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Research Article

Analytical and Numerical Solutions for Glial Cells Interactions between Immunotherapy and Cancer Cells

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Abstract. In this article, we investigate a mathematical modeling applying a system of differential equations, that explains a interaction of healthy cells, glioma cells, macrophages, CD8+ T cells, and immunotherapy. Further, analytical method has been investigated. Moreover, the stability analysis and numerical simulations are also given for our proposed model. Finally, the quality of our model is also examined by comparing the graph of the analytical method and numerical simulation.

Keywords. Brain tumor, Immunotherapy, Glial cells, Glioma cells, Analytical solution

Mathematics Subject Classification (2020). 34D20, 37M05, 92C50

1. Introduction

Plenty of mathematical models were proposed during the last forty years to suppress most cancer (brain tumor) proliferation and to treat tumor eradication. The mathematical models whose role is to describe, quantify, and predict such behavior, including collectively interacting immunity, tumor proliferation, and immunotherapy. Our models are simply speculation about system dynamics, verbalized through the concise formal language of mathematics.

Most cancers' immunotherapy goal at upsetting the capability of the host immune system to cast off cancer cells with the help of the recruitment and activation of CD cells. A near bonding takes place between the immunosurveillance or removal, equilibrium, and tumor break out may additionally explain cells, the innate and the adaptive immune cells. Dunn *et al*. [6] mentioned the idea of immunosurveillance or removal, equilibrium, and tumor break out may additionally provide an explanation for this interplay. The innate immune is first to eliminate most cancer cells and respond to natural killer cells, then by using antigen-precise Cytotoxic T cells to stimulate the precise immune reaction. However, on the equilibrium segment, the energy of the immune response regularly reduces. Subsequently, numerous awesome and nonexclusive mechanisms assist the tumor to break out of the immune system. Pioneering studies in the late 70s revealed a connection between the magnitude of a cancer and its potential to stimulate an immune reaction. One of the reasons these studies were groundbreaking is because they could not determine the mechanisms behind these complicated biological processes (Berendt *et al*. [3], Deckers *et al*. [4], and Vaage [16]).

Immunity has two phases: a monotone progression caused by the immune breakdown process and an increase in tumor size up to a certain point. The immune system and tumor growth rates correlate through a mathematical formula, this was evidenced in (Alexander *et al*. [1], Dubben *et al*. [5], Rzeski *et al*. [12], Segal *et al*. [13], Soliman *et al*. [14], and Werner-Wasik *et al*. [17]). The mathematical connection between the two is demonstrated by considering the product of the two processes. Tumors create antigens that cause an immune response in a specific way. The first mechanism causes the immune reaction curve to increase as the tumor gets larger. Tumor size affects how the immune response is neutralized with the second mechanism producing a lower part of the curve. This happens when the large amount of cancer cells in a tumor suppress the immune response.

Iarosz *et al*. [7] discussed the mathematical modeling of the brain tumor with chemotherapy and glial-neuron interactions, which is how glial cells react among most cancers and Chemotherapy, which impacts glial cells also. Khajanchi *et al*. [8] mentioned the glioma-immune interactions model under optimal therapy. They discussed the growth of gliomas, macrophages, and CD8+ T cells but did not investigate glial cells. The novelty of this paper is to know about growth of healthy cells. In this paper, we have introduced a new nonlinear differential equation that includes healthy (glial) cells in the described model (Khajanchi *et al*. [8]). While using immunotherapy, we know about the competition between healthy cells and cancer cells.

We organized the work as follows: In Section 2, we introduce new system of nonlinear differential equation using immunotherapy. In Section 3, the analytical method is investigated. In Section 4, stability analysis is discussed. In Section 5, we discuss the numerical simulations and Section 6 explains the discussion and conclusion.

2. Mathematical Modelling

We introduce a new system of differential equations in the described model (Khajanchi *et al*. [8]). In this dynamic model, we consider glioma (cancer) and glial (healthy) cells, and their

interactions with macrophages and CD8+ T cells. So, the modified system defined as follows:

$$\frac{dH_1}{dt} = \Omega_1 H_1\left(1-\frac{H_1}{K_1}\right) - \Psi_1 H_1 H_2, \tag{2.1}$$

$$\frac{dH_2}{dt} = \Omega_2 H_2\left(1-\frac{H_2}{K_2}\right) - \Psi_2 H_1 H_2 - \frac{(\overline{\alpha}_1 M_1 + \overline{\alpha}_2 M_2)H_2}{H_2+\overline{K}_1}, \tag{2.2}$$

$$\frac{dM_1}{dt} = rM_1\left(1-\frac{M_1}{V_1}\right) - \frac{\overline{\alpha}_3 H_2 M_1}{\overline{K}_2+H_2}, \tag{2.3}$$

$$\frac{dM_2}{dt} = \frac{\nu_1 H_2 M_2}{\overline{K}_3+H_2} - \mu_1 M_2 - \frac{\overline{\alpha}_4 H_2 M_2}{\overline{K}_4+H_2} + s_1 u_1. \tag{2.4}$$

Our model consists of four different components, namely density of glial cells (H_1(Kg/m^3)), the concentration of cancer cells (H_2(Kg/m^3)), the concentration of macrophages (M_1(Kg/m^3)), the concentrations of CD8+ T cells (M_2(Kg/m^3)).

First term in equations (2.1), (2.2), and (2.3) represents the proliferation of glial cells, glioma cells, macrophages. Second term in equations (2.1) and (2.2) represents interaction between healthy and cancer cells. Third term in equation (2.2) represents elimination of H_2 owing to interaction with M_1 and M_2. In equation (2.3), last term represents deactivation of M_1 owing to interaction with H_2. In equation (2.4), 1st term represents the imbued M_2 recruited by malignant H_2, 2nd term represents decay rate of M_2 owing to inflammatory reaction in brain naturally, 3rd term represents eliminations of M_2 by H_2, and last term s_1 is strength of the treatment, u_1 term is an external source of M_2.

Table 1. List of symbols and abbreviations

Parameter	Values	Description
Ω_1	0.0068 day^{-1}	Proliferation rate [11, 15]
Ω_2	0.012 day^{-1}	Proliferation rate [11, 15]
Ψ_1	3.6×10^{-5} day^{-1}	Competition coefficients [11]
Ψ_2	3.6×10^{-6} day^{-1}	Competition coefficients [11]

The normalized model of the system of equation from (2.1)-(2.4) is given by

$$\begin{cases} \frac{dh_1}{dt} = \Omega_1 h_1(1-h_1) - \beta_1 h_1 h_2, \\ \frac{dh_2}{dt} = \Omega_2 h_2(1-h_2) - \beta_2 h_1 h_2 - \frac{(\alpha_1 m_1+\alpha_2 m_2)h_2}{h_2+k_1}, \\ \frac{dm_1}{dt} = rm_1(1-m_1) - \frac{\overline{\alpha}_3 h_2 m_1}{k_2+h_2}, \\ \frac{dm_2}{dt} = \frac{\nu_1 h_2 m_2}{k_3+h_2} - \mu_1 m_2 - \frac{\overline{\alpha}_4 h_2 m_2}{k_4+h_2} + s_1 u_1, \end{cases} \tag{2.5}$$

where

$$h_1 = \frac{H_1}{K_1},\ h_2 = \frac{H_2}{K_2},\ m_1 = \frac{M_1}{V_1},\ m_2 = \frac{M_2}{\overline{K_3}},\ \beta_1 = \Psi_1 K_2,\ \beta_2 = \Psi_2 K_1,$$

$$\alpha_1 = \frac{\overline{\alpha_1} V_1}{K_2},\ \alpha_2 = \frac{\overline{\alpha_2}\,\overline{K_5}}{K_2},\ k_1 = \frac{\overline{K_1}}{K_2},\ k_2 = \frac{\overline{K_2}}{K_2},\ k_3 = \frac{\overline{K_3}}{K_2},\ \text{and}\ k_4 = \frac{\overline{K_4}}{K_2}.$$

Table 2. Values of normalized parameter

Parameter	Values	Source
α_1	0.069943	[2]
α_2	2.74492	[2]
k_1	0.90305	[9]
r	0.3307	[2]
α_3	0.0194	[2]
k_2	0.030584	[9]
ν_1	0.1245	[10]
k_3	2.8743	[10]
μ_1	0.0074	[2]
α_4	0.01694	[9]
k_4	0.378918	[9]
β_1	1.8×10^{-2} (day^{-1})	[7]
β_2	1.8×10^{-3} (day^{-1})	[7]

3. Analytical Method

Definition 3.1. Consider the general linear non-homogeneous system, $X'(t) = A(t)X + B$, $X(t_0) = X_0$ where both $A(t)$ and B are continuous on some interval I.

Theorem 3.2. *Let $\varphi(t)$ be a fundamental matrix of solutions of $X'(t) = A(t)X$, then the unique solution of $X'(t) = A(t)X + B$, $X(t_0) = X_0$ is given by $X(t) = \varphi(t)C + \varphi(t)\int_{t_0}^{t} \varphi^{-1}(s)B(s)ds$, where C is a arbitrary constant.*

The nonlinear differential system (2.5) is transformed into a linearized system using the following steps to obtain an analytical solution:

- Finding the equilibrium points.
- Finding the Jacobian matrix at the equilibrium point.

3.1 Finding the Equilibrium Points

System (2.5) has some points of equilibrium which are obtain by solving the system of equations $\dot{h_1} = \dot{h_2} = \dot{m_1} = \dot{m_2} = 0$, i.e.,

$$\begin{cases} \Omega_1 h_1(1-h_1) - \beta_1 h_1 h_2 = 0, \\ \Omega_2 h_2(1-h_2) - \beta_2 h_1 h_2 - \frac{(\alpha_1 m_1 + \alpha_2 m_2)h_2}{h_2+k_1} = 0, \\ r m_1(1-m_1) - \frac{\overline{\alpha}_3 h_2 m_1}{k_2+h_2} = 0, \\ \frac{\nu_1 h_2 m_2}{k_3+h_2} - \mu_1 m_2 - \frac{\overline{\alpha}_4 h_2 m_2}{k_4+h_2} + s_1 u_1 = 0. \end{cases} \tag{3.1}$$

On solving the above the system of equations (3.1), we get

$$\overline{h_1} = 1 - \left(\frac{\beta_1 h_2}{\Omega_1}\right), \quad \overline{h_2} = \frac{-Q \pm \sqrt{Q^2 - 4PR}}{2P},$$

$$\overline{m_1} = 1 - \left(\frac{\overline{\alpha}_3 h_2}{r(h_2+k_2)}\right), \quad \overline{m_2} = \frac{s_1 u_1}{\mu_1 + \frac{\overline{\alpha}_4 h_2}{h_2+k_4} - \frac{\nu_1 h_2}{k_3+h_2}},$$

where

$$P = \Omega_1\Omega_2, Q = k_1\Omega_1\Omega_2 - \Omega_1\Omega_2 + \beta_2 h_1\Omega_1 - \beta_1\beta_2 k_1,$$
$$R = \beta_2 k_1\Omega_1 + \alpha_1\Omega_1 m_1 + \alpha_2\Omega_1 m_2.$$

3.2 Finding the Jacobian Matrix at Equilibrium Point

The nonlinear system (2.5) can be written as:

$$\begin{cases} \frac{dh_1}{dt} = \Omega_1 h_1(1-h_1) - \beta_1 h_1 h_2 = f_1(h_1,h_2,m_1,m_2), \\ \frac{dh_2}{dt} = \Omega_2 h_2(1-h_2) - \beta_2 h_1 h_2 - \frac{(\alpha_1 m_1 + \alpha_2 m_2)h_2}{h_2+k_1} = f_2(h_1,h_2,m_1,m_2), \\ \frac{dm_1}{dt} = r m_1(1-m_1) - \frac{\overline{\alpha}_3 h_2 m_1}{k_2+h_2} = f_3(h_1,h_2,m_1,m_2), \\ \frac{dm_2}{dt} = \frac{\nu_1 h_2 m_2}{k_3+h_2} - \mu_1 m_2 - \frac{\overline{\alpha}_4 h_2 m_2}{k_4+h_2} + s_1 u_1 = f_4(h_1,h_2,m_1,m_2). \end{cases} \tag{3.2}$$

The nonlinear system (3.2) can be approximated into linear system as follows:

$$\begin{cases} \frac{dh_1}{dt} = f_1(h_1,h_2,m_1,m_2) \\ \quad \approx f_1(\overline{h_1},\overline{h_2},\overline{m_1},\overline{m_2}) + \frac{\partial f_1}{\partial h_1}(h_1-\overline{h_1}) + \frac{\partial f_1}{\partial h_2}(h_2-\overline{h_2}) + \frac{\partial f_1}{\partial m_1}(m_1-\overline{m_1}) + \frac{\partial f_1}{\partial m_2}(m_2-\overline{m_2}), \\ \frac{dh_2}{dt} = f_2(h_1,h_2,m_1,m_2) \\ \quad \approx f_2(\overline{h_1},\overline{h_2},\overline{m_1},\overline{m_2}) + \frac{\partial f_2}{\partial h_1}(h_1-\overline{h_1}) + \frac{\partial f_2}{\partial h_2}(h_2-\overline{h_2}) + \frac{\partial f_2}{\partial m_1}(m_1-\overline{m_1}) + \frac{\partial f_2}{\partial m_2}(m_2-\overline{m_2}), \\ \frac{dm_1}{dt} = f_3(h_1,h_2,m_1,m_2) \\ \quad \approx f_3(\overline{h_1},\overline{h_2},\overline{m_1},\overline{m_2}) + \frac{\partial f_3}{\partial h_1}(h_1-\overline{h_1}) + \frac{\partial f_3}{\partial h_2}(h_2-\overline{h_2}) + \frac{\partial f_3}{\partial m_1}(m_1-\overline{m_1}) + \frac{\partial f_3}{\partial m_2}(m_2-\overline{m_2}), \\ \frac{dm_2}{dt} = f_4(h_1,h_2,m_1,m_2) \\ \quad \approx f_4(\overline{h_1},\overline{h_2},\overline{m_1},\overline{m_2}) + \frac{\partial f_4}{\partial h_1}(h_1-\overline{h_1}) + \frac{\partial f_4}{\partial h_2}(h_2-\overline{h_2}) + \frac{\partial f_4}{\partial m_1}(m_1-\overline{m_1}) + \frac{\partial f_4}{\partial m_2}(m_2-\overline{m_2}). \end{cases} \tag{3.3}$$

At the equilibrium point,

$$f_i(\overline{h_1},\overline{h_2},\overline{m_1},\overline{m_2}) = 0, \quad i = 1,2,3,4.$$

Thus, we have the system as

$$\begin{cases} \frac{dh_1}{dt} = G_{11}(h_1-\overline{h_1}) + G_{12}(h_2-\overline{h_2}), \\ \frac{dh_2}{dt} = G_{13}(h_1-\overline{h_1}) + G_{14}(h_2-\overline{h_2}) + G_{15}(m_1-\overline{m_1}) + G_{16}(m_2-\overline{m_2}), \\ \frac{dm_1}{dt} = G_{17}(h_2-\overline{h_2}) + G_{18}(m_1-\overline{m_1}), \\ \frac{dm_2}{dt} = G_{19}(h_2-\overline{h_2}) + G_{20}(m_2-\overline{m_2}). \end{cases} \tag{3.4}$$

The equation (3.4) is a linearized system, where

$$G_{11} = \Omega_1 - 2\Omega_1 h_1 - \beta_1 h_2, \quad G_{12} = -\beta_1 h_1, \quad G_{13} = -\beta_2 h_2,$$
$$G_{14} = \Omega_2 - 2\Omega_2 h_2 - \beta_2 h_1 - \frac{k_1(\alpha_1 m_1 + \alpha_2 m_2)}{(k_1+h_2)^2},$$
$$G_{15} = -\left(\frac{\alpha_1 h_2}{h_2+k_1}\right), \quad G_{16} = -\left(\frac{\alpha_2 h_2}{h_2+k_1}\right), \quad G_{17} = -\frac{\overline{\alpha}_3 k_2 m_1}{(h_2+k_2)^2},$$

$$G_{18}=r-2rm_1-\frac{\overline{\alpha}_3h_2}{(h_2+k_2)},\ G_{19}=\frac{\nu_1k_3m_2}{(k_3+h_2)^2}-\frac{\overline{\alpha}_4k_4m_2}{(m_2+k_4)^2},\ G_{20}=\frac{\nu_1h_2}{k_3+h_2}-\mu_1-\frac{\overline{\alpha}_4h_2}{h_2+k_4}.$$

Hence the system (3.4) can be written as:

$$\begin{bmatrix}h_1'\\h_2'\\m_1'\\m_2'\end{bmatrix}=\begin{bmatrix}G_{11}&G_{12}&0&0\\G_{13}&G_{14}&G_{15}&G_{16}\\0&G_{17}&G_{18}&0\\0&G_{19}&0&G_{20}\end{bmatrix}\begin{bmatrix}h_1-\overline{h_1}\\h_2-\overline{h_2}\\m_1-\overline{m_1}\\m_2-\overline{m_2}\end{bmatrix},\tag{3.5}$$

where the Jacobian matrix is given by,

$$J=\begin{bmatrix}G_{11}&G_{12}&0&0\\G_{13}&G_{14}&G_{15}&G_{16}\\0&G_{17}&G_{18}&0\\0&G_{19}&0&G_{20}\end{bmatrix}.$$

Around the equilibrium point $(1,0,1,1.35135)$ and from the Table 1 and 2, the matrix representation of the linear system (3.4) can be written as

$$\begin{bmatrix}h_1'\\h_2'\\m_1'\\m_2'\end{bmatrix}=\begin{bmatrix}G_{11}&G_{12}&0&0\\G_{13}&G_{14}&G_{15}&G_{16}\\0&G_{17}&G_{18}&0\\0&G_{19}&0&G_{20}\end{bmatrix}\begin{bmatrix}h_1\\h_2\\m_1\\m_2\end{bmatrix}+\begin{bmatrix}b_{11}\\b_{12}\\b_{13}\\b_{14}\end{bmatrix},\tag{3.6}$$

where

$$b_{11}=0.0068,\ b_{12}=0,\ b_{13}=0.3307,\ b_{14}=0.00999999.$$

The fundamental matrix is given by

$$\varphi(t)=\begin{bmatrix}w_{11}e^{-\lambda_1t}&w_{12}e^{-\lambda_2t}&w_{13}e^{-\lambda_3t}&w_{14}e^{-\lambda_4t}\\w_{21}e^{-\lambda_1t}&w_{22}e^{-\lambda_2t}&w_{23}e^{-\lambda_3t}&w_{24}e^{-\lambda_4t}\\w_{31}e^{-\lambda_1t}&w_{32}e^{-\lambda_2t}&w_{33}e^{-\lambda_3t}&w_{34}e^{-\lambda_4t}\\w_{41}e^{-\lambda_1t}&w_{42}e^{-\lambda_2t}&w_{43}e^{-\lambda_3t}&w_{44}e^{-\lambda_4t}\end{bmatrix},\tag{3.7}$$

where

$$\lambda_1=4.17483,\ w_{11}=0.00426093,\ w_{21}=0.986649,\ w_{31}=0.162807,\ w_{41}=0.000445141,$$
$$\lambda_2=0.3307,\ w_{12}=w_{22}=w_{42}=0,\ w_{32}=1,\ \lambda_3=0.0074,\ w_{13}=w_{23}=w_{33}=0,\ w_{43}=1,$$
$$\lambda_4=0.0068,\ w_{14}=1,\ w_{24}=w_{34}=w_{44}=0.$$

By applying Theorem 3.2, the analytical solutions of the linear system (3.4) is given by

$$\begin{cases}h_1=a_{11}+a_{12}e^{\lambda_1t}+a_{15}e^{\lambda_4t},\\h_2=a_{22}e^{\lambda_1t},\\m_1=a_{31}+a_{32}e^{\lambda_1t}+a_{33}e^{\lambda_2t},\\m_2=a_{41}+a_{42}e^{\lambda_1t}+a_{44}e^{\lambda_3t},\end{cases}\tag{3.8}$$

where

$$a_{11}=1,\ a_{12}=0.000863716,\ a_{15}=-0.200864,\ a_{22}=0.2,\ a_{31}=1,\ a_{32}=0.033002,$$
$$a_{33}=0.483002,\ a_{41}=1.35135,\ a_{42}=0.0000902328,\ a_{44}=-1.15144.$$

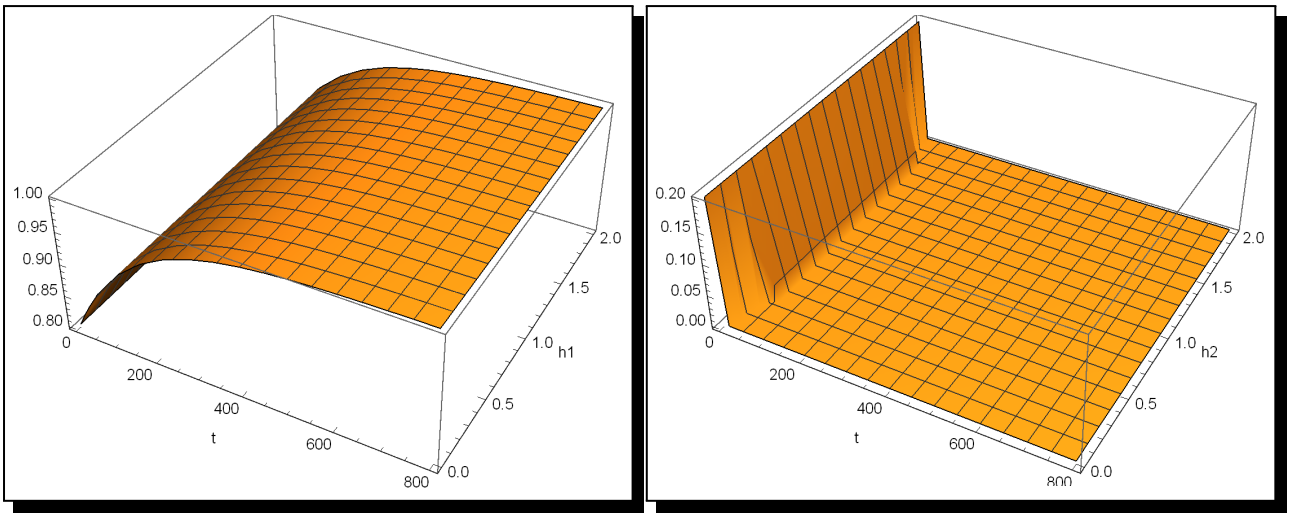
4. Stability Analysis

In this part, we use mathematical analysis to identify condition that can aid in the eradication of tumor cells. The characteristic equation of the linearized system is given by $|J - \lambda I| = 0$,

$$\lambda^4 + C_1\lambda^3 + C_2\lambda^2 + C_3\lambda + C_4 = 0, \tag{4.1}$$

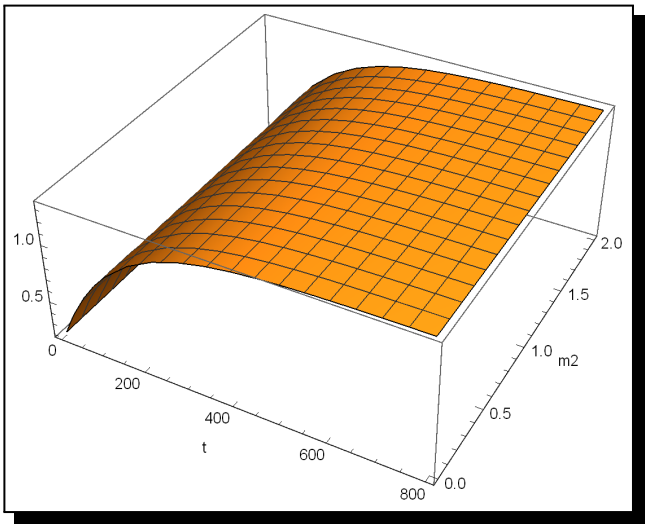
where $C_1 = 4.51973$, $C_2 = 1.44465$, $C_3 = 0.0198315$, $C_4 = 0.0000694726$.
The Eigen values of Jacobian matrix is given by

$$\lambda_1 = -4.17483, \quad \lambda_2 = -0.3307, \quad \lambda_3 = -0.0074, \quad \lambda_4 = -0.0068.$$



(a) Growth of glial cells

(b) Decrement of glioma cells



(c) Growth of CD8+ T cells

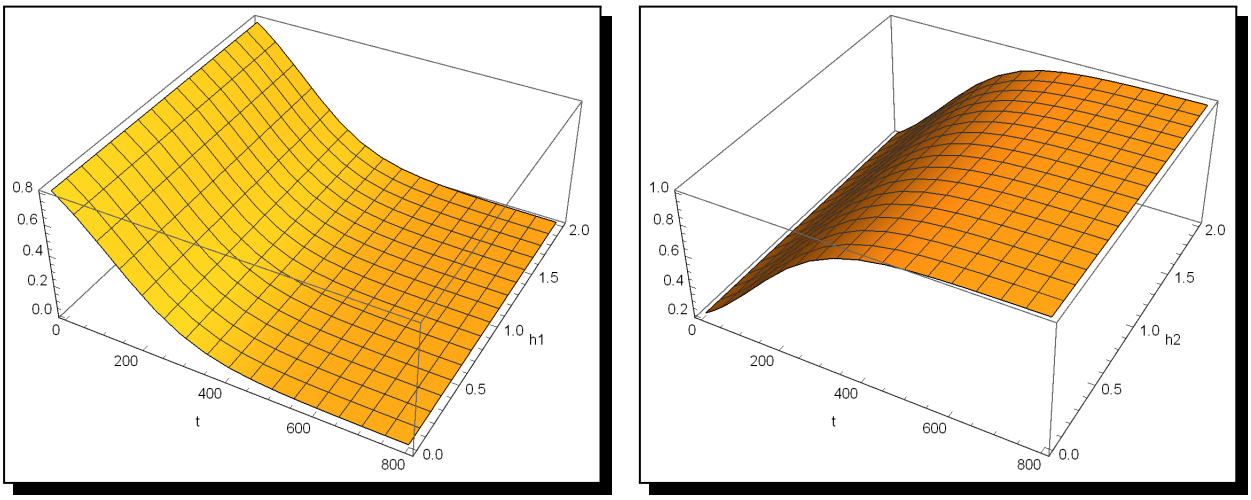
Figure 1. Analytical Solution of the model with Immunotherpy

This shows that our system is locally asymptotically stable because all Eigen values are negative. In Figure 1 show that the competence of immunotherapy model is represented analytically. Figure 1(a) clearly shows that the proliferation of glial cells which is increasing

gradually. Figure 1(b) shows the glioma cells suddenly decrease when CD8+ T cells counting is increasing in Figure 1(c). Finally, we conclude that this immunotherapy treatments can eliminate tumor cells while increasing the concentration of glial cells.

5. Numerical Simulations

The system (2.5) will be discussed in this part, and it will be solved using 4th order Runge-Kutta method. The numerical simulation is also completed by means of select out the parameter values represented in Tables 1 and 2 with initial conditions $h_1(0) = \frac{9}{10}, h_2(0) = \frac{1}{10}$, $m_1(0) = \frac{55}{100}$, $m_2(0) = \frac{2}{10}$. We have chosen two categories to analyze numerically for our model: without treatment and with immunotherapy. First, we now consider without treatment. Figure 2 show the result of the system without treatment. At this stage, the stability analysis showed that glial cells have decreased in Figure 2(a) because of gliomas gradually maximum size in Figure 2(b). This has happened at this stage because no treatment has been provided. So, next we recruit immunotherapy treatment for killing tumor cells.



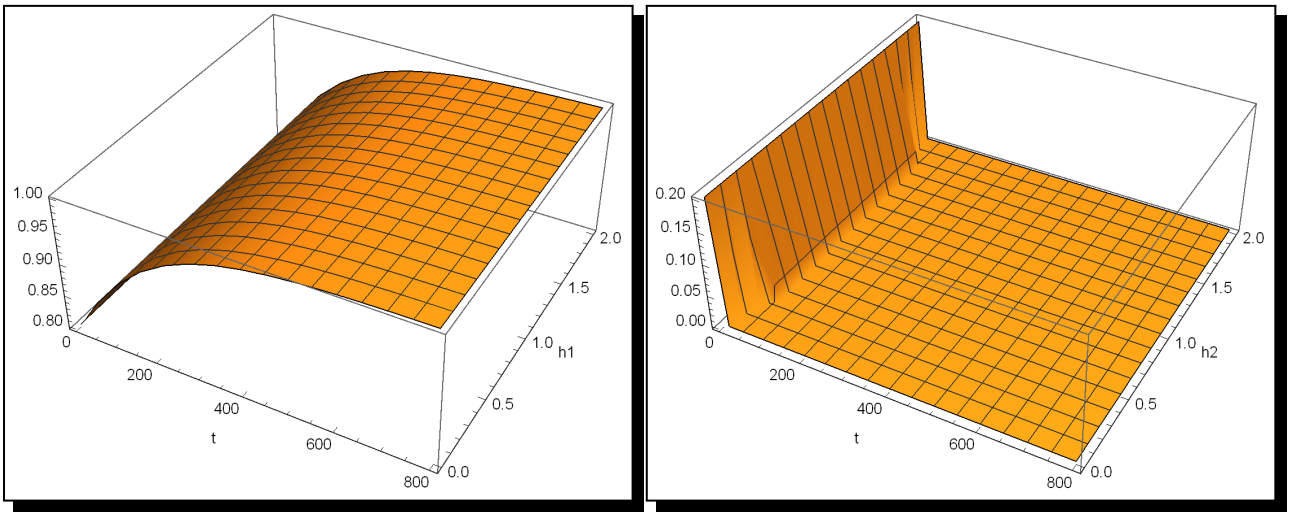
(a) Decrement of glial cells **(b)** Increment of glioma cells

Figure 2. Numerical solution of the model without any therapy

At this time, by providing immunotherapy treatment. We illustrate the findings for the scenario where the treatment regimens were used in Figure 3. This result can be seen in Figure 3(a), where glial cells are shown multiplying rapidly while decreasing tumor cells Figure 3(b) and Figure 3(c) shows that the concentration of CD8+ T cells are also increasing gradually.

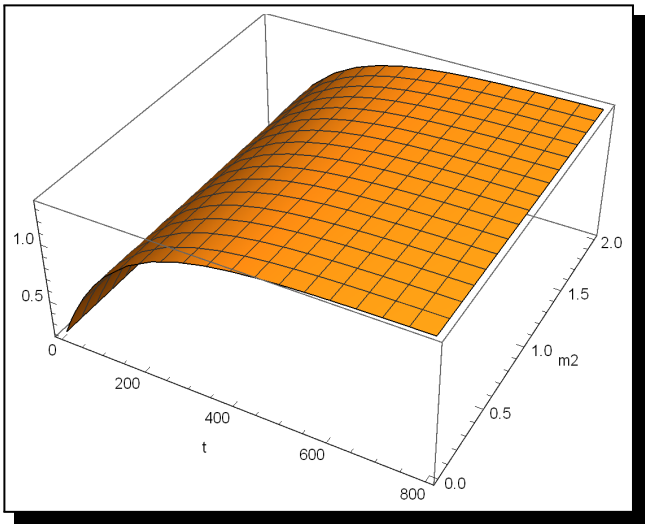
6. Discussion and Conclusion

In this paper, we proposed a mathematical model to observe the dynamics of the cancer cells' interplay with immunotherapy. We take into the $H_2(t)$ Cancer cells, $H_1(t)$ glial cells, $M_1(t)$ macrophages, $M_2(t)$ CD8+ T cells. In this nonlinear system, we couldn't get a exact solution.



(a) Increment of glial cells

(b) Decrement of glioma cells



(c) Increment of CD8+ T cells

Figure 3. Numerical solution of the model with immunotherapy

So we should cast off this situation. Therefore we recommend the linearization technique for changing nonlinear to linear. An analytical answer for the linearized system is picked up by way of the usage of a variation of the parameter formula. The steadiness of the linear version has been discussed. We construct a characteristics equation and after solve this we could get Eigen values. Next, our system is locally asymptotically stable on account of all our Eigen values are less than zero. Figures 1(a) and 1(c) show that density of glial cells and CD8+ T cells are Increasing while decreasing the density of gliomas cells in Figure 1(b).

We appear out for a numerical simulation for the system of equations. Numerical Simulations are constructed into two different categories. First, we now consider without treatment Figure 2 show the result of the system without treatment. Figure 2(a) shows decrement of glial cells because increment in glioma cell counting in Figure 2(b). Next, we consider the system (2.5)

with immunotherapy, Figures 3(a) and 3(c) show that proliferation of glial and CD8+ T cells while decreasing the concentration of Cancer cells in Figure 3(b).

While comparing Figures 1 and 3, we conclude that the numerical effects are similar to analytical consequences. We believe that the mathematical modeling is interplaying between most cancers cells and immunotherapy, constitutes a step in the direction of enhancing techniques for the curing of malignant tumors.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

All the authors contributed significantly in writing this article. The authors read and approved the final manuscript.

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