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Stability Analysis for Healthy Cells Interaction between Glioma and Immunotherapy

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Abstract : In this article, we propose a new system of differential equations, that explains a interaction of Glial (healthy) cells, Glioma (Cancer) cells, CD8+T cells, and Immunotherapy. Stability Analysis is discussed under two categories:, without any treatment, and with immunotherapy treatment. Moreover, numerical simulations are also given for our proposed model in three different categories. Finally, the last section explains discussion and conclusion.

IndexTerms **- Brain tumor, Immunotherapy, Glial cells, Glioma cells, Stability Analysis.**

I. INTRODUCTION

Immunotherapies are growing in significance in the multifaceted strategies being developed to treat certain cancers [1]. By enhancing the anticancer effect Immunotherapy may strengthen the function of the immune system. The body's own built-in capacity to fight cancer. Prior decades, the field of cancer immunology has advanced more and more converted into immuno based therapeutics being tested in humans to the treatment of cancer, such as the administration of monoclonal antibodies and the adoptive transfer of cytotoxic T cells. (ACT) [2, 3].

Specifically, this method [4] requires the identification of autologous or allogeneic cells having anticancer activity, which are then administered to patients with cancer, often combined with the right growth factors (like IL-2) to encourage their survival. Only a modest number of identifications are essential. Producing anticancer cells with the necessary characteristics that can then be multiplied in size ex vivo for therapy [5]. Tests performed in vitro can pinpoint the precise populations and effector functions necessary for the reversal of cancer, which may then choose for enlargement [6]. The activated cells in the brain are the Endogenous inhibitory factors may be removed in the laboratory and therefore may be encouraged to display the necessary anticancer effector functions.

Clinical research has recently shown that using the immune system's strength in addition to conventional chemotherapy may have some advantages [7]. Chemotherapy is now included in the treatment plans of the majority of cancer patients as a standard treatment. Chemotherapy seeks to reduce initial tumor sizes, limit tumor development, and eradicate tumor cells that might have metastasized (spread) from the main tumor to other body areas.

There are already more than 50 different chemotherapy medications on the market, and several more are being investigated to see whether they can also kill cancer cells [8]. Chemotherapy destroys normal fast-dividing cells as well as cancer cells, which has major negative effects on patients even though it is one of the main therapeutic options for cancer patients.

The novelty of this paper is to know about growth of healthy cells while interaction between cancer and interaction. 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, stability analysis is discussed. In Section 4, we discuss the numerical simulations and Section 5 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 A1 is strength of the treatment, B1 term is an external source of R(t).

Parameter	Values	Source & Description
δ_1	0.0068 day−1	Proliferation rate [10, 11]
δ_2	0.012 day−1	Proliferation rate [10, 11]
$\overline{\phi_1}$	3.6 × 10-5 day−1	Competition Coefficients [10]
$\overline{\phi_2}$	3.6 × 10-6 day−1	Competition Coefficients [10]

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,

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

$$\phi_1 = \overline{\phi_1} N_2, \quad \phi_2 = \overline{\phi_2} N_1, \quad \alpha_1 = \frac{\overline{\alpha_1}\,\overline{K_2}}{\overline{K_1}}, \quad \mathrm{k}_1 = \frac{\overline{K_1}}{N_2},$$

$$\mathrm{k}_2 = \frac{\overline{K_2}}{N_2}, \quad \mathrm{k}_3 = \frac{\overline{K_3}}{N_2}.$$

Parameter	Values	Source
α_1	0.069943	[12]
k_1	0.90305	[13]
β_1	0.12445	[14]
k_2	2.8743	[14]
μ	0.0074	[12]
α_2	0.01694	[13]
k_3	0.378918	[13]

Table: 2. Values of Parameter

III. LOCAL STABILITY ANALYSIS

Our focus is on their stability of the system of the equation.

Equilibria and Local Stabiility analysis:

The eigenvalues λ_i (i = 1, 2, 3) of the variational matrix decide the local stability of the system (4) around each of the singular points

$$J = \begin{bmatrix} M_{11} & \phi_1 p(t) & 0 \\ \phi_2 q(t) & M_{12} & \dfrac{-\alpha_1 q(t)}{q(t)+k_1} \\ 0 & M_{13} & M_{14} \end{bmatrix}$$

Where,

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

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

$$M_{13} = \frac{\beta k_2 r(t)}{(q(t)+k_2)^2} - \frac{\alpha_2 k_3 r(t)}{(q(t)+k_3)^2},$$

$$M_{14} = \frac{\beta q(t)}{k_2 + q(t)} - \mu - \frac{\alpha_2 q(t)}{q(t)+k_3}.$$

The existence of equilibrium points and their stability analysis are discussed further below in three types: ˆ

- Without therapy ˆ
- With immunotherapy

Without therapy:

The system (4) has a ”extinct” equilibrium point $E_0(0, 0, 0)$ for any set of parameters, in which all four cell populations are dead

$$J = \begin{bmatrix} \delta_1 & 0 & 0 \\ 0 & \delta_2 & 0 \\ 0 & 0 & -\mu \end{bmatrix}$$

The corresponding eigenvalues for this equilibrium point E_0 are

$$\lambda_1 = \delta_1 > 0, \quad \lambda_2 = \delta_2 > 0, \quad \lambda_3 = -\mu < 0.$$

Here, two of our Eigen values are greater than zero. This clearly shows that the our equilibrium is unstable .

With Immunotherapy

The system (4) has a "extinct" equilibrium point E_1 (1, 0, 1.62162) for any set of parameters

$$J = \begin{bmatrix} -\delta_1 & 0 & 0 \\ 0 & M_{15} & 0 \\ 0 & M_{16} & -\mu \end{bmatrix}$$

Where,

$$M_{15} = \frac{-\phi_2 k_1 + \delta_2 k_1 - \alpha_1 r(t)}{k_1}.$$

$$M_{16} = \frac{\beta r(t)}{k_2} - \frac{\alpha_2 r(t)}{k_3}$$

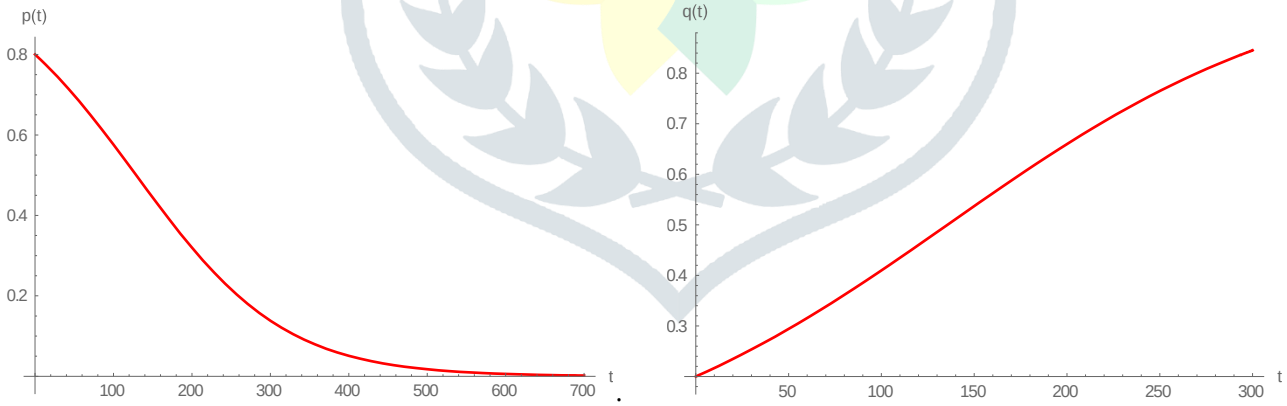
The corresponding eigenvalues for this equilibrium point E_1 are

$$\lambda_1 = -\delta_1 < 0, \quad \lambda_2 = M_{15} < 0, \quad \lambda_3 = -\mu < 0.$$

But this time, all of our Eigen values are less than zero. Our system is locally asymptotically stable.

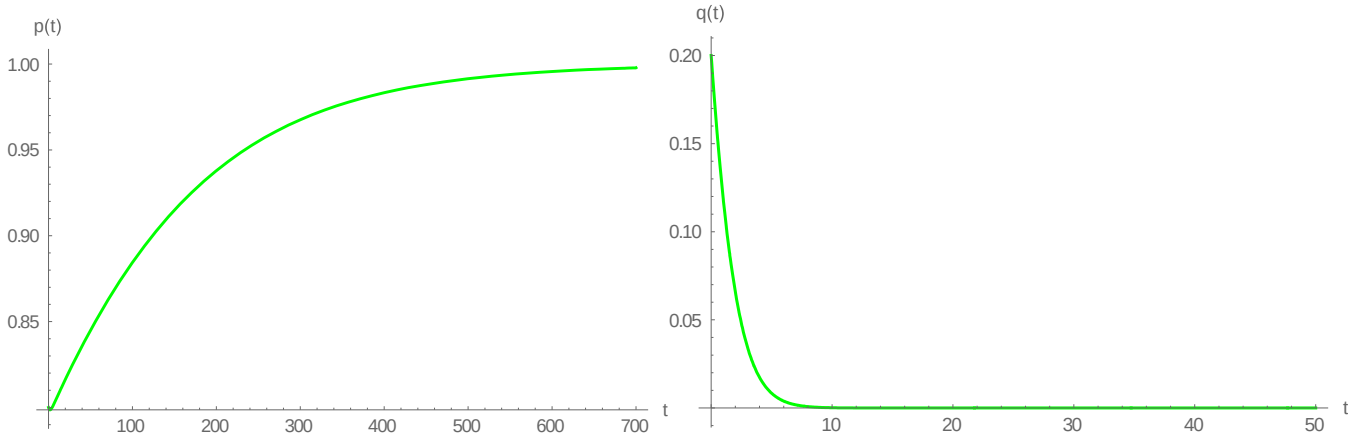
IV. NUMERICAL SIMULATION

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 analyse numerically for our model: without treatment and with Immunotherapy. First, we now consider without treatment. Fig.1 show the result of the system without treatment. At this stage, the stability analysis showed that Glial cells have decreased in Fig.1(a) because of Gliomas gradually maximum size in Fig.1(b). This has happened at this stage because no treatment has been provided. So, next we recruit immunotherapy treatment for killing tumour cells. At this time, by providing Immunotherapy treatment. We illustrate the findings for the scenario where the treatment regimens were used in Fig.2. This result can be seen in Fig.2(a), where glial cells are shown multiplying rapidly while decreasing tumour cells Fig.2(b)



a)Decrement of Healthy cells b) Increment of Cancer cells

Fig. 1 Numerical solution of model without any therapy



(a) Increment of Glial cells (b) Decrement of Glioma cells

Figure 2: Numerical Solution of the model with Immunotherapy

V. 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. 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. 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 Fig.1 show the result of the system without treatment. Fig.1(a) shows decrement of Glial cells because increment in Glioma cell counting in Fig.1(b). Next, we consider the system (4) with Immunotherapy, Figs.2(a) shows that proliferation of Glial while decreasing the concentration of Cancer cells in Fig.2(b). 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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