Some Mathematical Models Of Cancer Growth And Tumor Cell-Immune Interaction: A Study Of Tumor-Immune Dynamics And Chemotherapy Applications

Jitendra Singh[1*], Atar Singh[2]

[1*,2]Department of Mathematics, Agra College, Agra (U.P), India 282004, Email: jitendrabhandari1989@gmail.com[1], atarsinghbbc1968@gmail.com[2]

Abstract

There is a complex system that can be represented by mathematical modeling, and that system is the proliferation of cancer and its interaction with the immune system. The purpose of this work is to investigate the interactions between tumors and immune systems, with a particular emphasis on logistic growth models and an investigation into the equilibrium points of these models. In the following section, we will investigate the role that chemotherapy plays in relation to these equilibrium states as a therapeutic method. For the purpose of providing evidence for the theory and analysis, the research draws from a wide variety of sources. This highlights the usefulness of mathematical models in understanding the dynamics of the immune system and the formation of tumors.

Keywords: mathematical modeling, cancer, equilibrium points, therapeutic method, chemotherapy

1. Introduction

The majority of deaths that occur around the world are caused by cancer, and it is critical to have a solid understanding of its dynamics in order to develop more effective treatment methods [1-5]. Over the years, mathematical modeling has evolved into a powerful tool that serves the purpose of shedding light on the evolution of tumors and the ways in which they interact with the immune system. There are a great number of mathematical models that have been proposed in order to shed light on the growth of tumors and the responses of the immune system [6-10]. These models range from the most fundamental exponential growth models to the more complicated nonlinear models, such as the logistic growth model [11, 12].

Intricate and ever-changing is the dynamic interaction that takes place between immune cells and tumor cells. Through a variety of activities, including cytotoxic reactions, the immune system is able to identify and eliminate malignant cells [13]. Yet, tumor cells have the ability to change in order to avoid the immune response, which ultimately leads to the progression of the tumor. For the purpose of evaluating the effectiveness of a variety of medications, particularly chemotherapy, the mathematical modeling of this interaction has gained increasing significance [14].

Specifically, logistic growth models will be the focus of this investigation, which will also involve the description and analysis of mathematical models addressing cancer proliferation and interactions between the immune system and tumors [15]. Additionally, equilibrium points in these models will be discovered and examined in order to determine whether the tumor is dormant or is propagating [16]. This study will investigate the role that chemotherapy plays in the process of upsetting these equilibrium points in the context of cancer treatments.

2. Mathematical Models of Tumor Growth

The mathematical modeling of cancer growth is an effective tool for understanding tumor proliferation dynamics and the impacts of medicines such as chemotherapy. These models enable the prediction of tumor responses to various biological stimuli and treatments across time by encapsulating the evolution of tumor cells through equations [17]. Furthermore, they offer a framework for comprehending the essential mechanisms that govern tumor proliferation, immune responses, and therapeutic strategies. The necessity to integrate the intricate and nonlinear dynamics of tumor proliferation propels the advancement of mathematical models for cancer [18]. These models must consider phases of fast multiplication, periods of hibernation, and interactions with the host's immune system.

Fundamental theories indicate that tumor cells proliferate at an exponential rate, signifying that the growth rate correlates directly with the current quantity of tumor cells. Nonetheless, even the most basic models neglect to consider the biological constraints of finite resources and the body's immune response [19]. To achieve a more precise representation of tumor proliferation in a confined setting, advanced models like the logistic growth model integrate ideas of growth saturation. Moreover, various supplementary models enhance this methodology to investigate the connections between the immune system and cancer cells. This facilitates the examination of the intricate interactions between the immune system and malignancies [20].

The Gompertzian model, the von Bertalanffy model, and differential equation-based models that simulate the interactions between tumor cells and immune cells are commonly examined mathematical frameworks. The forecasting of treatment regimen effectiveness is one of the several practical applications that fully utilize these models, which are also extensively employed for theoretical scientific investigation. They enable the identification of factors essential for tumor formation,

including growth rates, immune responses, and treatment-induced apoptosis, thereby providing insights into the advancement of tailored therapy [21].

2.1 Logistic Growth Model

The logistic growth model is a widely used model in cancer research for describing the constrained growth of tumor cells. It addresses the key limitation of the exponential growth model, which assumes indefinite, unchecked growth. The logistic growth model introduces the concept of a carrying capacity, which reflects the fact that tumors do not grow without limits but are restricted by factors such as nutrient availability, space, and the body's ability to sustain the tumor mass. This model is given by the following differential equation:

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right)$$

where:

- *N(t)* is the population of tumor cells at time t,
- *r* is the intrinsic growth rate of the tumor cells,
- *K* is the carrying capacity, which represents the maximum tumor size that the surrounding environment can support.

In this equation, $\frac{dN}{dt}$ represents the rate of change of the tumor cell population over time. When *N* is much smaller than *K*, the tumor grows approximately exponentially since the term $\left(1 - \frac{N}{K}\right)$ is close to 1. However, as *N* approaches *K*, the term $\left(1 - \frac{N}{K}\right)$ decreases, slowing the growth rate and eventually bringing it to a halt as *N* reaches *K*.

This model is biologically pertinent since it illustrates that tumor cells require access to essential resources such as oxygen and nutrients, which are constrained within the body. The proliferation of tumors is limited by physical reasons, including the availability of space within tissues and organs. The logistic growth model addresses these constraints, providing a more accurate representation of tumor dynamics than models that presume unlimited growth [22].

2.1.1 Biological Interpretation of Parameters

- **Intrinsic Growth Rate (*r*):** This metric indicates the rate of tumor cell proliferation in the absence of resource constraints. The tumor's biological property is fundamental and varies among different cancer types. Aggressive tumors exhibit elevated *r* values, resulting in fast proliferation, while slower-growing cancers display diminished *r* values.
- **Carrying Capacity (*K*):** This metric indicates the maximal tumor cell number that the environment can sustain, limited by resources including nutrients, oxygen, and space. *K* may be influenced by the tumor's vascular supply, the architecture of the surrounding tissue, and the immunological response. Tumors exhibiting elevated *K* values may attain greater dimensions prior to stabilizing, whereas those with diminished *K* values may reach a reduced equilibrium size.
-

2.1.2 Logistic Growth Dynamics

At the outset, when the tumor size is diminutive relative to the carrying capacity, growth is nearly exponential as the tumor remains unconstrained by resource limitations. This period of accelerated growth aligns with clinical observations of early-stage cancers, which typically exhibit aggressive expansion throughout their earliest phases. As the tumor proliferates, it begins to encounter resource constraints. At this juncture, growth commences to decrease and ultimately stabilizes when the population attains *K*.

This plateau signifies a condition of equilibrium where tumor size stabilizes due to a balance between cellular proliferation and cell death or senescence resulting from resource depletion. The principle of logistic growth indicates that tumors can attain a latent phase, during which their size remains relatively stable unless influenced by external events, such as treatment or immune system response [23].

2.1.3 Limitations of the Logistic Growth Model

Despite being an advancement over exponential growth models, the logistic growth model possesses limitations when utilized in the biological setting of cancer. The model notably omits interactions between tumor cells and the immune system, which significantly influence tumor growth regulation. The immune system continuously endeavors to recognize and eradicate tumor cells via mechanisms including cytotoxic activity, which is not accounted for in the logistic growth model.

Moreover, the logistic model presupposes that the carrying capacity is constant across time. The tumor's microenvironment may alter due to variables such as angiogenesis or the immune system's reaction to the tumor. These factors can modify the carrying capacity and, hence, the dynamics of tumor proliferation [24].

2.2 Extensions to the Logistic Model:

To mitigate these constraints, numerous adaptations of the logistic model have been created. Models that integrate immune responses can yield a more thorough comprehension of tumor dynamics. These models incorporate further terms to depict the elimination of tumor cells by immune cells and the mobilization of immune cells in reaction to the tumor's presence. Additional extensions may let the carrying capacity to fluctuate over time, mirroring alterations in the tumor microenvironment resulting from angiogenesis or tissue remodeling.

Moreover, integrating the logistic growth model with treatment modalities (such as chemotherapy or immunotherapy) might elucidate the effects of these interventions on tumor dynamics. Chemotherapy may diminish the growth rate or directly reduce the tumor population, altering the tumor's growth trajectory and potentially leading it to a new, lower equilibrium size [25].

3. Tumor-Immune Interaction Models

Tumor-immune interactions exhibit significant nonlinearity and can be represented by systems of differential equations. These models generally depict populations of tumor cells, immune cells (including T-cells), and parameters of the immunological response. The Stepanova model is a frequently analyzed framework that elucidates the interactions between tumor cells and immune cells by integrating terms that signify immunological responses and tumor evasion tactics.

3.1 Tumor-Immune System Model

A basic mathematical depiction of tumor-immune interaction can be expressed as follows:

$$\frac{dT}{dt} = rT\left(1 - \frac{T}{K}\right) - \alpha TI$$

$$\frac{dI}{dt} = sI + \beta TI - \gamma I$$

where:

- $T(t)$ is the tumor cell population,
- $I(t)$ is the immune cell population,
- r is the tumor cell growth rate,
- K is the carrying capacity,
- α is the rate of immune-induced tumor cell death,
- s is the natural immune cell recruitment rate,
- β is the rate of immune cell activation by tumor cells,
- γ is the immune cell death rate.

This model elucidates the relationship between neoplastic cells and immune cells. The term αTI denotes the immune system's capacity to eliminate tumor cells, whereas βTI pertains to the activation of immune cells induced by tumor cells.

4. Equilibrium Points

Equilibrium points in tumor-immune interaction models are crucial for comprehending the system's long-term dynamics. These marks denote conditions in which the tumor and immune cell populations maintain stability across time, indicating that neither group is experiencing growth or decline. This transpires mathematically when the rate of change of both tumor cells T and immune cells I equals zero. That is:

$$\frac{dT}{dt} = 0 \text{ and } \frac{dI}{dt} = 0$$

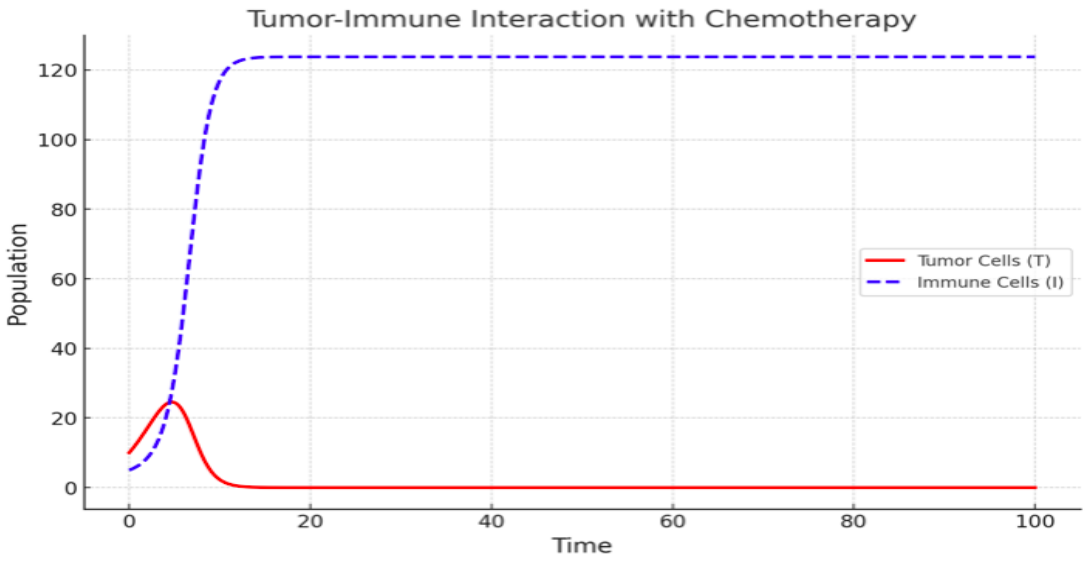

Figure 1: Tumor-immune chemotherapy interaction graph

Figure 1 illustrates the connection between chemotherapy and the immune system and the tumor. Over the course of time, the tumor cell population is represented by the red curve, while the immune cell population is represented by the blue dashed curve.

1. Initial growth of the tumor population is slowed down by the effects of chemotherapy and immunological responses, which begin to shrink the size of the tumor gradually.
2. The immune cells first grow as a response to the presence of the tumor; however, over time, they either stabilize or decrease, depending on the dynamics of interactions between the tumor and the immune system as well as the effects of chemotherapy itself.
3. A better understanding of how the system develops over time and how treatment influences the equilibrium points of the tumor-immune dynamics can be gained via the use of this depiction.

At equilibrium, the populations of tumor cells and immune cells attain a stable condition. To determine the equilibrium points, we employ the tumor-immune interaction model, wherein the dynamics of tumor cells T and immune cells I are dictated by a series of nonlinear differential equations. The equations governing tumor-immune interactions, encompassing tumor cell proliferation, immunological response, and immune cell recruitment, can be expressed as follows:

$$rT\left(1-\frac{T}{K}\right) = \alpha TI$$

$$sI + \beta TI = \gamma I$$

In these equations:

- $T(t)$ represents the tumor cell population at time t,
- $I(t)$ represents the immune cell population at time t,
- r is the intrinsic growth rate of the tumor cells,
- K is the carrying capacity of the tumor's environment,
- α is the rate at which immune cells kill tumor cells,
- s is the natural recruitment rate of immune cells,
- β represents the rate of immune cell activation by the tumor,
- γ is the immune cell death rate.

The equilibrium points can be determined by equating both $\frac{dT}{dt} = 0$ and $\frac{dI}{dt} = 0$, leading to the subsequent system of equations:

$$\frac{dT}{dt} = rT\left(1-\frac{T}{K}\right) - \alpha TI - \delta T$$

Resolving these equations produces multiple equilibrium points, each associated with a distinct biological scenario:

1. Tumor-Free Equilibrium: This transpires when the tumor cell population is null, i.e., T=0. At this juncture, the immune system has effectively eliminated the tumor, leaving just the immune cell population active. The system has attained a condition in which no tumor cells remain to elicit additional immune responses.

2. Tumor Dormancy: This equilibrium emerges when tumor and immune cells live in a state of balance. The tumor remains present but is being controlled by the immune system. In this circumstance, the immune cells are effectively regulating the tumor's growth, inhibiting its further expansion, yet they are unable to eradicate it entirely. Tumor dormancy frequently occurs in clinical environments where the tumor exhibits stability without significant growth or reduction.

3. Uncontrolled Tumor Growth: In this scenario, the immune response is incapacitated, allowing the tumor to proliferate uncontrollably. This occurs when the tumor cell population attains a condition in which the immune system can no longer effectively inhibit its proliferation. The tumor attains or surpasses the carrying capacity K, and the immune cell population is inadequate to impede its advancement. This equilibrium signifies a malignant condition in which the tumor poses a life-threatening risk.

4. Immune Escape: A different potential equilibrium arises when tumor cells develop strategies to evade immune identification, leading to a diminished or ineffective immune response. The tumor proliferates unrestrained due to minimal opposition from the immune system.

Comprehending these balance points is essential for devising successful cancer treatments. By delineating the criteria that govern each equilibrium, researchers can formulate strategies to transition the system from detrimental equilibria (such as uncontrolled tumor proliferation) to more favorable states, such as tumor dormancy or tumor-free equilibrium [26].

5. Chemotherapy and Equilibrium Shifts

Chemotherapy is a prevalent cancer medication that functions by exterminating tumor cells or obstructing their capacity to proliferate and develop. In mathematical models, chemotherapy is frequently incorporated as an extra variable that influences the tumor cell population by generating cell mortality [27]. We amend the tumor cell growth equation to integrate chemotherapy into the tumor-immune interaction model as follows:

$$\frac{dT}{dt} = rT\left(1-\frac{T}{K}\right) - \alpha TI - \delta T$$

In this context, δ denotes the pace at which chemotherapy eradicates tumor cells or diminishes their proliferation. The term $-\delta T$ represents the impact of treatment by diminishing the tumor growth term. The value of δ is contingent upon parameters including the chemotherapy dosage and the tumor cells' susceptibility to the treatment.

The incorporation of chemotherapy into the model modifies the system's dynamics by diminishing the tumor population [28]. Chemotherapy can alter the system from a state of equilibrium characterized by tumor growth to a new equilibrium where the tumor is managed or eradicated [29]. The efficacy of chemotherapy in modifying equilibrium points is contingent upon various factors:

1. **Dosage**: Increased chemotherapy dosages (δ) may result in more substantial decreases in tumor populations, thereby transitioning the system towards a tumor-free equilibrium. Nevertheless, high dosage might adversely affect healthy cells and undermine the immune system.
2. **Timing**: The timing of chemotherapy is essential in ascertaining its efficacy. If delivered promptly while the tumor population remains minimal, chemotherapy may inhibit the tumor from attaining an uncontrolled development phase. Conversely, using chemotherapy at a later stage may merely inhibit the tumor's growth rather than eliminate it entirely.
3. **Tumor-Immune Interaction**: The efficacy of chemotherapy is also affected by the immune system's reaction to the tumor. When the immune system is actively managing the tumor, approaching a dormant equilibrium, chemotherapy may enhance the system's progression towards a tumor-free condition. Nonetheless, if the immune response is inadequate or the tumor has evaded immune recognition, chemotherapy alone may prove insufficient for tumor elimination.

The modified tumor-immune system model can be utilized to examine chemotherapy-induced alterations in equilibrium points. By simulating diverse values of δ (indicative of varied chemotherapy regimens), researchers can forecast the long-term treatment outcomes and identify best ways for reducing tumor development while maintaining immune function [30].

6. Conclusion

There is a great amount of information that can be gained from mathematical models of tumor growth and immune interactions regarding the dynamics of cancer progression and therapeutic approaches. In contrast to tumor-immune interaction models, which offer a framework for analyzing immunological responses, logistic growth models are able to capture the limitations that are associated with tumor proliferation. In these models, equilibrium points represent critical stages of the system, such as the dormancy or development of the tumor. Additionally, chemotherapy can be added into these models in order to provide light on the ways in which treatment can change the system in order to achieve a more favorable outcome.

References

1. De Pillis, L. G., & Radunskaya, A. E. (2003). A mathematical model of immune response to tumor invasion. *Cancer Research*, 63(17), 1-17.
2. Kuznetsov, V. A., et al. (1994). Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcation analysis. *Bulletin of Mathematical Biology*, 56(2), 295-321.
3. Stepanova, N. V. (1980). Course of the immune reaction during the development of a malignant tumor. *Biophysics*, 24(5), 917-923.
4. Murray, J. D. (2003). *Mathematical Biology: I. An Introduction*. Springer.
5. Bellomo, N., et al. (2008). Multiscale modeling and mathematics of cancer: the contributions of mathematical modeling to understanding cancer mechanisms and to improving cancer treatment. *Mathematical Models and Methods in Applied Sciences*, 18(04), 593-646.
6. Robertson-Tessi, M., El-Kareh, A., & Goriely, A. (2012). A mathematical model of tumor–immune interactions. *Journal of theoretical biology*, *294*, 56-73.
7. Özköse, F., Şenel, M. T., & Habbireeh, R. (2021). Fractional-order mathematical modelling of cancer cells-cancer stem cells-immune system interaction with chemotherapy. *Mathematical Modelling and Numerical Simulation with Applications*, *1*(2), 67-83.
8. Mahasa, K.J., 2017. *Mathematical Modelling of Tumour-Immune Interactions and Cancer Therapy* (Doctoral dissertation, Stellenbosch: Stellenbosch University).
9. Yu, J. L., & Jang, S. R. J. (2019). A mathematical model of tumor-immune interactions with an immune checkpoint inhibitor. *Applied Mathematics and Computation*, *362*, 124523.
10. Sancho-Araiz, A., Mangas-Sanjuan, V., & Trocóniz, I. F. (2021). The role of mathematical models in immuno-oncology: challenges and future perspectives. *Pharmaceutics*, *13*(7), 1016.
11. Makaryan, S. Z., Cess, C. G., & Finley, S. D. (2020). Modeling immune cell behavior across scales in cancer. *Wiley Interdisciplinary Reviews: Systems Biology and Medicine*, *12*(4), e1484.
12. Robertson-Tessi, M., El-Kareh, A., & Goriely, A. (2010). A mathematical model of tumor-immune interactions.
13. Gökgöz, N. (2014). Modeling stochastic hybrid systems with memory with an application to immune response of cancer dynamics.
14. Panchal, M. M., & Patel, H. S. (2020). Mathematical Modelling and Analysis of System of Tumor–Immune Interaction by Differential Transform Method. *Solid State Technology*, *63*(6), 22591-22598.
15. Alharbi, S. A., & Rambely, A. S. (2020). A new ODE-based model for tumor cells and immune system competition. *Mathematics*, *8*(8), 1285.
16. EMMANUEL, N. E. (2021). *ORDINARY DIFFERENTIAL EQUATION BASED MODEL FOR TUMOR CELLS AND IMMUNE SYSTEM COMPETITION* (Doctoral dissertation, DEPARTMENT OF MATHEMATICS, FACULTY OF SCIENCE, UNIVERSITY OF IBADAN).

17. Rihan, F. A., & Rajivganthi, C. (2021). Dynamics of tumor-immune system with random noise. *Mathematics*, *9*(21), 2707.
18. Leschiera, E., Lorenzi, T., Shen, S., Almeida, L., & Audebert, C. (2022). A mathematical model to study the impact of intra-tumour heterogeneity on anti-tumour CD8+ T cell immune response. *Journal of Theoretical Biology*, *538*, 111028.
19. Griffiths, J. I., Wallet, P., Pflieger, L. T., Stenehjem, D., Liu, X., Cosgrove, P. A., ... & Bild, A. H. (2020). Circulating immune cell phenotype dynamics reflect the strength of tumor–immune cell interactions in patients during immunotherapy. *Proceedings of the National Academy of Sciences*, *117*(27), 16072-16082.
20. Seager Jr, R. J. (2020). *Toward a quantitative understanding of cancer cell signaling: mathematical models, computational tools, applications, and beyond* (Doctoral dissertation, Boston University).
21. Lai, X., & Friedman, A. (2017). Combination therapy of cancer with cancer vaccine and immune checkpoint inhibitors: A mathematical model. *PLoS One*, *12*(5), e0178479.
22. Robertson-Tessi, M. (2010). *Mathematical models of tumor growth and therapy*. The University of Arizona.
23. Li, J., Liu, F., Chen, Y., & Zhang, D. (2022). Dynamic analysis of a model on tumor-immune system with regulation of PD-1/PD-L1 and stimulation delay of tumor antigen. *Qualitative Theory of Dynamical Systems*, *21*(3), 90.
24. Mehdizadeh, R., Shariatpanahi, S. P., Goliaei, B., Peyvandi, S., & Rüegg, C. (2021). Dormant tumor cell vaccination: A mathematical model of immunological dormancy in triple-negative breast cancer. *Cancers*, *13*(2), 245.
25. Norton, K. A., Gong, C., Jamalian, S., & Popel, A. S. (2019). Multiscale agent-based and hybrid modeling of the tumor immune microenvironment. *Processes*, *7*(1), 37.
26. Makinde, F. L. (2018). *Systems level cancer disease target identification using tumor microenvironment dynamics*(Doctoral dissertation, Stellenbosch: Stellenbosch University).
27. PAUL, R. STABILITY ANALYSIS OF CRITICAL POINTS TO CONTROL GROWTH OF TUMOR IN AN IMMUNE-TUMOR-NORMAL CELL-DRUG MODEL.
28. Awang, N. A., Maan, N., & Sulain, M. D. (2022). Tumour-natural killer and cD8+ t cells interaction model with delay. *Mathematics*, *10*(13), 2193.
29. Agrawal, T., Saleem, M., & Sahu, S. K. (2014). Optimal control of the dynamics of a tumor growth model with Hollings' type-II functional response. *Computational and Applied Mathematics*, *33*, 591-606.
30. Babbs, C. F. (2021). Raising the bar during early immunotherapy for cancer: simple mathematical models may help distinguish temporary vs. ultimate progression.