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Steady States and Stability Analysis of Brain Tumour Growth Model

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Abstract:- Brain tumors have been reported to be among the highest causes of mortality. Based on the information from the Central Brain Tumor Registry of the United States (CBTRUS), it was projected that about 84,000 new cases of primary malignant and non-malignant brain and other central nervous system tumors were expected to be diagnosed in the United states in 2021.

Brain Tumour is one of the illness that affect the Central Nervous System (CNS). Its effects are so critical and thereby requires an overhauling treatment. Over the years, different treatments have been employed to remove or alleviate the effects of this tumour. One of such treatments is the Chemotherapy approach.

In this work, growth of brain tumour together with its treatment was modeled as a system of nonlinear ordinary differential equations. The existence and uniqueness of solution of this system were established. The steady states (equilibrium points) of this system were obtained and used to analyze its stability. The result shows that the system is locally asymptotically stable if the chemotherapy infusion rate $\Phi > \frac{\zeta\omega_1(1-2\bar{g})(a_1+\bar{g})^2}{a_1p_1}$ and $\Phi > \frac{a_2\zeta(\omega_2-\beta_2\bar{g})}{p_2}$ as well as $\Phi > \frac{\zeta\omega_2(1-2\bar{c})(a_2+\bar{c})^2}{a_2p_2}$ and $\Phi > \frac{a_1\zeta(\omega_1-\beta_1\bar{c})}{p_1}$

Keywords:- *Brain, Tumour, Chemotherapy, Steady States, Stability.*

I. INTRODUCTION

Brain tumour is an abnormal growth or mass of cells in or around the brain. It is also called a central nervous system tumour. Brain tumours can be malignant (cancerous) or benign (not cancerous). Some tumours grow quickly; others are slow-growing. Acccording to Elshaikh et al (2021), brain tumors have been reported to be among the highest causes of mortality. In their work, they concluded that the incidences of primary malignant brain tumours are slightly more in men than women, while women have higher non-malignant tumours, for example meningiomas. The rates, based on their findings are also higher in developed countries but this could be attributed to the advanced diagnostic facilities. In the work of De Angelis (2001), Gliomas are the common tumours in adults and paediatric age group. In the adult population, Anaplastic Astrocytoma and Glioblastoma Multiforme are the most common glial tumours with an annual incidence of 3 to 4 per 100,000 populations.

In the study of Chikani et al (2020), it was concluded that Metastatic brain tumours (MBTs) were the most common brain neoplasms viewed clinically and were often associated with poor outcomes. In most cases, a brain tumour diagnosis requires immediate surgery or alternative treatment. The standard treatments for brain tumours include and not limited to surgery, radiotherapy and chemotherapy. Advanced treatments such as targeted therapy, stereo-tactic radiosurgery and robotic surgery are also being used to treat brain tumours. In addition, Palliative care as well as neuro-rehabilitaion services, helps support the patient's recovery. Different sections of the brain perform different tasks, as a result brain tumour symptoms vary depending on the location of the tumour.

The aim of this work is to formulate and analyse a mathematical model of brain tumour. The objectives are to:

- Develop a model in form of nonlinear differential equations
- Verify the existence and uniqueness of the solution of the model
- Obtain the steady states (equilibrium points) of the formulated model
- Perform the stability analysis of the steady states

II. LITERATURE REVIEW

In this section, related literature of mathematical modelling of brain tumours are reviewed.

Ladkat et al (2022) provided an automated brain tumor segmentation method based on a mathematical model and deep neural networks (DNNs). Their study includes a mathematical model for tumor pixel enhancement as and a 3D attention U-Net to separate the pixels. In the work of Jaroudi (2017), mathematical method for the inverse problem of locating the brain tumour source (origin) based on the reaction-diffusion model was discussed. He gave full 3-dimensional simulations of the tumour in time on two types of data, the 3d Shepp-Logan phantom and an MRI T1-weighted brain scan from the Internet Brain Segmentation Repository (IBSR). The simulations, he obtained numerically by the standard finite difference discretization of the space and time-derivatives, generating a simplistic approach that performs well. In a research carried out by Trobia et al (2020), a mathematical model which describes glia-neuron interaction, glioma, and chemotherapeutic agent was studied. In their research, they considered drug sensitive and resistant glioma cells. Their result showed that

continuous and pulsed chemotherapy can terminate glioma cells with a minimal loss of neurons.

Suveges et al (2021) studied Mathematical Modelling of Glioblastomas Invasion within the Brain using a 3D Multi-Scale Moving-Boundary Approach. They used T1 weighted and DTI scans as initial conditions for their model. Their results show that including an anisotropic diffusion term may sometimes lead to significant changes in tumour morphology, while sometimes has no effect. Chikani et al (2020) conducted a year study of patients with MBT at the neurosurgery unit of the University of Nigeria Teaching Hospital, Enugu. Their findings show that of the 31 patients with MBTs, 58% were female and 42% male. The most common presenting features were limb weakness (77.4%), headache (58.1%), and personality changes (54.8%). Wei (2018) worked on modified mathematical model of tumour growth with combined immune-therapy and chemotherapy treatments. Search time, which was neglected in his previous published model, was included in the new model. The model exhibits bi-stability where a tumour-cell population threshold exists.

Khan et al (2022) proposed a Hierarchical Deep Learning-Based Brain Tumor (HDL2BT) classification with the help of CNN for the detection and classification of brain tumors. The proposed system categorizes the tumor into four types: glioma, meningioma, pituitary, and no-tumor. Their suggested model achieves 92% exactness, making it better than earlier approaches for detection and segmentation of brain tumors. In the work of Ganji et al (2021), they described brain tumor growth (Glioblastomas) under medical treatment by fractional operator. Their model, which is an extension to a simple two-dimensional mathematical model of glioma growth and diffusion is derived from fractional operator, called the Fractional Burgess Equations (FBEs). In their research, Usman et al (2021) solved the equation of Glioblastoma multiforme (GBM) brain tumor model with the effect of treatment using Runge Kutta Fehlberg method. The result of their research shows that the numerical solution to the effect of treatment using the Runge Kutta Fehlberg method has a good accuracy in solving nonlinear common differential equations of GBM brain tumor mode.

Also, Song et al (2020) formulated a model describing tumor-immune cell interactions. Their work centers on the role of the natural killer (NK) cells and CD8+ cytotoxic T lymphocytes (CTLs) in immune surveillance. In their results, obtained experimentally and clinically, they determined part of the model parameters to reduce the model parameter space. From another perspective, Saravanan et al (2022) suggested the convolutional neural network database learning along with neighboring network limitation (CDBLNL) technique for brain tumor image classification in medical image processing domain. Their suggested system was constructed with multilayer-based metadata learning, and they have integrated with CNN layer to deliver the accurate information. As an alternative method of treating GBM, Sun (2018) presented a Tumor Treating Fields (TTFields) which reduces the growth of cancer cells. He formulated a 3-D finite element head model consisting of the scalp, the skull, the dura, the cerebrospinal fluid, and the brain to study the electric field distribution under various applied potentials and electrode configurations

III. RESEARCH METHODOLOGY

Mathematical modelling has been used severally to explain the growth and treatment of brain tumour. There are many treatment approaches which are used to treat tumour, such as surgery, immunotherapy, chemotherapy, radiotherapy, drug therapy and clinical approaches. Here, a model (predator-prey) that represent the growth of brain tumour, together with treatment techniques is formulated. Some mathematical theorems and tools will be used to discuss the qualitative and quantitative analysis of the formulated model.

The model consists of the Glial cells, Tumour (Cancer) cells and the Neurons cells concentrations. It also consists of the concentration of the Chemotherapy agent, which serve as a predator acting on all the cells.

A. The Flow Diagram of the Model

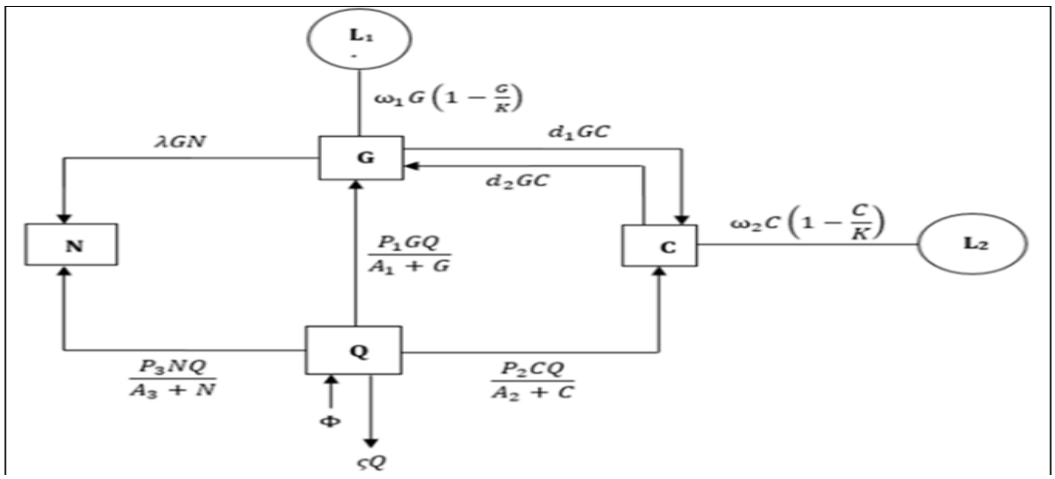

Fig 1 The Flow Diagram of the Model

➢ *Model Equation*

$$\left.\begin{aligned}\frac{dG(t)}{dt} &= \omega_1 G\left(1-\frac{G}{K}\right) - d_1 GC - \frac{P_1 GQ}{A_1+G}\\ \frac{dC(t)}{dt} &= \omega_2 C\left(1-\frac{G}{K}\right) - d_2 GC - \frac{P_1 CQ}{A_2+C}\\ \frac{dN(t)}{dt} &= \lambda GN - \frac{P_3 NQ}{A_3+N}\\ \frac{dQ(t)}{dt} &= \Phi - \zeta Q\end{aligned}\right\} \qquad (3.1.1)$$

➢ *Description of Variables for the Model*

Table 1 Description of Variables for the Model

VARIABLES	DESCRIPTION
$G(t)$	Glial Cells Concentration
$C(t)$	Cancer Cells Concentration
$N(t)$	Neurons Cell Concentration
$Q(t)$	Concentration of the Chemotherapy Agent
$L_1(t)$	Logistic growth of Glial Cells
$L_2(t)$	Logistic growth of Cancer Cells

➢ *Description of Parameters for the Model*

Table 2 Description of Parameters for the Model

PARAMETERS	DESCRIPTION
ω_1	Proliferation rate for Glial cells
ω_2	Proliferation rate for Cancer cells
λ	Loss influence for N due to Glial cells
P_1	Predation coefficient for Glial cells
P_2	Predation coefficient for Cancer cells
P_3	Predation coefficient for Neurons
Φ	Chemotherapy infusion rate
ζ	Chemotherapy washout/absorption rate
A_1, A_2, A_3	Holling type 2
d_1	Competition coefficient between Glial cells and Cancer cells
d_2	Competition coefficient between Cancer cells and Glial cells
K	Carrying capacity

B. Normalization of Variables in the Model Equation

Let

$$g = \frac{G}{K_1},\ c = \frac{C}{K_2},\ n = \frac{N}{K_3} \qquad (3.2.1)$$

Where K_1, K_2 and K_3 are the carrying capacities of the glial, cancer, and neural cells concentration respectively.

Substituting (3.2.1) in (3.1.1), we have:

$$\frac{dG}{dt} = \omega_1 G\left(1 - \frac{G}{K_1}\right) - d_1 GC - \frac{P_1 GQ}{A_1 + G}$$
$$\frac{d}{dt}(gK_1) = \omega_1 (gK_1)(1-g) - d_1 (gK_1)(cK_2) - \frac{P_1 (gK_1)Q}{A_1 + gK_1}$$
$$K_1 \frac{dg}{dt} = K_1 \omega_1 g(1-g) - K_1 K_2 d_1 gc - \frac{K_1 P_1 gQ}{A_1 + gK_1}$$
$$\frac{dg}{dt} = \omega_1 g(1-g) - K_2 d_1 gc - \frac{P_1 gQ}{A_1 + gK_1}$$
$$= \omega_1 g(1-g) - K_2 d_1 gc - \frac{P_1 gQ}{K_1\left(\frac{A_1}{K_1} + g\right)}$$

On simplification, we have

$$\frac{dg(t)}{dt} = \omega_1 g(t)(1 - g(t)) - \beta_1 g(t)c(t) - \frac{p_1 g(t)Q(t)}{a_1 + g(t)} \qquad (3.2.2)$$

Similarly

$$\frac{dC}{dt} = \omega_2 C\left(1 - \frac{C}{K_2}\right) - d_2 GC - \frac{P_2 CQ}{A_2 + C}$$
$$\frac{d}{dt}(cK_2) = \omega_2 (cK_2)(1-c) - d_2 (gK_1)(cK_2) - \frac{P_2 (cK_2)Q}{A_2 + cK_2}$$
$$K_2 \frac{dc}{dt} = K_2 \omega_2 c(1-c) - K_1 K_2 d_2 gc - \frac{K_2 P_2 cQ}{A_2 + cK_2}$$
$$\frac{dc}{dt} = \omega_2 c(1-c) - d_2 K_1 gc - \frac{P_2 cQ}{A_2 + cK_2}$$
$$= \omega_2 c(1-c) - d_2 K_1 gc - \frac{P_2 cQ}{K_2\left(\frac{A_2}{K_2} + c\right)}$$

On simplification, we have

$$\frac{dc(t)}{dt} = \omega_2 c(t)(1 - c(t)) - \beta_2 g(t)c(t) - \frac{p_2 c(t)Q(t)}{a_2 + c(t)} \qquad (3.2.3)$$

Also

$$\frac{dN}{dt} = \lambda GN - \frac{P_3 NQ}{A_3 + N}$$
$$\frac{d}{dt}(nK_3) = \lambda (gK_1)(nK_3) - \frac{P_3 (nK_3)Q}{A_3 + nK_3}$$
$$K_3 \frac{dn}{dt} = K_1 K_3 \lambda gn - \frac{K_3 P_3 nQ}{A_3 + nK_3}$$
$$\frac{dn}{dt} = K_1 \lambda gn - \frac{P_3 nQ}{A_3 + nK_3}$$
$$= K_1 \lambda gn - \frac{P_3 nQ}{K_3\left(\frac{A_3}{K_3} + n\right)}$$

On simplification, we have

$$\frac{dn(t)}{dt} = \beta_3 g(t)n(t) - \frac{p_3 n(t)Q(t)}{a_3 + n(t)} \qquad (3.2.4)$$

The normalized mathematical model is

$$\left.\begin{aligned}
\frac{dg(t)}{dt} &= \omega_1 g(t)(1 - g(t)) - \beta_1 g(t)c(t) - \frac{p_1 g(t)Q(t)}{a_1 + g(t)} \\
\frac{dc(t)}{dt} &= \omega_2 c(t)(1 - c(t)) - \beta_2 g(t)c(t) - \frac{p_2 c(t)Q(t)}{a_2 + c(t)} \\
\frac{dn(t)}{dt} &= \beta_3 g(t)n(t) - \frac{p_3 n(t)Q(t)}{a_3 + n(t)} \\
\frac{dQ(t)}{dt} &= \Phi - \zeta Q
\end{aligned}\right\} \qquad (3.2.5)$$

$$g(0) = g_0 > 0, c(0) = c_0 > 0, n(0) = n_0 > 0, Q(0) = Q_0 > 0$$

Where

$$\left.\begin{aligned}
\beta_1 &= d_1 K_2,\ a_1 = \frac{A_1}{K_1},\ p_1 = \frac{P_1}{K_1} \\
\beta_2 &= d_2 K_1,\ a_2 = \frac{A_2}{K_2},\ p_2 = \frac{P_2}{K_2} \\
\beta_3 &= K_1 \lambda,\ a_3 = \frac{A_3}{K_3},\ p_3 = \frac{P_3}{K_3}
\end{aligned}\right\} \qquad (3.2.6)$$

A healthy individual, in this normalised model, would be described by the variables g = 1, c = 0 and n = 1.

For this model to be more realistic, we impose certain conditions among the parameters. It is known that cancer cells grow at a much faster rate than glial and neuron cells, irrespective of the associated initial conditions. Furthermore, the chemotherapy agent should be considerably more effective in killing cancer cells than in killing glial and neuron cells, for the treatment to be effective. These lead to the following set of inequalities:

$$\omega_2 > \omega_1$$

And

$$p_2 > p_1, \quad p_2 > p_3$$

C. Basic Properties of the Model

➢ *Existence and Uniqueness of the Solution*

- *Theorem 1 (Derrick and Grossman, 1976)*

Derrick and Grossman theorem which is outlined in Adewole (2009), Peter (2017), shall be applied to verify the existence and uniqueness of solution to the model. Let D denote the region $|t - t_0| \leq a$, $||x - x_0|| \leq b$, $x = (x_1, x_2, ..., x_n)$, $x_0 = (x_10, x_20, ..., x_n0)$ and suppose f(t, x) satisfies the Lipschitz condition $||f(t, x1) - f(t, x2)|| \leq k||x_1 - x_2||$. The pairs (t, x_1) and (t, x_2) belong to D and k is a positive constant, hence there is a constant $\delta > 0$ such that there exists a unique continuous vector solution x(t) of the system in the interval $t - t_0 \leq 0$. It is important to note that the condition is satisfied by the requirement that $\frac{\partial f_i}{\partial f_j}$, i = 1, 2, ..., be continuous and bounded in D. We shall return to the model (3.2.5) and we consider the region $0 \leq a \leq \Re$. We look for a bounded solution in this region whose partial derivatives satisfy $\delta \leq a \leq 0$, where a and δ are constants.

- *Theorem 2*

Let D denotes the region $0 \leq a \leq \Re$. Then the model system (3.2.5) has a unique solution if it is established that $\frac{\partial f_i}{\partial f_j}$, i = 1, 2, 3, 4 are continuous and bounded in D. In order to proof the existence and uniqueness of the model, it is required to show that the absolute value of the partial derivatives with respect to each of the concentrations is less than infinity. Equation (3.2.5) is renamed as follows:

$$\left.\begin{aligned} f_1 &= \omega_1 g(t)(1-g(t)) - \beta_1 g(t)c(t) - \frac{p_1 g(t)Q(t)}{a_1 + g(t)} \\ f_2 &= \omega_2 c(t)(1-c(t)) - \beta_2 g(t)c(t) - \frac{p_2 c(t)Q(t)}{a_2 + c(t)} \\ f_3 &= \beta_3 g(t)n(t) - \frac{p_3 n(t)Q(t)}{a_3 + n(t)} \\ f_4 &= \Phi - \zeta Q \end{aligned}\right\} \qquad (3.3.1)$$

$$\frac{\partial f_1}{\partial g} = \omega_1 g(1-2g) - \beta_1 c - \frac{a_1 p_1 Q}{(a_1+g)^2} \Longrightarrow \left|\frac{\partial f_1}{\partial g}\right| = \left|\omega_1 g(1-2g) - \beta_1 c - \frac{a_1 p_1 Q}{(a_1+g)^2}\right| < \infty$$

$$\frac{\partial f_1}{\partial c} = -\beta_1 g \Longrightarrow \left|\frac{\partial f_1}{\partial c}\right| = \left|-\beta_1 g\right| < \infty$$

$$\frac{\partial f_1}{\partial n} = 0 \Longrightarrow \left|\frac{\partial f_1}{\partial n}\right| = 0 < \infty$$

$$\frac{\partial f_1}{\partial Q} = -\frac{p_1 g}{(a_1+g)} \Longrightarrow \left|\frac{\partial f_1}{\partial Q}\right| = \left|-\frac{p_1 g}{(a_1+g)}\right| < \infty$$

$$\frac{\partial f_2}{\partial g} = -\beta_2 c \Longrightarrow \left|\frac{\partial f_2}{\partial g}\right| = \left|-\beta_2 c\right| < \infty$$

$$\frac{\partial f_2}{\partial c} = \omega_2 c(1-2c) - \beta_2 g - \frac{a_2 p_2 Q}{(a_2+c)^2} \Longrightarrow \left|\frac{\partial f_2}{\partial c}\right| = \left|\omega_2 c(1-2c) - \beta_2 g - \frac{a_2 p_2 Q}{(a_2+c)^2}\right| < \infty$$

$$\frac{\partial f_2}{\partial n} = 0 \Longrightarrow \left|\frac{\partial f_2}{\partial n}\right| = 0 < \infty$$

$$\frac{\partial f_2}{\partial Q} = -\frac{p_2 c}{(a_2+c)} \Longrightarrow \left|\frac{\partial f_2}{\partial Q}\right| = \left|-\frac{p_2 c}{(a_2+c)}\right| < \infty$$

$$\frac{\partial f_3}{\partial g} = \beta_3 n \Longrightarrow \left|\frac{\partial f_3}{\partial g}\right| = \beta_3 n < \infty$$

$$\frac{\partial f_3}{\partial c} = 0 \Longrightarrow \left|\frac{\partial f_3}{\partial c}\right| = 0 < \infty$$

$$\frac{\partial f_3}{\partial n} = \beta_3 g - \frac{p_3 a_3 Q}{(a_3+n)^2} \Longrightarrow \left|\frac{\partial f_3}{\partial n}\right| = \left|\beta_3 g - \frac{p_3 a_3 Q}{(a_3+n)^2}\right| < \infty$$

$$\frac{\partial f_3}{\partial Q} = -\frac{p_3 n}{(a_3+n)} \Longrightarrow \left|\frac{\partial f_3}{\partial Q}\right| = \left|-\frac{p_3 n}{(a_3+n)}\right| < \infty$$

$$\frac{\partial f_4}{\partial g} = 0 \Longrightarrow \left|\frac{\partial f_4}{\partial g}\right| = 0 < \infty$$

$$\frac{\partial f_4}{\partial c} = 0 \Longrightarrow \left|\frac{\partial f_4}{\partial c}\right| = 0 < \infty$$

$$\frac{\partial f_4}{\partial n} = 0 \Longrightarrow \left|\frac{\partial f_4}{\partial n}\right| = 0 < \infty$$

$$\frac{\partial f_4}{\partial Q} = -\zeta \Longrightarrow \left|\frac{\partial f_4}{\partial Q}\right| = \left|-\zeta\right| < \infty$$

Since the absolute value of the partial derivatives with respect to each of the concentrations is finite, then the system has a unique solution.

D. Steady States of the Model

The steady states (or equilibrium points) of the model are the points where the system do not change with time. That is the points where $\frac{dg(t)}{dt} = \frac{dc(t)}{dt} = \frac{dn(t)}{dt} = \frac{dQ(t)}{dt} = 0$. Now, we establish the steady states of our model. It is obvious that any steady state of system (3.2.5) satisfies the following algebraic equations:

$$\left.\begin{aligned} &\omega_1 g(t)(1-g(t)) - \beta_1 g(t)c(t) - \frac{p_1 g(t)Q(t)}{a_1+g(t)} = 0 \\ &\omega_2 c(t)(1-c(t)) - \beta_2 g(t)c(t) - \frac{p_2 c(t)Q(t)}{a_2+c(t)} = 0 \\ &\beta_3 g(t)n(t) - \frac{p_3 n(t)Q(t)}{a_3+n(t)} = 0 \\ &\Phi - \zeta Q = 0 \end{aligned}\right\} \qquad (3.4.1)$$

➢ *Unavailability of Treatment*

Here, we will discuss the case where treatment is not available in (3.2.5). We derive, list and analyse the local stability of the steady states. The model is modified to the form:

$$\left.\begin{aligned}\frac{dg(t)}{dt} &= \omega_1 g(t)(1-g(t)) - \beta_1 g(t)c(t)\\ \frac{dc(t)}{dt} &= \omega_2 c(t)(1-c(t)) - \beta_2 g(t)c(t)\\ \frac{dn(t)}{dt} &= \beta_3 g(t)n(t)\end{aligned}\right\} \qquad (3.4.2)$$

- *Equilibria*

We denote the equilibria by variations on E. Based on (3.4.2), the following equilibria points (physiologically feasible) exist: E_0 (0, 0, n), E_1 (0, 1, n) and E_2 (1, 0, 0)

- *Local Stability*

The study of the local stability is important to verify if the suppression of cancer is stable or unstable or to understand whether a non-desired state is stable. The Jacobian matrix for a general equilibrium $E(\bar{g}, \bar{c}, \bar{n})$ is

$$J = \begin{pmatrix} J_{11} & -\beta_1 g & 0 \\ -\beta_2 c & J_{22} & 0 \\ \beta_3 n & 0 & \beta_3 g \end{pmatrix}$$

Where

$$J_{11} = \omega_1(1-2g) - \beta_1 c$$
$$J_{22} = \omega_2(1-2c) - \beta_2 g$$

The eigenvalues of E_0, E_1, E_2 and E_3 are respectively:

$$E_0 \begin{cases} \lambda_1^{(0)} = \omega_1 > 0 \\ \lambda_2^{(0)} = \omega_2 > 0 \\ \lambda_3^{(0)} = 0 \end{cases}$$

$$E_1 \begin{cases} \lambda_1^{(1)} = -\omega_2 < 0 \\ \lambda_2^{(1)} = \omega_1 - \beta_1 \\ \lambda_3^{(1)} = 0 \end{cases}$$

$$E_2 \begin{cases} \lambda_1^{(2)} = \omega_2 - \beta_2 \\ \lambda_2^{(2)} = -\omega_1 < 0 \\ \lambda_3^{(2)} = \beta_3 > 0 \end{cases}$$

The above steady states E_0, E_1 and E_2 are non-hyperbolic (at least one eigenvalue of the Jacobian matrix is zero). With these steady states, the system is not stable, structurally.

➢ *Regular Availability of Treatment*

Based on (3.2.5), the following equilibria points (physiologically feasible) exist:

$$F_0(0,0,0,\Phi\zeta^{-1}),\ F_1(g,0,0,\Phi\zeta^{-1}) \text{ and } F_2(0,c,0,\Phi\zeta^{-1})$$

- *Local Stability*

The Jacobian matrix for a generic equilibrium $F(g,c,n,Q)$ is:

$$J^* = \begin{pmatrix} J_{11}^* & -\beta_1 g & 0 & -\frac{p_1 g}{a_1+g} \\ -\beta_2 c & J_{22}^* & 0 & -\frac{p_2 c}{a_2+c} \\ 0 & 0 & J_{33}^* & -\frac{p_3 n}{a_3+n} \\ 0 & 0 & 0 & -\zeta \end{pmatrix}$$

Where

$$J_{11}^* = \omega_1(1-2g) - \beta_1 c - \frac{a_1 p_1 Q}{(a_1+g)^2}$$
$$J_{22}^* = \omega_2(1-2c) - \beta_2 g - \frac{a_2 p_2 Q}{(a_2+c)^2}$$
$$J_{33}^* = \beta_3 g n - \frac{a_3 p_3 Q}{(a_3+n)^2}$$

- *Analysis of* $\boldsymbol{F_0(0,0,0,\Phi\zeta^{-1})}$

In this case, the Jacobian matrix is given by

$$J_1^* = \begin{pmatrix} \omega_1 - \frac{p_1\Phi}{a_1\zeta} & 0 & 0 & 0 \\ 0 & \omega_2 - \frac{p_2\Phi}{a_2\zeta} & 0 & 0 \\ 0 & 0 & -\frac{p_3\Phi}{a_3\zeta} & 0 \\ 0 & 0 & 0 & -\zeta \end{pmatrix}$$

The eigenvalues of the Jacobian matrix are

$$F_0 \begin{cases} \mu_1^{(0)} = \omega_1 - \frac{p_1\Phi}{a_1\zeta} \\ \mu_2^{(0)} = \omega_2 - \frac{p_2\Phi}{a_2\zeta} \\ \mu_3^{(0)} = -\frac{p_3\Phi}{a_3\zeta} < 0 \\ \mu_4^{(0)} = -\zeta < 0 \end{cases}$$

In a hyperbolic equilibrium, if the real part of each eigenvalue is strictly negative, then the equilibrium point is locally asymptotically stable. If positive, then the equilibrium point is unstable. For the equilibrium point $F_0(0,0,0,\Phi\zeta^{-1})$ to be stable, it is sufficient that

$$\mu_1^{(0)} = \omega_1 - \frac{p_1\Phi}{a_1\zeta} < 0$$
$$\Longrightarrow \Phi > \frac{\omega_1\zeta a_1}{p_1}$$

And

$$\mu_2^{(0)} = \omega_2 - \frac{p_2\Phi}{a_2\zeta} < 0$$
$$\Longrightarrow \Phi > \frac{\omega_2\zeta a_2}{p_2}$$

- *Theorem 3*
  Suppose that $\Phi > \frac{\omega_1\zeta a_1}{p_1}$ and $\Phi > \frac{\omega_2\zeta a_2}{p_2}$, then F_0 is locally asymptotically stable

- *Analysis of* $\boldsymbol{F_1(\bar{g}, 0, 0, \Phi\zeta^{-1})}$
  With this equilibrium point, the first equation in (3.2.5) becomes:

$$\omega_1\bar{g}(1-\bar{g}) - \frac{p_1\bar{g}\Phi}{\zeta(a_1+\bar{g})} = 0$$

Which can be rewritten as:

$$\omega_1\bar{g}(1-\bar{g}) - \frac{p_1\bar{g}\Phi}{\zeta(a_1+\bar{g})} = 0$$

With solution

$$\bar{g} = \frac{1 - a_1 \pm \sqrt{(a_1-1)^2 + 4(a_1 - \frac{p_1\Phi}{\omega_1\zeta})}}{2}$$

The Jacobian matrix is given by

$$J_2^* = \begin{pmatrix} \omega_1(1-2\bar{g}) - \frac{p_1 a_1 \Phi}{\zeta(a_1+\bar{g})^2} & -\beta_1\bar{g} & 0 & -\frac{p_1\bar{g}}{a_1+\bar{g}} \\ 0 & \omega_2 - \beta_2\bar{g} - \frac{p_2\Phi}{a_2\zeta} & 0 & 0 \\ 0 & 0 & -\frac{p_3\Phi}{a_3\zeta} & 0 \\ 0 & 0 & 0 & -\zeta \end{pmatrix}$$

The eigenvalues of the Jacobian matrix are:

$$F_1 \begin{cases} \mu_1^{(1)} = \omega_1(1-2\bar{g}) - \frac{p_1 a_1 \Phi}{\zeta(a_1+\bar{g})^2} \\ \mu_2^{(1)} = \omega_2 - \beta_2\bar{g} - \frac{p_2\Phi}{a_2\zeta} \\ \mu_3^{(1)} = -\frac{p_3\Phi}{a_3\zeta} < 0 \\ \mu_4^{(1)} = -\zeta < 0 \end{cases}$$

For the equilibrium point $F_1(\bar{g}, 0, 0, \Phi\zeta^{-1})$ to be stable, it is sufficient that:

$$\mu_1^{(1)} = \omega_1(1-2\bar{g}) - \frac{p_1 a_1 \Phi}{\zeta(a_1+\bar{g})^2} < 0$$
$$\Longrightarrow \Phi > \frac{\zeta\omega_1(1-2\bar{g})(a_1+\bar{g})^2}{a_1 p_1}$$

And

$$\mu_2^{(1)} = \omega_2 - \beta_2\bar{g} - \frac{p_2\Phi}{a_2\zeta} < 0$$
$$\Longrightarrow \Phi > \frac{a_2\zeta(\omega_2-\beta_2\bar{g})}{p_2}$$

- *Theorem 4*

  Suppose that $\Phi > \frac{\zeta\omega_1(1-2\bar{g})(a_1+\bar{g})^2}{a_1 p_1}$ and $\Phi > \frac{a_2\zeta(\omega_2-\beta_2\bar{g})}{p_2}$, then F_1 is locally asymptotically stable.

- *Analysis of* $\boldsymbol{F_2(0, \bar{c}, 0, \Phi\zeta^{-1})}$

  With this equilibrium point, the second equation in (3.2.5) becomes:

$$\omega_2\bar{c}(1-\bar{c}) - \frac{p_2\bar{c}\Phi}{\zeta(a_2+\bar{c})} = 0$$

Which can be rewritten as:

$$\bar{c}^2 + (a_2-1)\bar{c} - a_2 + \frac{p_2\Phi}{\omega_2\zeta} = 0$$

With solution

$$\bar{c} = \frac{1-a_2 \pm \sqrt{(a_2-1)^2 + 4(a_2 - \frac{p_2\Phi}{\omega_2\zeta})}}{2}$$

The Jacobian matrix is given by

$$J_3^* = \begin{pmatrix} \omega_1 - \beta_1\bar{c} - \frac{p_1\Phi}{a_1\zeta} & 0 & 0 & 0 \\ -\beta_2\bar{c} & \omega_2(1-2\bar{c}) - \frac{a_2p_2\Phi}{\zeta(a_2+\bar{c})^2} & 0 & -\frac{p_2\bar{c}}{a_2+\bar{c}} \\ 0 & 0 & -\frac{p_3\Phi}{a_3\zeta} & 0 \\ 0 & 0 & 0 & -\zeta \end{pmatrix}$$

The eigenvalues of the Jacobian matrix are:

$$F_2 \begin{cases} \mu_1^{(2)} = \omega_1 - \beta_1\bar{c} - \frac{p_1\Phi}{a_1\zeta} \\ \mu_2^{(2)} = \omega_2(1-2\bar{c}) - \frac{a_2p_2\Phi}{\zeta(a_2+\bar{c})^2} \\ \mu_3^{(2)} = -\frac{p_3\Phi}{a_3\zeta} < 0 \\ \mu_4^{(2)} = -\zeta < 0 \end{cases}$$

For the equilibrium point $F_2(0, \bar{c}, 0, \Phi\zeta^{-1})$ to be stable, it is sufficient that:

$$\mu_1^{(2)} = \omega_1 - \beta_1\bar{c} - \frac{p_1\Phi}{a_1\zeta} < 0$$
$$\Longrightarrow \Phi > \frac{a_1\zeta(\omega_1 - \beta_1\bar{c})}{p_1}$$

And

$$\mu_2^{(2)} = \omega_2(1-2\bar{c}) - \frac{a_2p_2\Phi}{\zeta(a_2+\bar{c})^2} < 0$$
$$\Longrightarrow \Phi > \frac{\zeta\omega_2(1-2\bar{c})(a_2+\bar{c})^2}{a_2p_2}$$

- *Theorem 5*

Suppose that $\Phi > \frac{a_1\zeta(\omega_1-\beta_1\bar{c})}{p_1}$ and $\Phi > \frac{\zeta\omega_2(1-2\bar{c})(a_2+\bar{c})^2}{a_2p_2}$, then F_2 is locally asymptotically stable

IV. CONCLUSION

There exist different types of brain tumour. The treatments of these tumours depend on their characteristics. In this work, mathematical model that describes the interactions among glial cells, neurons, and cancer, with a chemotherapy to repress the brain tumour was proposed.

The steady states of the model were obtained and stability analysis was performed. The equilibrium points, for unavailability of treatment are not stable. On the other hand, the stability of the equilibrium points (for availability of treatment) depends on the chemotherapy infusion rate, Φ

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