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Analytical and Numerical Solutions for Healthy Cells Interaction between Glioma and Immunotherapy

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ABSTRACT: In this article, we go into mathematical modeling applying a system of differential equations, that explains a interaction of healthy cells, Glioma cells, 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

I. INTRODUCTION

Primary malignant gliomas in adults (MG) belong to the worst types of cancer. For Grade IV GBM, the median survival ranges from one year to three to four years. For grade III MG, 5 years [21, 22]. They have genomic their behaviour exhibits volatility, variety, and infiltration located in a secure area outside of the blood–brain barrier (BBB),MG are resistant to traditional therapies, such as Radiation therapy, chemotherapy, and surgery. As a result, researchers are looking for new treatments, including immunotherapy provide a chance for survival.

Passively aCTL immunotherapy, which is but technically more challenging, solves two fundamental issues with systemic immunotherapy: (1) it is not reliant on the patient's own, often anergic immune system; and (2) cerebral infusion crosses the BBB. According to Prof. Carol Kruse (Sidney Kimmel Cancer Centre), in-person contact, the aforementioned clinical study was successful since two of the grade III patients lived for at least 12 years following therapy and one patient survived for 40 months after treatment. All GBM patients, however, passed away within afew months. The failure of GBM immunotherapy and the variance in the treatment of grade III MG suggest to a significant distinction in the system dynamics that characterise the two indications. By comparing the response rates regulating the two processes, this distinction may be made clearer. In addition to cytotoxic processes, cytokine modulation, extracellular matrix proteins involved in tumour and immune cell migration, as well as negative and positive feedbacks via paracrine and autocrine factors, the dynamics of tumor-immune system interactions are complicated. Different strategies are used by tumour cells to avoid the immune response. One of these is a sharp decline in the expression of major histocompatibility complex (MHC) molecules on their surface [35, 48], which makes it harder for cytotoxic T cells (CD8+) to recognise them. TGF-b, prostaglandin E, and interleukin (IL)-10 are examples of tumor-produced substances that may inhibit helper T lymphocytes (CD4+), as well as activate and mobilise regulatory T cells (Tregs). TGF-b has a significant role in immunotherapy resistance, notably in the context of CTL treatment resistance [9, 12, 13, 44], and it also exhibits a negative connection with dendritic cell responses to immunotherapy [27].

The existence of the selective BBB in the central nervous system (CNS) affects the cellular interactions between the immune system and malignancy. The only T cells that can enter the brain are active ones [17]. Brain-infiltrating lymphocytes may become less active or may primarily be of the immunosuppressive Treg type [2, 18, 34, 39]. Additionally, the CNS's typically high amounts of the cytokine TGF-b may affect how they operate [17]. Antigen-presenting cells (APCs) are able to

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produce IL-1 and MHC class II less often when TGF-b is present [40, 42]. TGF-b also inhibits CTL stimulation and growth. Other inflammatory substances, such as IFN-c, which may boost production of MHC class I and class II molecules on the surface of tumour cells and microglia, can counteract this down-regulation [8, 31, 37, 47]. Additionally, T cell migration across the BBB is accelerated by IFN-c [17].

The novelty of this paper is to know about analytical and numerical solutions for glial cells interaction between immunotherapy and cancer cells . In this paper, we have introduced a new nonlinear differential equation that includes healthy (Glial) cells in the described model [9]. While using Immunotherapy, we know about the competition between healthy cells and cancer cells.

We organized the work as follows: In section two, we introduce new system of nonlinear differential equation using Immunotherapy. In section three,

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.

II. MATHEMATICAL MODELLING

We introduce a new system of differential equations in the described model [9]. In this dynamic model, we consider Glioma (cancer) and Glial (healthy) cells, and their interactions with CD8+ T cells. So, the modified system defined as follows:

$$\frac{dP}{dt} = \delta_1 P(t)(1-\frac{P(t)}{N_1}) - \overline{\phi_1} P(t)Q(t), \quad (1)$$

$$\frac{dQ}{dt} = \delta_2 Q(t)(1-\frac{Q(t)}{N_2}) - \overline{\phi_2} P(tQ(t) - \frac{\overline{\alpha_1} Q(t)R(t)}{Q(t)+\overline{K_1}}, \quad (2)$$

$$\frac{dR}{dt} = \frac{\beta Q(t)R(t)}{Q(t)+\overline{K_2}} - \mu R(t) - \frac{\overline{\alpha_2} Q(t)R(t)}{Q(t)+\overline{K_3}} + A_1 B_1(t). \quad (3)$$

Our model consists of three different components, namely density of Glial cells (P(t)(Kg/m3)), the concentration of cancer cells (Q(t)(Kg/m3)), the concentrations of CD8+T cells (R(t)(Kg/m3)).

First term in equations (1), (2), represents the proliferation of Glial cells, Glioma cells. Second term in equations (1) and (2) represents interaction between healthy and cancer cells. Third term in equation (2) represents elimination of Q(t) owing to interaction with R(t). In equation (3), 1st term represents the imbued R(t) recruited by malignant Q(t), 2nd term represents decay rate of R(t) owing to inflammatory reaction in brain naturally, 3rd term represents eliminations of R(t) by Q(t), and last term A_1 is strength of the treatment, B_1 term is an external source of R(t).

Parameter	Values	Source & Description
δ_1	0.0068 day−1	Proliferation rate [22, 23]
δ_2	0.012 day−1	Proliferation rate [22, 23]
$\overline{\phi_1}$	3.6 × 10-5 day−1	Competition Coefficients [22]
$\overline{\phi_2}$	3.6 × 10-6 day−1	Competition Coefficients [22]

Table: 1. Values of Parameter

The normalized model of the system of equation from (1)-(3) is given by

$$\begin{cases} \frac{dp}{dt} = \delta_1 p(t)(1-p(t)) - \phi_1 p(t)q(t), \\ \frac{dq}{dt} = \delta_2 q(t)(1-q(t)) - \phi_2 p(t)q(t) - \frac{\alpha_1 q(t)r(t)}{q(t)+k_1}, \\ \frac{dr}{dt} = \frac{\beta q(t)r(t)}{q(t)+k_2} - \mu r(t) - \frac{\alpha_2 q(t)r(t)}{q(t)+k_3} + A_1 B_1(t). \end{cases} \quad (4)$$

Where,

$$p(t) = \frac{P(t)}{N_1}, \quad q(t) = \frac{Q(t)}{N_2}, \quad r(t) = \frac{R(t)}{\overline{K_2}},$$

$$\phi_1 = \overline{\phi_1} N_2, \quad \phi_2 = \overline{\phi_2} N_1, \quad \alpha_1 = \frac{\overline{\alpha_1}\,\overline{K_2}}{\overline{K_1}}, \quad k_1 = \frac{\overline{K_1}}{N_2},$$

$$k_2 = \frac{\overline{K_2}}{N_2}, \quad k_3 = \frac{\overline{K_3}}{N_2}.$$

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Parameter	Values	Source
α_1	0.069943	[24]
k_1	0.90305	[25]
β_1	0.12445	[26]
k_2	2.8743	[26]
μ	0.0074	[26]
α_2	0.01694	[25]
k_3	0.378918	[25]

Table: 2. Values of Parameter

III. ANALYTICAL METHOD

Definition:

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

Theorem:

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

The nonlinear differential system (4) 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.

Finding the equilibrium point

System (4) has some points of equilibrium $E(\bar{p}, \bar{q}, \bar{r})$ which are obtain by solving the system of equations $\dot{p} = \dot{q} = \dot{r} = 0$

$$\delta_1 p(t)(1-p(t)) - \phi_1 p(t)q(t) = 0 \quad (5)$$

$$\delta_2 q(t)(1-q(t)) - \phi_2 p(t)q(t) - \frac{\alpha_1 q(t)r(t)}{q(t)+k_1} = 0 \quad (6)$$

$$\frac{\beta q(t)r(t)}{q(t)+k_2} - \mu r(t) - \frac{\alpha_2 q(t)r(t)}{q(t)+k_3} + A_1B_1(t) = 0 \quad (7)$$

On solving the above system of equations, we get

$$p(t) = \frac{\lambda_1 - \phi_1 q(t)}{\lambda_1},$$

$$q(t) = \left(\frac{(q+k_2)\left(\mu + \frac{\alpha q}{q+k_3} - A_1B_1(t)\right)}{\beta} \right),$$

$$r(t) = \left(\frac{(q+k_1)(\lambda_2 - \lambda_2 q - \phi_2\beta)}{\alpha} \right).$$

Using the parameter values in Tables- 1 and 2, we consider the interior equilibrium point of the system (4)

$$E(\bar{p}, \bar{q}, \bar{r}) = (1,0,1.62162)$$

Finding the Jacobian matrix at the equilibrium point

The nonlinear system (4) can be written as,

$$\begin{cases} \frac{dp}{dt} = \delta_1 p(t)(1-p(t)) - \phi_1 p(t)q(t) = f_1(p,q,r) \\ \frac{dq}{dt} = \delta_2 q(t)(1-q(t)) - \phi_2 p(t)q(t) - \frac{\alpha_1 q(t)r(t)}{q(t)+k_1} = f_2(p,q,r) \\ \frac{dr}{dt} = \frac{\beta q(t)r(t)}{q(t)+k_2} - \mu r(t) - \frac{\alpha_2 q(t)r(t)}{q(t)+k_3} + A_1B_1(t) = f_3(p,q,r) \end{cases} \quad (9)$$

The nonlinear system (9) can be approximated into a linear system as follows:

$$\begin{cases} \frac{dp(t)}{dt} = f_1(p,q,r) \approx f_1(\bar{p},\bar{q},\bar{r}) + \frac{\partial f_1}{\partial p}(p-\bar{p}) + \frac{\partial f_1}{\partial q}(q-\bar{q}) \\ \qquad + \frac{\partial f_1}{\partial r}(r-\bar{r}), \\ \frac{dq(t)}{dt} = f_2(p,q,r) \approx f_2(\bar{p},\bar{q},\bar{r}) + \frac{\partial f_2}{\partial p}(p-\bar{p}) + \frac{\partial f_2}{\partial q}(q-\bar{q}) \\ \qquad + \frac{\partial f_2}{\partial r}(r-\bar{r}), \\ \frac{dr(t)}{dt} = f_3(p,q,r) \approx f_3(\bar{p},\bar{q},\bar{r}) + \frac{\partial f_3}{\partial p}(p-\bar{p}) + \frac{\partial f_3}{\partial q}(q-\bar{q}) \\ \qquad + \frac{\partial f_3}{\partial r}(r-\bar{r}). \end{cases} \quad (10)$$

At the equilibrium point,

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$$f_i = (\bar{p}, \bar{q}, \bar{r}) = 0, \qquad i = 1,2,3.$$

Thus, we have the system as

$$\begin{cases} \frac{dp}{dt} = g_{11}(p-\bar{p}) - \phi_1 p(q-\bar{q}), \\ \frac{dq}{dt} = -\phi_2 q(p-\bar{p}) + g_{12}(q-\bar{q}) + g_{13}(r-\bar{r}), \\ \frac{dr}{dt} = g_{14}(q-\bar{q}) + g_{15}(r-\bar{r}). \end{cases} \tag{11}$$

Where,

$$g_{11} = \delta_1 - 2\delta_1 p(t) - \phi_1 q(t),$$

$$g_{12} = \delta_2 - 2\delta_2 q(t) - \phi_2 p(t) - \frac{k_1(\alpha_1 r(t))}{(k_1 + q(t))^2}, g_{13} = -\frac{\alpha_1 q(t)}{q(t)+k_1},$$

$$g_{14} = \frac{\beta k_2 r(t)}{(k_2 + q(t))^2} - \frac{\alpha_2 k_3 r(t)}{(q(t)+k_3)^2},$$

$$g_{15} = \frac{\beta q(t)}{(k_2 + q(t))} - \mu - \frac{\alpha_2 q(t)}{q(t)+k_3}.$$

is a linearized system.

Hence system can be written as

$$\begin{bmatrix} p' \\ q' \\ r' \end{bmatrix} = \begin{bmatrix} q_{11} & -\phi_1 p(t) & 0 \\ -\phi_2 q(t) & q_{12} & q_{13} \\ 0 & q_{14} & q_{15} \end{bmatrix} \begin{bmatrix} p-\bar{p} \\ q-\bar{q} \\ r-\bar{r} \end{bmatrix}, \tag{12}$$

Where the Jacobian matrix is given by,

$$J = \begin{bmatrix} q_{11} & -\phi_1 p(t) & 0 \\ -\phi_2 q(t) & q_{12} & q_{13} \\ 0 & q_{14} & q_{15} \end{bmatrix}, \tag{13}$$

Around the equilibrium point

(1, 0, 1.62162)

From the table 1 and 2 the linear system can be written as

$$\begin{bmatrix} p' \\ q' \\ r' \end{bmatrix} = \begin{bmatrix} q_{11} & -\phi_1 p(t) & 0 \\ -\phi_2 q(t) & q_{12} & q_{13} \\ 0 & q_{14} & q_{15} \end{bmatrix} \begin{bmatrix} p \\ q \\ r \end{bmatrix} + \begin{bmatrix} b_{11} \\ b_{12} \\ b_{13} \end{bmatrix}, \tag{14}$$

Where,

$b_{11} = 0.0068, b_{12} = 0, b_{13} = 0.012.$

The fundamental matrix of the system is given by

$$\varphi(t) = \begin{bmatrix} w_{11}e^{-\lambda_1 t} & w_{12}e^{-\lambda_2 t} & w_{13}e^{-\lambda_3 t} \\ w_{21}e^{-\lambda_1 t} & w_{22}e^{-\lambda_2 t} & w_{23}e^{-\lambda_3 t} \\ w_{31}e^{-\lambda_1 t} & w_{32}e^{-\lambda_1 t} & w_{33}e^{-\lambda_3 t} \end{bmatrix}, \tag{15}$$

Where,

$\lambda_1 = -4.91889, w_{11} = 0.0036644, w_{21} = 0.999993,$
$w_{31} = 0.000459376, \lambda_2 = -0.0074, w_{21} = w_{22} = 0, w_{23} = 1,$
$\lambda_3 = -0.0068, w_{31} = 1, w_{32} = w_{33} = 0.$

By variation of constant formula, the analytical solutions of the linear system is given by

$$\begin{cases} \frac{dp(t)}{dt} = a_{11} + a_{12}e^{\lambda_1 t} + a_{14}, \\ \frac{dq(t)}{dt} = a_{22}e^{\lambda_2 t}, \\ \frac{dr(t)}{dt} = a_{31} + a_{32}e^{\lambda_1 t} + a_{33}e^{\lambda_2 t}. \end{cases} \tag{16}$$

Where,

$a_{11} = 1, a_{12} = 0.000732884, a_{14} = -0.200733,$
$a_{22} = 0.2, a_{31} = 1.62162, a_{32} = 0.000091857, a_{33} = -1.42171.$

IV. STABILITY ANALYSIS

The characteristic equation of the linearized system is given by $|J - \lambda I| = 0$

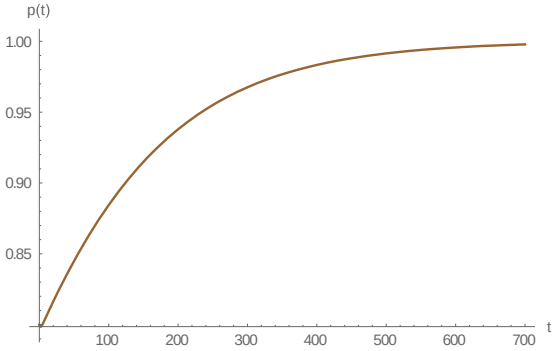
$$\lambda^3 + C_1\lambda^2 + C_2\lambda + C_3 = 0. \tag{17}$$

$C_1 = -4.93309, C_2 = 0.0698985, C_3 = 0.000248.$

The Eigenvalues of the Jacobian matrix are

$\lambda_1 = -4.91889, \lambda_2 = -0.0074, \lambda_3 = -0.0068.$

1.(a)



1.(b)

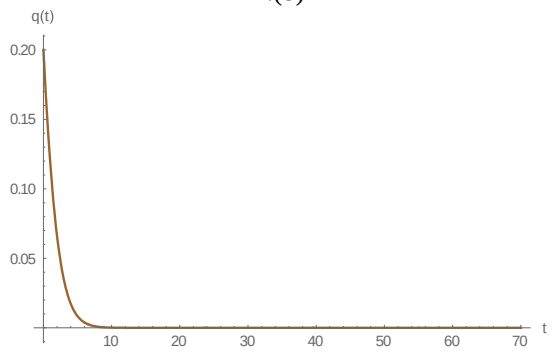


Fig.1 Analytical solutions for a) Glial cells, (b) Cancer cells, with immunotherapy.

Here all the Eigen value are negative. Hence the system is locally asymptotically stable.

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The Competence of the Immunotherapy model is shown analytically in Fig. 1. Immunotherapy treatment can be assigned to eliminate deadly dangerous tumors cells.

The proliferation of glial cells is also explained by Fig. 1(a), while decreasing the concentration of cancer cells in Fig.1(b).

V. NUMERICAL SIMULATION

The system (4) 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 p(0) = 0.80 , q(0) = 0.2 , r(0) = 0.20.

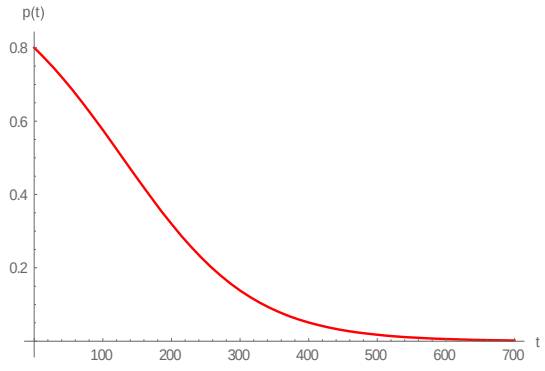
We have chosen two categories to analyze numerically for our model: without treatment and with Immunotherapy. First, we now consider without treatment. Fig.2 show the result of the system without treatment. At this stage, the stability analysis showed that Glial cells have decreased in Fig.2(a) because of Gliomas gradually maximum size in Fig.2(b).

This has happened at this stage because no treatment has been provided. So, next we recruit immunotherapy treatment for killing tumor cells.

At this time, by providing Immunotherapy treatment. We illustrate the findings for the scenario where the treatment regimens were used in Fig.3.

This result can be seen in Fig.3(a), where glial cells are shown multiplying rapidly while decreasing tumor cells Fig.3(b).

2.(a) Decrement of Healthy cells



2.(b) Increment of Cancer cells

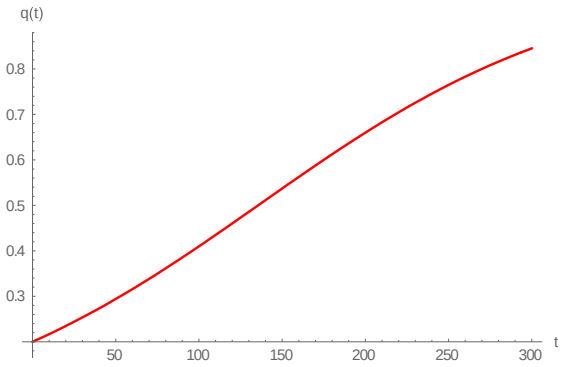
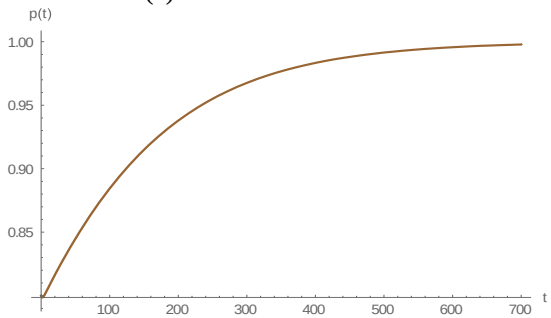


Fig. 2 Numerical solution of model without any therapy.

3.(a)Increment of Glial cells



3.(b)Decrement of Glioma cells

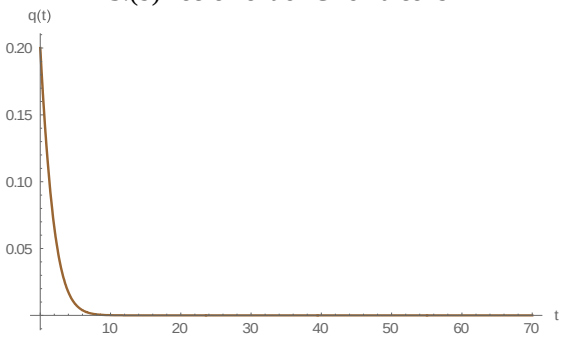


Figure 3.Numerical Solution of the model with Immunotherapy.

VI. 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 q(t) Cancer cells, p(t) Glial cells, r(t) CD8+ T cells. In this nonlinear system, we couldn't get a exact solution. 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. Figs.1(a) shows that density of Glial cells are Increasing while decreasing the density of Gliomas cells in Fig. 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 Figs. 2(a) and 2(b) show the result of the system without treatment. Fig. 2(a) shows decrement of Glial cells because increment in Glioma cell counting in Fig.2(b). Next, we consider the system (4) with Immunotherapy, Figs. 3(a) shows that proliferation of Glial decreasing the concentration of Cancer cells in Fig.3(b). While comparing Figs.(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.

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