliferation rate is represented by the term $\lambda T(1 - \mu T)$. The parameters ω, ρ and γ represent the interactions between the tumor and dendritic cells, natural killer cells, and CD8+ T cells, respectively.

$$D_t(T) = \lambda T(1 - \mu T) - (\omega N + \rho D + \gamma L)T - \mathcal{K}_T \Lambda T \qquad (2)$$

Modelling of Natural Killer Cells

The natural killer cell term, denoted as N, is influenced by a constant source term represented by the variable ν. This source term is modified by the Michaelis-Menten term, which takes into account the interaction between NK cells and tumor cells.

$$g_1 \cdot \frac{T^2}{h_1 + T^2} \cdot N$$

The interaction is governed by the parameters g_1, h_1, and T. Additionally, the dynamics of NK cells are affected by the interaction between NK cells and dendritic cells, represented by the parameters ω and α. The equation governing the dynamics of NK cells, denoted as $D_t(N)$, includes terms for the source term, the NK-tumor cell interaction, the NK-dendritic cell interaction, a specific parameter effect term, and a natural death rate term.

$D_t(N) = \upsilon + \mathcal{M}_{mt} - (\omega T - \alpha D)N - \mathcal{K}_N \Lambda N - \mathcal{E}N$ (3)

Modelling of Dendritic Cells

The mathematical model describing the dynamics of dendritic cells in the presence of tumor cells, CD8+T cells, and the following equation gives natural killer (NK) cells.

$D_t(D) = \beta - (\eta L + \alpha N - \sigma T)D - \mathcal{K}_D \Lambda D - jD$ (4)

The equation describes the dynamics of dendritic cells D in relation to tumor cells T, CD8+T cells L, and NK cells N. It includes terms for the constant source of dendritic cells β, the killing rate of dendritic cells and NK cells by tumor cells α, the proliferation rate of dendritic cells , the interaction rate between dendritic cells and CD8+ T cells η, and the natural death rate of dendritic cells *j*. The equation also considers the recruitment and migration of dendritic cells $\mathcal{K}_D$ and Λ respectively.

Modelling of Cytotoxic CD8+T Cells

In this model cytotoxic cells help to kill or diffuse tumor cells, ρ is a corresponding parameter of interaction between dendritic cells and tumor cells, τ defines the interaction between CD8+T cells and tumor cells, ζ is the recruitment term of CD8+t cells which is several natural cell kills by the tumor cell, and χ is the term to define cytotoxic cells dynamics and cells activities (high level, low level and diffusion). $\mathcal{P}_{LI}$ is defined as the drug activation and efficiency term with immunotherapy IL-2 which is written as $\frac{P_I LI}{g_I + I}$ and governing equation of cytotoxic cell

$D_t(L) = \rho DT - \gamma LT - \chi NL^2 + \omega NT + \mathcal{P}_{LI} - \mathcal{K}_L \Lambda L - \mathcal{g}L$ (5)

Modelling of Drug and Vaccine Interventions

v_l is an effective drug and vaccine that improved the immune system. Chemotherapy and immunotherapy drug interventions recruit CD8+T cells by antigen immune cells to be specified by cytolytic cells.

$D_t(L) = \rho DT - \gamma LT - \chi NL^2 + \omega NT + \mathcal{P}_{LI} - \mathcal{K}_L \Lambda L - \mathcal{g}L + v_l$ (6)

But in the bloodstream, the congregation of chemotherapy and immunotherapy in cells defines the behavior of the cell after drug intervention.

$D_t(M) = \mathfrak{z}(t) - \ell$ (7)

$D_t(I) = \mathfrak{z}_\mathrm{I}(t) - cI$ (8)

Here, ℓM and cI are the amount of drug intervention, which is the quantity of chemotherapy and immune-therapy drugs that work on the body concerning time and reduce from the body due to a proportional rate of drug concentration.

T(0)>0, N(0)≥0, D(0)≥0, L(0)≥0, M(0)≥0, I(0)≥0.

Brief Analysis of the Modelling of Equation

$D_t(T) = \lambda T(1 - \mu T) - (\omega N + \rho D + \gamma L)T - \mathcal{K}_T \Lambda T$

$D_t(N) = \upsilon + \mathcal{M}_{mt} - (\omega T - \alpha D)N - \mathcal{K}_N \Lambda N - \mathcal{E}N$

$D_t(D) = \beta - (\eta L + \alpha N - \sigma T)D - \mathcal{K}_D \Lambda D - jD$

$D_t(L) = \rho DT - \gamma LT - \chi NL^2 + \omega NT + \mathcal{P}_{LI} - \mathcal{K}_L \Lambda L - \mathcal{g}L + v_l$

$D_t(M) = \mathfrak{z}(t) - \ell M$

$D_t(I) = \mathfrak{z}_\mathrm{I}(t) - cI$

RESULTS AND DISCUSSION

The governing equations of the model are solved using the 4th-order Runge-Kutta method in Matlab serves as a robust numerical tool for considering a system of ordinary differential equations characterizing the dynamics of the immune response and tumor growth. The parameter in the cells is assumed to be in units of day^{-1}. Specifically, the recruitment term of CD8+T cells $\zeta = 0$ and the elimination rate of CD8+T cells $\mathcal{M}_{mt} = 0$, as there is no demand for cytotoxic and natural killer cell, activeness. Effect and elimination rate of CD8+T cells ($\mathcal{P}_{LI} = \chi = 0$) are also excluded from the model. The drug-killing terms of chemotherapy ($\mathcal{K}_T = \mathcal{K}_N = \mathcal{K}_L = \mathcal{K}_D = 0$), and the intervention of vaccine and drugs ($v_l = \mathfrak{z} = \mathfrak{z}_\mathrm{I} = 0$) are not included in the model. Similarly, the growth rate of dendritic cells, chemotherapy and immunotherapy drugs ($\sigma = \ell = c = 0$) are omitted from the model. The initial conditions for the model are set to 100 T cells, 1 NK cell, 1 D cell and 1 CD8+T cell. The figure illustrates that the tumor cell population initially increases to peak levels. However, the immune system plays a crucial role in halting further tumor cell growth, leading to

stabilization at a certain point. This suggests that the importance of the immune response may act as a vital factor in controlling tumor progression in this model, highlighting the potential significance of immune-based interventions in cancer therapy.

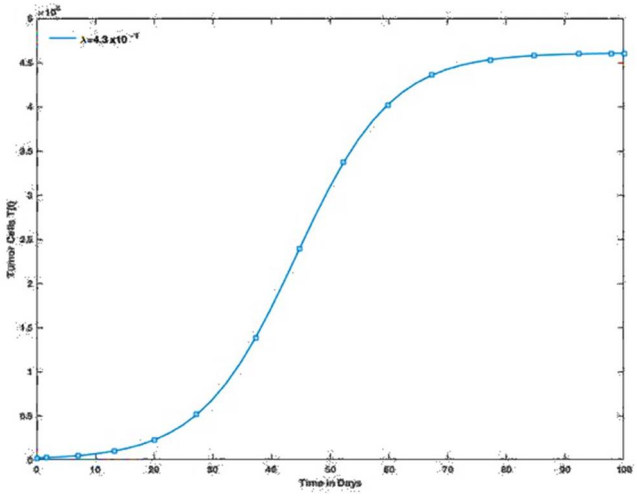

Figure 1. The initial tumor cell population growth, expanding at a rate of 43% per unit of time, attributed to its intrinsic growth rate of 0.43.

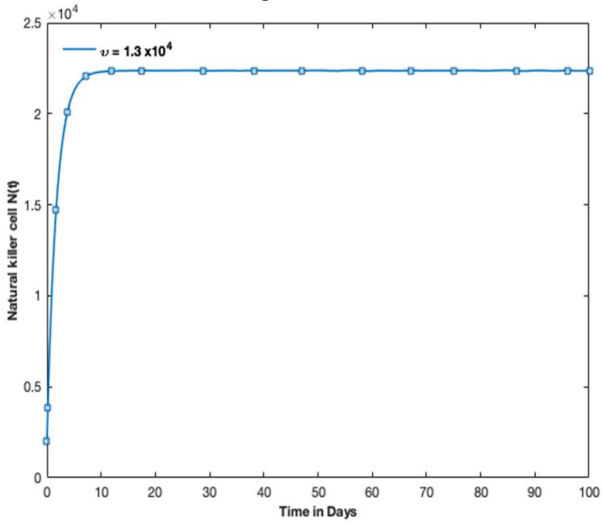

Figure 2. The dynamics of natural killer cells, with a source term adding 13,000 cells per unit of time (at a rate of 1.3 × 10^4) to their population.

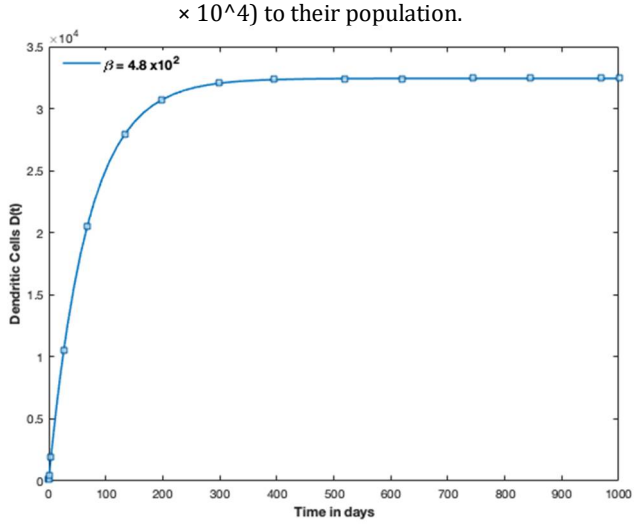

Figure 3. The dynamics of dendritic cells, with a source term (β) contributing 480 cells per unit of time (at a rate of 4.8×10^2)

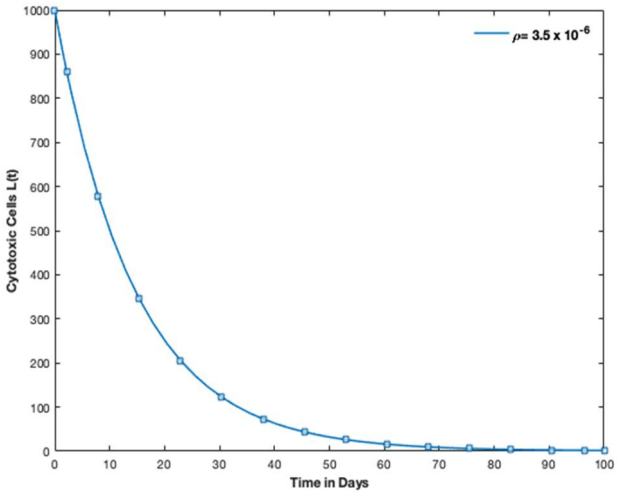

Figure 4. The initial CD8+ T cell dynamics, influenced by the combined effect of dendritic and tumor cells (with a combination parameter $\rho = 1.0 \times 10^{-7}$

The introduction of the source term β into our model is a significant which accounts for the effects of NK, tumor, and CD8+T cells on cell dynamics. By increasing the dendritic cell source term rate, we observed a corresponding increase in the rates of NK and CD8+T cells. This phenomenon, in turn, exerts a profound impact on the tumor microenvironment. The resultant halt in tumor growth being stopped at a particular point and eventually decreasing over time. Our study suggests that increasing the source term rate of dendritic cells can increase NK and CD8+T cell growth, which could help fight against tumor cells and potentially lead to their destruction. This study sheds light on a promising avenue for cancer immunotherapy research.

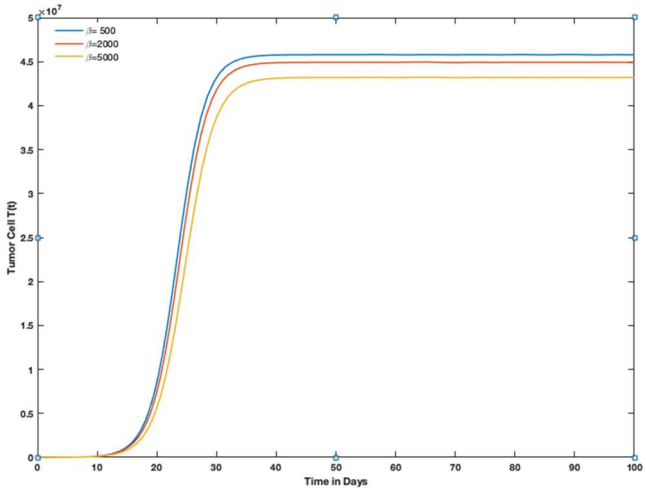

Figure 5. The effect of different dendritic cell source term (β) values (500, 2000, and 5000) on tumor cell dynamics

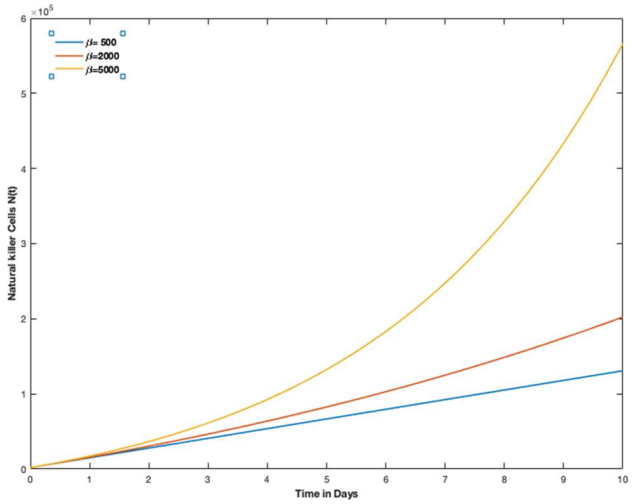

Figure 6. The influence of varying dendritic cell source term (β) values (500, 2000, and 5000) on the dynamics of natural killer cells.

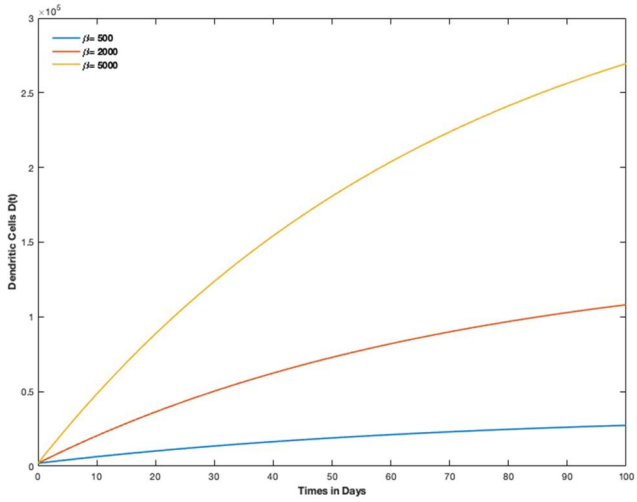

Figure 7. The varying dendritic cell source term (β) values (500, 2000, and 5000) affect dendritic cell dynamics.

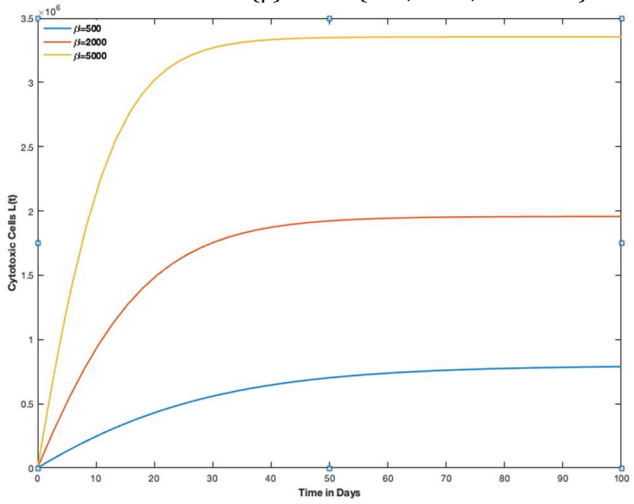

Figure 8. The effect of different dendritic cell source term (β) values (500, 2000, and 5000) on cytotoxic cell (CD8+T) dynamics.

In the study, the dynamics of dendritic cells are considered by a system of equations that take into account the intervention of dendritic cells with NK cells, CD8+T cells and tumor cells. The parameter σ represents the interaction between the tumor and dendritic cells. Figures shows that σ not only affects dendritic cells but also CD8+T cells. This effect changes sigma's proliferation rate, which is doubled in this experiment.

Specifically, the value of σ value is 1×10^{-4}. Then doubled the values are 2×10^{-4}, 4×10^{-4}, and 8×10^{-4}. To observe its impact on the system.

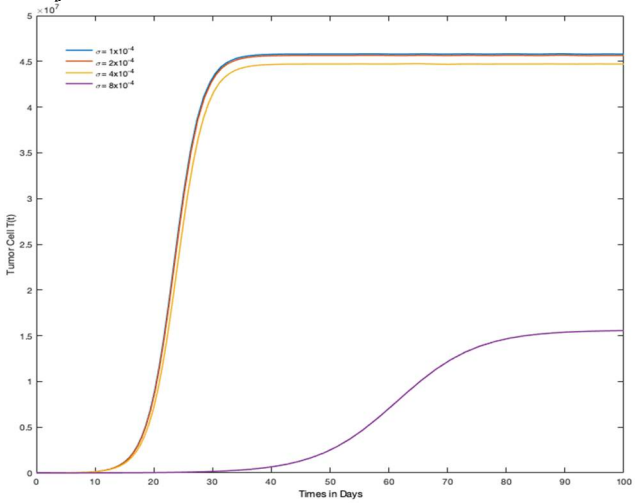

Figure 9. The tumor cell dynamics are influenced by varying immunology-related rates (σ) of tumor cell and dendritic cell (1×10^{-4}, 2×10^{-4}, 4×10^{-4}, and 8×10^{-4})

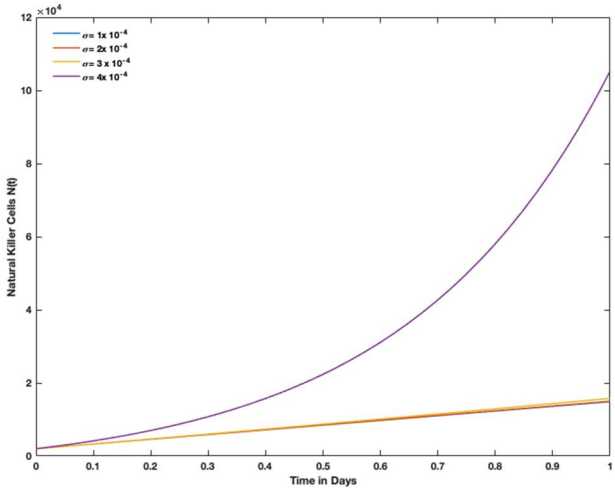

Figure 10. The impact of different immunology-related rates (σ) of tumor cell and dendritic cell (1×10^{-4}, 2×10^{-4}, 4×10^{-4}, and 8×10^{-4}) on the dynamics of natural killer cells.

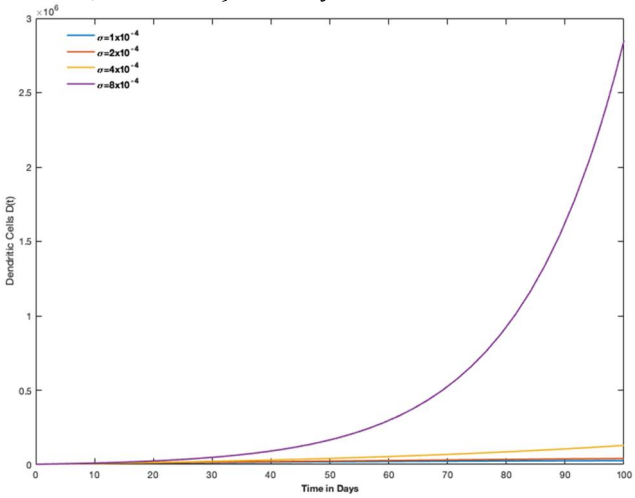

Figure 11. The effect of different immunology-related rates (σ) for tumor cell and dendritic cell (1×10^{-4}, 2×10^{-4}, 4×10^{-4}, and 8×10^{-4}) on the dynamics of dendritic cells.

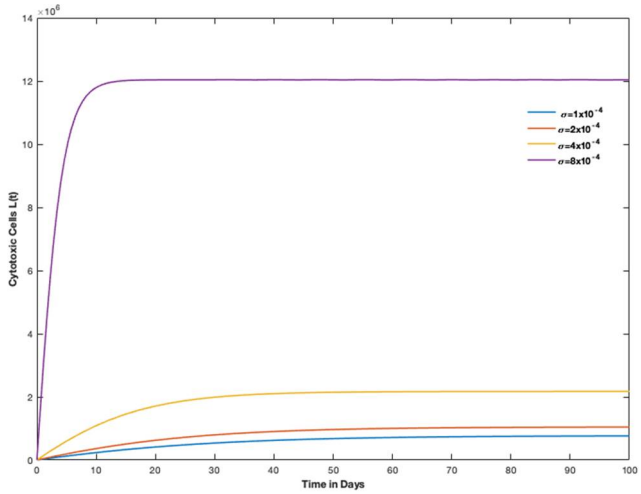

Figure 12. The impact of different immunology-related rates (σ) for tumor cell and dendritic cell (1×10^{-4}., 2×10^{-4}, 4×10^{-4}, and 8×10^{-4}) on the dynamics of cytotoxic cells.

To elaborate further, the Michel-Menten interaction term $\mathcal{M}_{mt}$ is a term in the governing equations that accounts for the interaction between dendritic cells and cytotoxic cells. In this case, it has been found to have a negligible effect on all four cells, indicating that this particular interaction is not a significant factor in the system's dynamics. However, the nonlinear term χ in the equation that governs the activity of CD8+T cells has a significant impact on the system dynamics. When the value of $\chi = 0$, there is no CD8+T cell activity, and the tumor cell growth rate remains stable. But when the value of χ is increased to 3×10^{-10}, the CD8+T cells become more active, destabilising the tumor cell growth rate and reducing the tumour growth rate. This sensitivity to the level of CD8+T cell activity underscores the critical role played by these cells in orchestrating the immune response against tumor cells. The ability to modulate \chiχ offers a promising avenue for potential therapeutic interventions aimed at enhancing CD8+T cell activity, which may prove instrumental in curbing tumor growth and advancing cancer immunotherapy strategies. These findings contribute valuable insights to our understanding of the intricate dynamics between the immune system and tumor cells, potentially paving the way for novel treatment approaches.

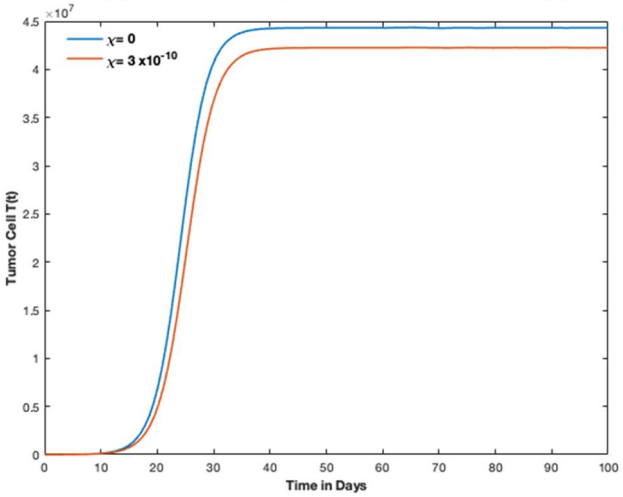

Figure 13. The impact of CD8+ T cell elimination rates due to inactivity (χ) on tumor cell dynamics, with values of 0 and 3×10^{-10}.

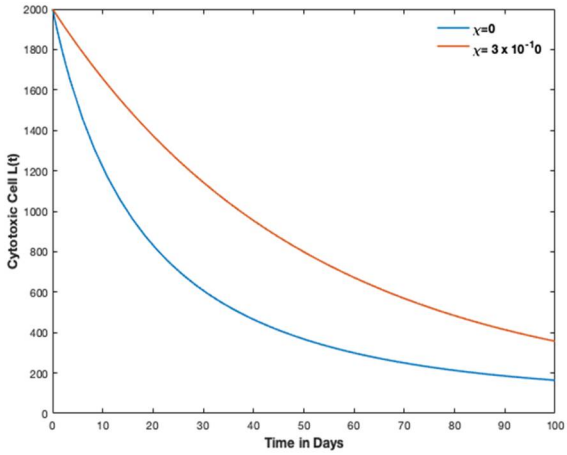

Figure 14. The dynamics of cytotoxic cells are affected by different CD8+ T cell elimination rates due to inactivity (χ), with values of 0 and 3×10^{-10}.

The study suggests increasing the dose of CD8+ T cells at a slow pace, with a value of v_l ranging from 1 to 10^4. This drug intervention aims to enhance the immune system by activating antigen-specific cytolytic immune cells. However, the results presented in Figure shows that there is only a minor effect on tumor growth, despite the slow increase in the dose quantity of CD8+ T cells.

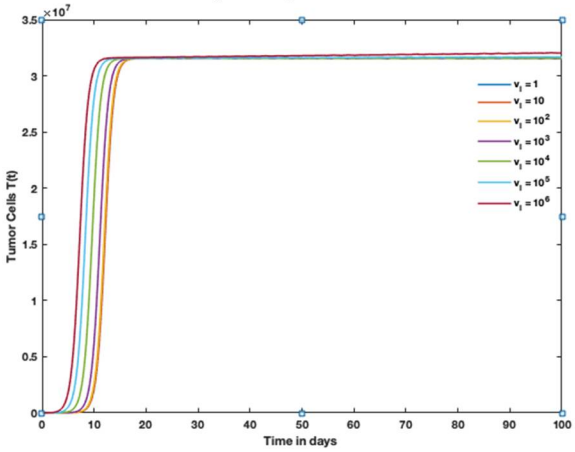

Figure 15. The effect of drug and vaccine (v_l) on tumor cell dynamics, with v_l values ranging from 1 to 10^4.

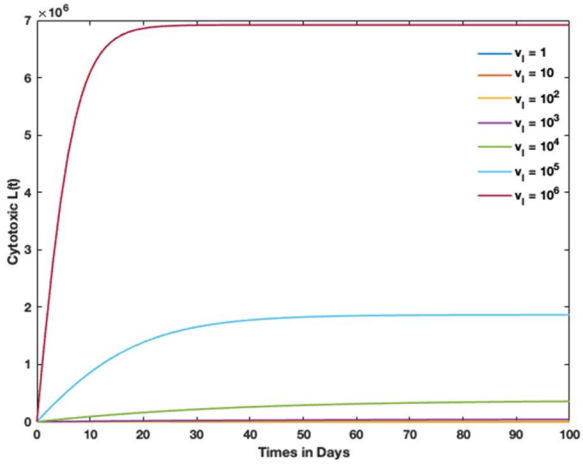

Figure 16. The dynamics of cytotoxic cells are impacted by varying drug and vaccine effectiveness (v_l), with values ranging from 1 to 10^4.

The next term introduced is denoted by $\mathfrak{z}$ which represents the influence of the chemotherapy drug on the parameter $\mathcal{K}_T$. When is set to 1, it is observed that the chemotherapy drug's effect on the killing of tumor cells is reflected in the parameter $\mathcal{K}_T$, which leads to a decrease in tumor growth. The next intervention involves the immune system, specifically the regulation of CD8+T cells through a combination of drug and vaccine interventions, denoted by the term $\mathfrak{z}_l$.

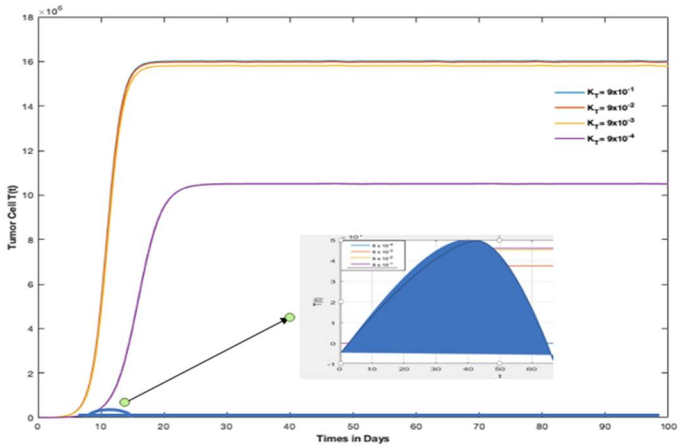

Figure 17. The effect of chemotherapy drug on tumor cell killing (represented by $\mathcal{K}_T$), with values ranging from 9×10^{-1} to 9×10^{-4}.

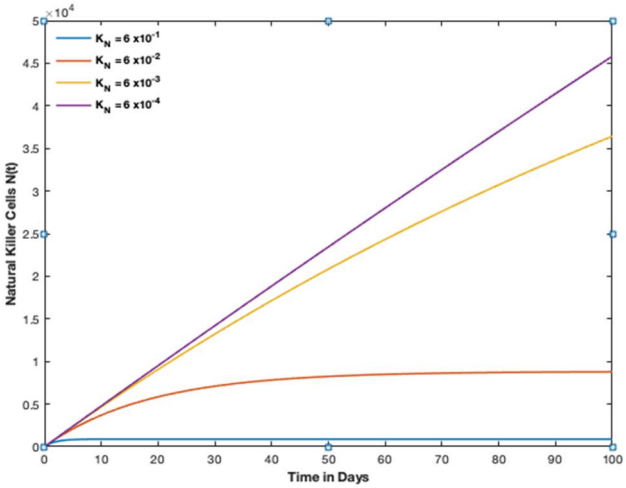

Figure 18. The impact of drug and treatment on natural killer cell killing (represented by $\mathcal{K}_N$), with values ranging from $6{\times}10^{-1}$ to $6{\times}10^{-4}$.

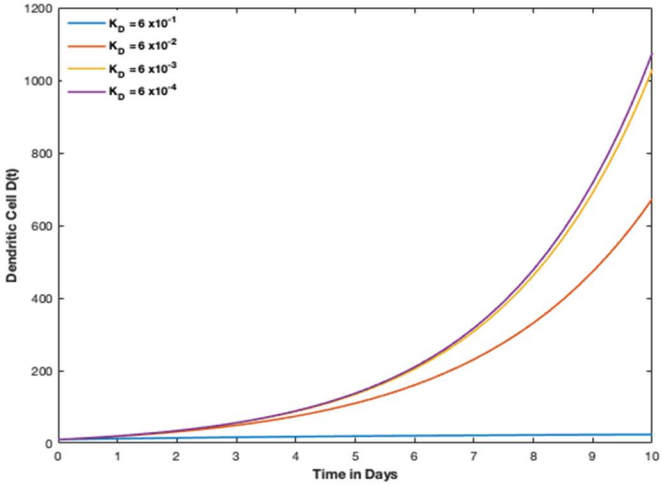

Figure 19. The killing rate of dendritic cells by drug and vaccine (represented by $\mathcal{K}_D$) is influenced, with values ranging from $6{\times}10^{-1}$ to $6{\times}10^{-4}$.

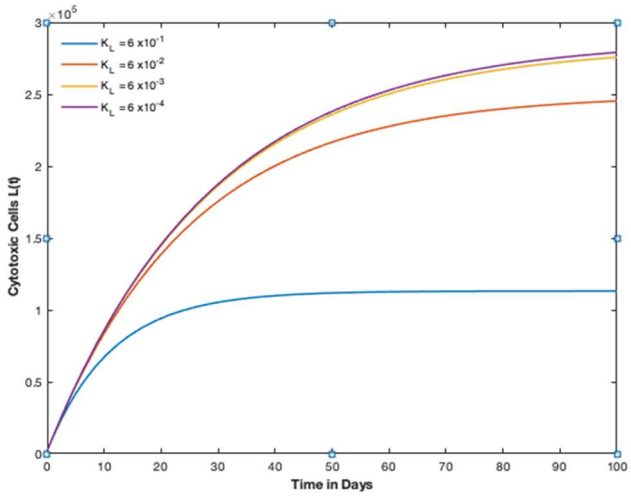

Figure 20. The impact of drug and vaccine effectiveness on the killing activity of CD8+T cells (represented by $\mathcal{K}_L$), with values ranging from 6×10^{-1} to 6×10^{-4}.

Table 1: Nomenclature notation with parameters

λ	Intrinsic growth rate of tumor cells	α	combination parameter between dendritic and NK cells
μ	growth declaration rate of tumor cells	σ	Rate of tumor cell and dendritic cell due to immunology
ω	combination parameter between tumor and natural killer cells	$\mathcal{K}_N$	natural killer cell killing term by drug and treatment
ρ	combination parameter between tumor and dendritic cells	$\mathcal{E}$	natural death rate of natural killer cells
γ	combination parameter between tumor and CD8+T cells	β	source term of dendritic cells
$\mathcal{K}_T$	tumor cell killing cell term due to chemotherapy drug effect	η	combination parameter between CD8+T and dendritic cells
Λ	rate of drug effectiveness of chemotherapy	$\mathcal{K}_D$	dendritic cells killing rate by drug and vaccine
υ	source term of natural killer cells	j	natural death rate of dendritic cells
$\mathcal{M}_m$	proliferation rate of natural killer cells	χ	elimination rate of CD8+T cells due to inactivity
$\mathcal{K}_L$	activeness of killing cell term of CD8+T cells by drug and vaccine	v_l	effect of drug and vaccine
$\mathcal{g}$	natural death rate of CD8+T cells	$\mathfrak{z}$	drug intervention term of chemotherapy
$\mathcal{P}_{LI}$	rate of CD8+T cells activity due to the effect of immunotherapy	$\mathfrak{z}_\mathrm{I}$	drug intervention term of immunotherapy
ℓM	amount of chemotherapy drug used interaction between cells	cI	amount of immunotherapy drug used interaction between cells

CONCLUSION

Our study uses mathematical modeling to explore tumor growth and assess the impacts of chemotherapy, immunotherapy, and vaccine therapy. The governing equations allow us to test the combination of four types of cells: tumor cells, dendritic cells, natural killer cells, and cytotoxic cells. We also examine the interaction between tumor growth cells and immune cells, with drug delivery cells to reduce tumor growth. When analyzing the mathematical modelling in the absence of any treatment, we find that the dendritic cell source term affects the system equation on three different values, which helps to stop tumor growth at certain points and increase the immune system. The proliferation rate of dendritic cells has significant effects, and the rate of cytotoxic cells has a negligible effect on the governing equation of tumor cells and cytotoxic cells. The results show that in the presence of dendritic cells, natural killer cells, and CD8+T cells, tumor growth stops, and their growth rate remains stable. We also investigate the effect of treatments such as immunotherapy on the system parameters. The results show that immunotherapy changes the stability in tumor cells, and CD8+T cells become more stable, making the treatment more effective. Chemotherapy, drugs, and vaccine treatments help to reduce tumor growth slightly. In conclusion, this study demonstrates that drug intervention helps to diffuse tumor cells, and the growth rate of CD8+T cells, dendritic cells, and natural killer cells increases, helping to reduce tumor growth cells. Mathematical modelling enriches our understanding of tumor dynamics and computational techniques, guiding new combinations and

treatments for cancer. Mathematical modeling enhances our grasp of tumor dynamics and computation, guiding innovative cancer treatment combinations.

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