# MATHEMATICAL MODELING OF CHEMOTHERAPY EFFECTS ON BRAIN TUMOUR GROWTH

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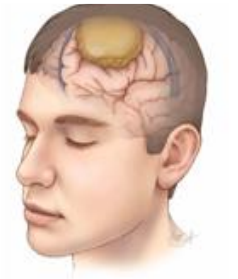
# OUTLINE

- Introduction
- Aim and Objectives
- Methodology
- Result and discussion
- Conclusion and recommendation
- References

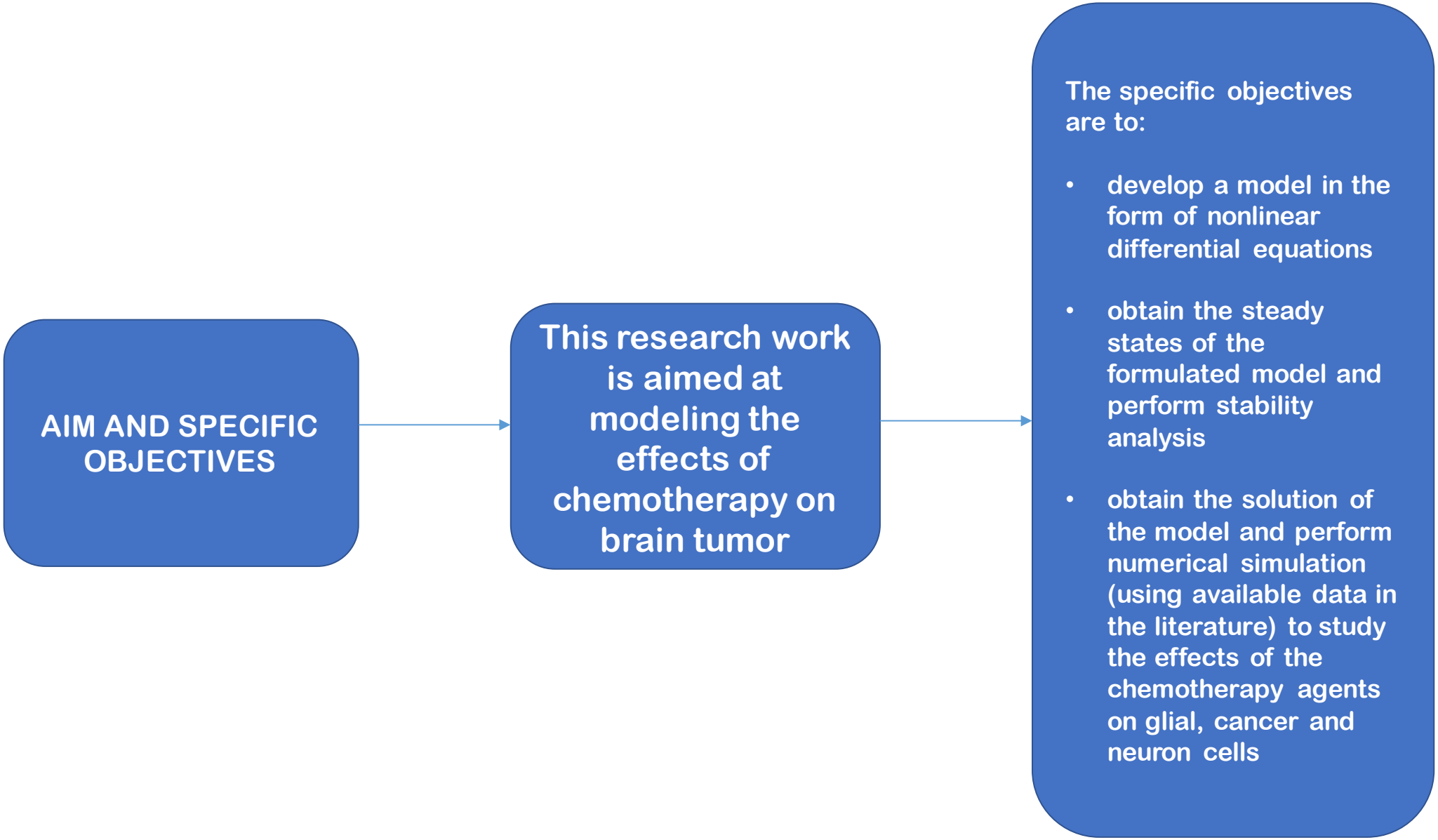
# INTRODUCTION

Image of Brain Tumor



A brain tumor is an abnormal growth or mass of cells in or around the brain. It is also called a central nervous system tumor. Brain tumors can be malignant (cancerous) or benign (not cancerous). Chemotherapy uses anti-cancer (cytotoxic) drugs to destroy brain tumor cells (cancerresearchuk.org). The effect of chemotherapy on the brain results in cognitive disturbances with an uncertain long-term effect (Lee et al., 2020).

Chemotherapy is a form of chemical drug therapy used to destroy rapidly growing cells in the body. It is used to treat cancer, as cancer cells grow and divide faster than any other cells (Kaur et al., 2022). Postoperative chemotherapy and radiotherapy have become the standard therapy for brain tumors (Zhao et al., 2023). Chemotherapy is sometimes used with a combination of other therapies, like surgery, radiotherapy, and hormone therapy. Chemotherapeutic techniques have a range of side effects that depend on the type of medications used (Kaur et al, 2022).


AIM AND SPECIFIC OBJECTIVES
This research work is aimed at modeling the effects of chemotherapy on brain tumor
The specific objectives are to:
• develop a model in the form of nonlinear differential equations
• obtain the steady states of the formulated model and perform stability analysis
• obtain the solution of the model and perform numerical simulation (using available data in the literature) to study the effects of the chemotherapy agents on glial, cancer and neuron cells

# METHODOLOGY

**FLOW DIAGRAM OF THE MODEL**

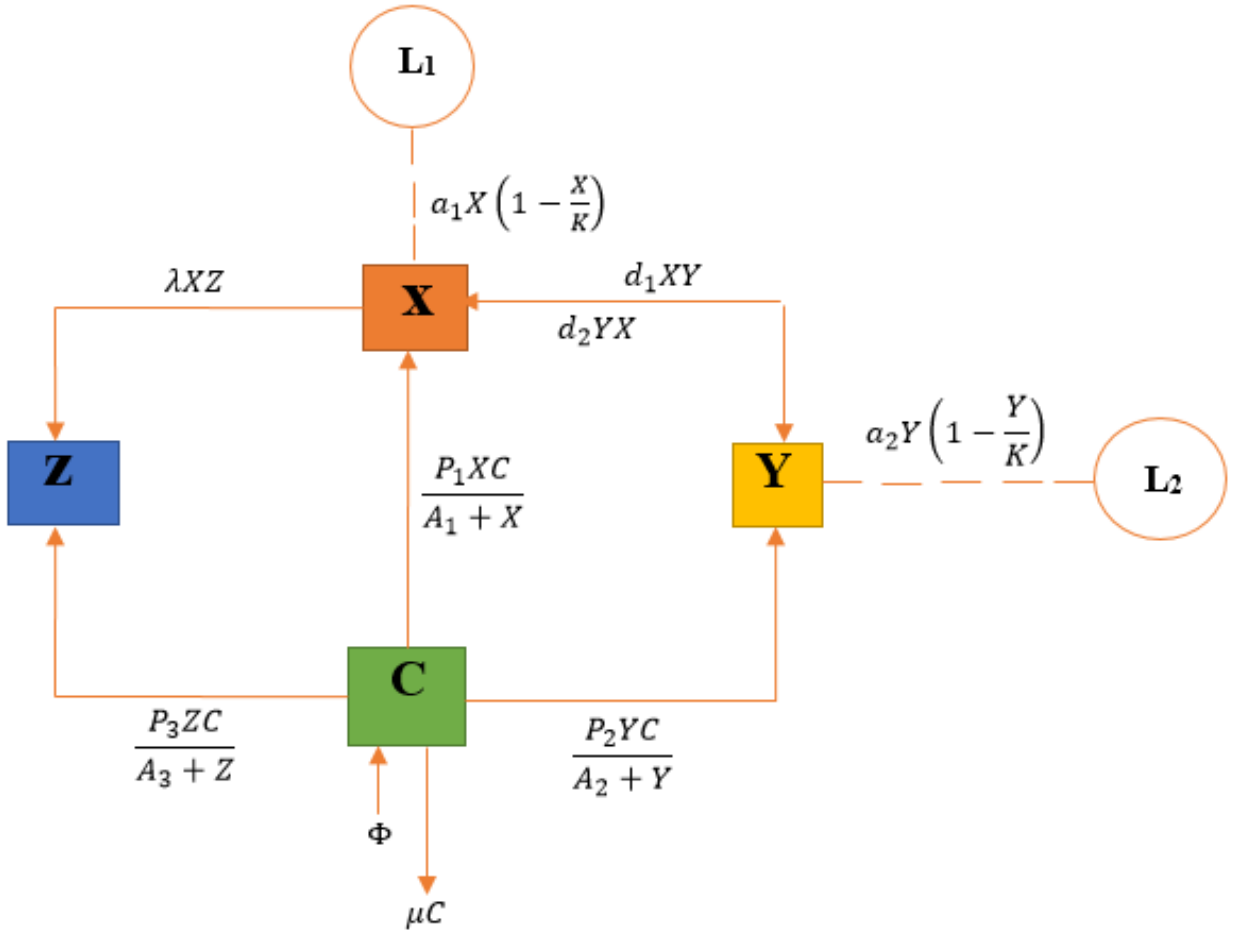



Figure 1: Flow Diagram of the Model

# METHODOLOGY…

## The Model System of Equations

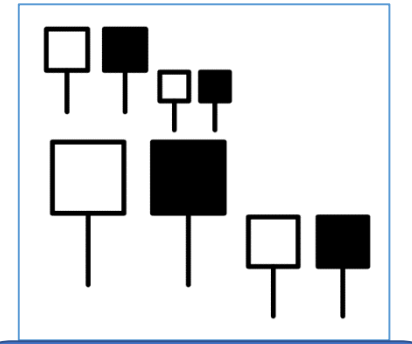
$$\frac{dX(t)}{dt} = a_1 X\left(1 - \frac{X}{K}\right) - d_1 XY - \frac{P_1 XC}{A_1 + X}$$

$$\frac{dY(t)}{dt} = a_2 Y\left(1 - \frac{Y}{K}\right) - d_2 YX - \frac{P_2 YC}{A_2 + Y}$$

$$\frac{dZ(t)}{dt} = \lambda XZ - \frac{P_3 ZC}{A_3 + Z}$$

$$\frac{dC(t)}{dt} = \Phi - \mu C$$

# METHODOLOGY…



VARIABLES AND PARAMETERS

| VARIABLES/PARAMETERS | DESCRIPTION |
|---|---|
| $X(t)$ | Glial Cells Concentration |
| $Y(t)$ | Cancer Cells Concentration |
| $Z(t)$ | Neuron Cells Concentration |
| $C(t)$ | Concentration of the Chemotherapy Agent |
| $\alpha_1$ | Rate of proliferation of the Glial Cells |
| $\alpha_2$ | Rate of proliferation of the Glial Cells |
| $\lambda$ | Loss influence for Neurons due to Glial Cells |
| $P_1$ | Influence of Chemotherapy on Glial Cells |
| $P_2$ | Influence of Chemotherapy on Cancer Cells |
| $P_3$ | Influence of Chemotherapy on Neuron Cells |
| $\phi$ | Rate of Chemotherapy Infusion |
| $\mu$ | Chemotherapy washout rate |
| $A_1, A_2, A_3$ | Holling Type II |
| $d$ | Competition coefficient between Glial and Cancer Cells |
| $K$ | Carrying Capacity |

Figure 2: Description of variables and parameters

# METHODOLOGY…

**NORMALIZATION OF VARIABLES IN THE MODEL EQUATION**

Letting:

$$x = \frac{X}{K}, y = \frac{Y}{K} \text{ and } z = \frac{Z}{K}$$

where

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

The normalized model is given as:

$$\frac{dx(t)}{dt} = \gamma_1 x(1-x) - \beta_1 xy - \frac{p_1 xC}{a_1 + x}$$

$$\frac{dy(t)}{dt} = \gamma_2 y(1-y) - \beta_2 xy - \frac{p_2 yC}{a_2 + y}$$

$$\frac{dz(t)}{dt} = \beta_3 xz - \frac{p_3 zC}{a_3 + z}$$

$$\frac{dC(t)}{dt} = \phi - \mu C$$

$$\boldsymbol{x(0) = x_0 \geq 0, y(0) = y_0 \geq 0, z(0) = z_0 \geq 0, C(0) = C_0 \geq 0}$$

# METHODOLOGY…

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 $\frac{dx(t)}{dt} = \frac{dy(t)}{dt} = \frac{dz(t)}{dt} = \frac{dC(t)}{dt} = 0$. Now, we establish the steady states of our model. It is obvious that any steady state of system satisfies the following algebraic equations:

$$\gamma_1 x(1-x) - \beta_1 xy - \frac{p_1 xC}{a_1 + x} = 0$$

$$\gamma_2 y(1-y) - \beta_2 xy - \frac{p_2 yC}{a_2 + y} = 0 \qquad (1)$$

$$\beta_3 xz - \frac{p_3 zC}{a_3 + z} = 0$$

$$\phi - \mu C = 0$$

# METHODOLOGY…

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

UNAVAILABILITY OF TREATMENT

$$\frac{dx(t)}{dt} = \gamma_1 x(1-x) - \beta_1 xy$$

$$\frac{dy(t)}{dt} = \gamma_2 y(1-y) - \beta_2 xy$$

$$\frac{dz(t)}{dt} = \beta_3 xz$$

# METHODOLOGY…

We denote the steady states by variations on E. Based on the last equation, the following equilibria points exist: $E_0$ (0, 0, z), $E_1$ (0, 1, z) and $E_2$ (1, 0, 0)

UNAVAILABILITY OF TREATMENT

The Jacobian matrix for a general equilibrium point $E(\bar{x}, \bar{y}, \bar{z})$ is

$$J = \begin{pmatrix} J_{11} & -\beta_1 x & 0 \\ -\beta_2 x & J_{22} & 0 \\ \beta_3 z & 0 & \beta_3 x \end{pmatrix}$$

Where

$$J_{11} = \gamma_1(1 - 2x) - \beta_1 y$$

$$J_{22} = \gamma_2(1 - 2y) - \beta_2 x$$

**The eigenvalues of $E_0$, $E_1$ and $E_2$ are respectively:**

$$E_0 = \begin{cases} \lambda_1^{(0)} = \gamma_1 > 0 \\ \lambda_2^{(0)} = \gamma_2 > 0 \\ \lambda_3^{(0)} = 0 \end{cases}$$

$$E_1 = \begin{cases} \lambda_1^{(1)} = -\gamma_1 < 0 \\ \lambda_2^{(1)} = \gamma_1 - \beta_1 > 0 \\ \lambda_3^{(1)} = 0 \end{cases}$$

$$E_2 = \begin{cases} \lambda_1^{(2)} = \gamma_2 - \beta_2 \\ \lambda_2^{(2)} = -\gamma_1 < 0 \\ \lambda_3^{(2)} = \beta_3 > 0 \end{cases}$$

**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**

The following steady points exist:

$$F_0(0, 0, 0, \phi\mu^{-1})$$

$$F_1(x, 0, 0, \phi\mu^{-1})$$

$$F_2(0, y, 0, \phi\mu^{-1})$$

AVAILABILITY OF TREATMENT

The Jacobian matrix for a generic equilibrium $F(\bar{x}, \bar{y}, \bar{z}, \bar{C})$ is:

$$J^* = \begin{pmatrix} J_{11}^* & -\beta_1 x & 0 & -\frac{p_1 x}{a_1 + x} \\ -\beta_2 y & J_{22}^* & 0 & -\frac{p_2 y}{a_2 + y} \\ 0 & 0 & J_{33}^* & -\frac{p_3 z}{a_3 + z} \\ 0 & 0 & 0 & -\mu \end{pmatrix}$$

where

$$J_{11}^* = \gamma_1(1 - 2x) - \beta_1 y - \frac{a_1 p_1 C}{(a_1 + x)^2}$$

$$J_{22}^* = \gamma_2(1 - 2y) - \beta_2 x - \frac{a_2 p_2 C}{(a_2 + y)^2}$$

$$J_{33}^* = \beta_3 xz - \frac{a_3 p_3 C}{(a_3 + z)^2}$$

**Analysis of $F_0(0,0,0,\phi\mu^{-1})$: The eigenvalues of the steady states are**

$$F_0 \begin{cases} \mu_1^{(0)} = \gamma_1 - \dfrac{p_1\phi}{a_1\mu} \\ \mu_2^{(0)} = \gamma_2 - \dfrac{p_2\phi}{a_2\mu} \\ \mu_3^{(0)} = -\dfrac{p_3\phi}{a_3\mu} < 0 \\ \mu_4^{(0)} = -\mu \end{cases}$$

**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 $F_0(0,0,0,\Phi\mu^{-1})$ to be stable, it is sufficient that**

$$\mu_1^{(0)} = \gamma_1 - \frac{p_1\phi}{a_1\mu} < 0$$

$$\Rightarrow \phi > \frac{\gamma_1\mu a_1}{p_1}$$

and

$$\mu_2^{(0)} = \gamma_2 - \frac{p_2\phi}{a_2\mu} < 0$$

$$\Rightarrow \phi > \frac{\gamma_2\mu a_2}{p_2}$$

## Analysis of $F_1(\bar{x}, 0, 0, \phi\mu^{-1})$:

With this equilibrium point, the first equation in (1) becomes:

$$\gamma_1 \bar{x}(1-\bar{x}) - \frac{p_1 \bar{x}\phi}{\mu(a_1+\bar{x})} = 0$$

with solution

$$\bar{x} = \frac{1 - a_1 \pm \sqrt{(a_1-1)^2 + 4\left(a_1 - \frac{p_1\phi}{\gamma_1\mu}\right)}}{2}$$

## The Jacobian matrix of the equilibrium point $F_1(\bar{x}, 0, 0, \phi\mu^{-1})$ is given as

$$J_2^* = \begin{pmatrix} \gamma_1(1-2\bar{x}) - \frac{a_1 p_1 \phi}{\mu(a_1+\bar{x})^2} & -\beta_1\bar{x} & 0 & -\frac{p_1\bar{x}}{a_1+\bar{x}} \\ 0 & \gamma_2 - \beta_2\bar{x} - \frac{p_2\phi}{a_2\mu} & 0 & 0 \\ 0 & 0 & -p_3\phi(a_3\mu)^{-1} & 0 \\ 0 & 0 & 0 & -\mu \end{pmatrix}$$

The eigenvalues of the steady state $F_1(\bar{x}, 0, 0, \phi\mu^{-1})$ are

$$F_1 \begin{cases} \mu_1^{(1)} = \gamma_1(1-2\bar{x}) - \dfrac{a_1 p_1 \phi}{\mu(a_1+\bar{x})^2} \\ \mu_2^{(1)} = \gamma_2 - \beta_2\bar{x} - \dfrac{p_2\phi}{a_2\mu} \\ \mu_3^{(1)} = -\dfrac{p_3\phi}{a_3\mu} < 0 \\ \mu_4^{(1)} = -\mu < 0 \end{cases}$$

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

$$\mu_1^{(1)} = \gamma_1(1-2\bar{x}) - \frac{a_1 p_1 \phi}{\mu(a_1+\bar{x})^2} < 0$$

$$\Rightarrow \phi > \frac{\mu\gamma_1(1-2\bar{x})(a_1+\bar{x})^2}{a_1 p_1}$$

and

$$\mu_2^{(1)} = \gamma_2 - \beta_2\bar{x} - \frac{p_2\phi}{a_2\mu} < 0$$

$$\Rightarrow \phi > \frac{a_2\mu(\gamma_2 - \beta_2\bar{x})}{p_2}$$

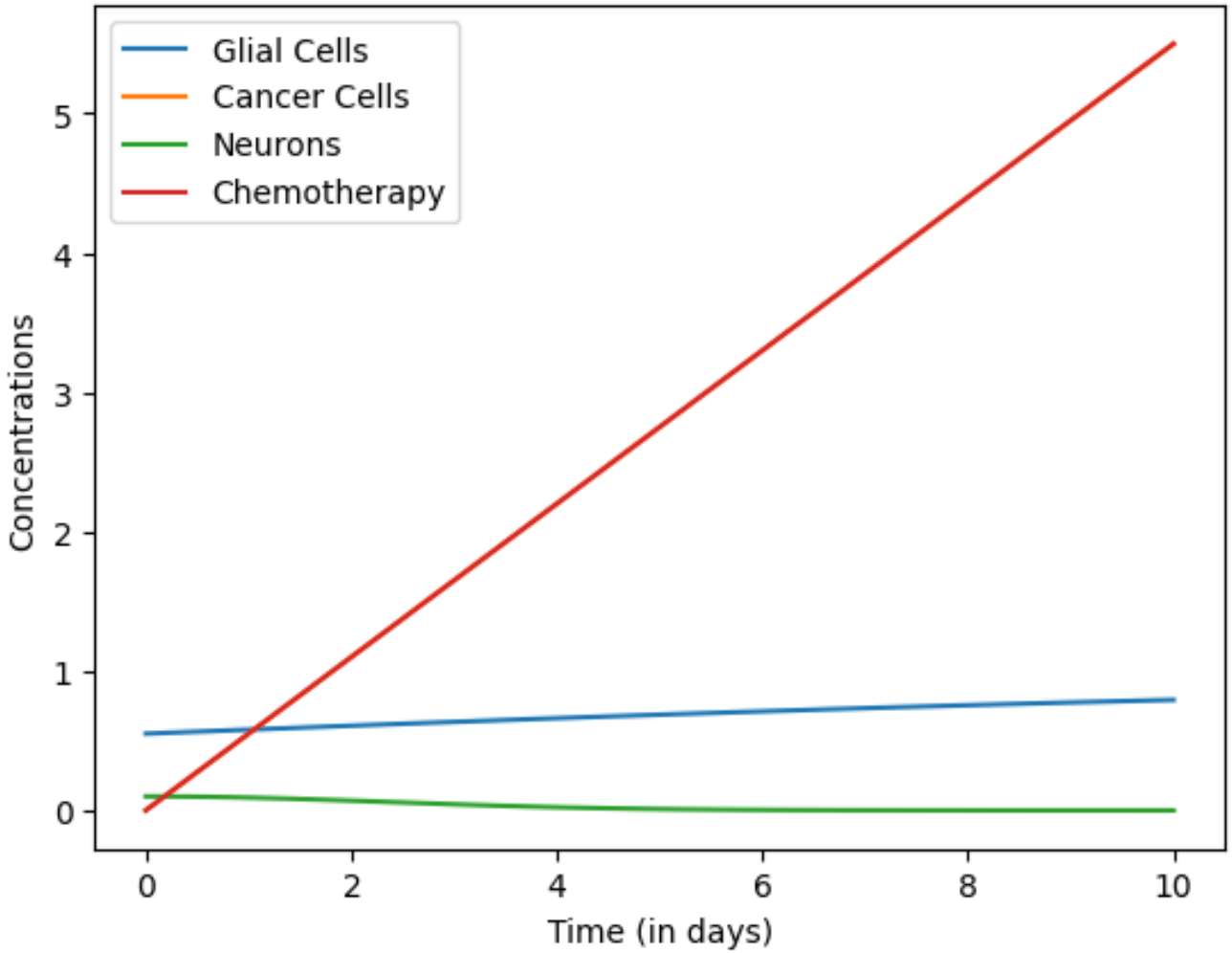
# Values of the normalized parameters

| Parameters | Values |
|---|---|
| $\gamma_1$ | 0.0068 $day^{-1}$ (Larosz et al., 2013) |
| $\gamma_2$ | 0.012 $day^{-1}$ (Larosz et al., 2013) |
| $\beta_1$ | 1.8 x $10^{-2}$ $day^{-1}$ (Larosz et al., 2013) |
| $\beta_2$ | 1.8 x $10^{-3}$ $day^{-1}$ (Larosz et al., 2013) |
| $\beta_3$ | 1.8 x $10^{-3}$ $day^{-1}$ (Assumed) |
| $a_1 = a_2 = a_3$ | 1 (Assumed) |
| $p_1 = p_3$ | 4.7 x $10^{-8}$ $m^2$ $(mg.day)^{-1}$ (Larosz et al., 2013) |
| $p_2$ | 4.7 x $10^{-7}$ $m^2$ $(mg.day)^{-1}$ (Larosz et al., 2013) |

Figure 3: Values of parameters used for simulation

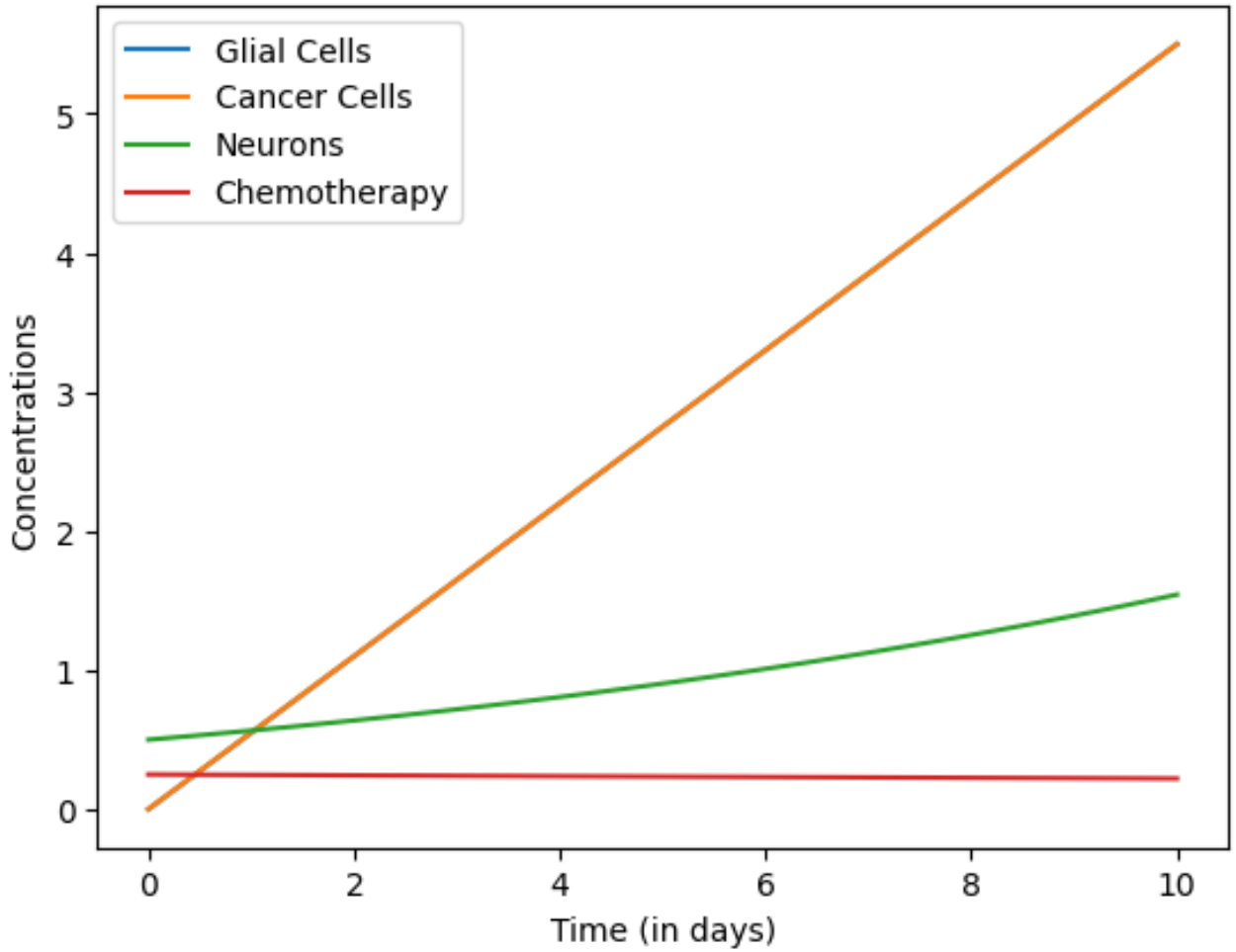
Firstly, we check the behavior of the cancer with the infusion of a chemotherapeutic agent. Since there is treatment the cancer cells die and there is a reduction in the strength of the glial and neuron cells

Solution and Simulation



We also check the behavior of the cancer without the infusion of a chemotherapeutic agent. Since there is no treatment, the cancer cells kill the glial cells while the cancer cells grow

Solution and Simulation



## Conclusion

There exist different types of brain tumors. The treatments of these tumors depend on their characteristics. In this work, a mathematical model that describes the interactions among glial cells, neurons, and cancer, with chemotherapy to repress the brain tumor 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, $\Phi$

## REFERENCES


Kaur, S., Mayanglambam, P., Bajwan, D and Thakur, N. (2022). Chemotherapy and its Adverse Effects – A Systematic Review. *International Journal of Nursing Education and Research*. 10(4)

Zhao, Y., Yue, P., Peng, Y., Sun, Y., Chen, X., Zhao, Z., & Han, B. (2023). Recent advances in drug delivery systems for targeting brain tumors. *Drug delivery*, 30(1), 1–18.
https://www.cancerresearchuk.org/about-cancer/brain-tumours/treatment/chemotherapy-treatment (accessed on 26th May, 2024)

Lee, M., Chong, W. Q., Tan, H. L., Chan, G., Ho, J., Sundar, R., Chee, C. E., Nasrallah, F., Koo, E. H. and Yong, W. (2020). The chemo-brain effect in colorectal cancer patients. *Journal of Clinical Oncology*, 38 (15).

Elshaikh, B., Omer, H., Garelnabi, M., Sulieman, A., Abdella, N., Algadi, S. and Toufig, H. (2021). Incidence, Diagnosis and Treatment of Brain Tumours. *Journal of Research in Medical and Dental Science*, 9, 340-347

Saravanan, S., Kumar, V. V., Sarveshwaran, V., Indirajithu, A., Elangovan, D., and Allayear, S. M. (2022). Computational and Mathematical Methods in Medicine Glioma Brain Tumor Detection and Classification Using Convolutional Neural Network. *Computational and mathematical methods in medicine*, 2022

Usman, P.; Juhari; Ahmad, S. and Marwan, D. I. (2021). Numerical Solution Model of Brain Tumors Glioblastoma multiforme with Treatment Effect Using Runge Kutta Fehlberg Methods. *Proceedings of the International Conference on Engineering, Technology and Social Science (ICONETOS 2020)*, 767-776, doi.org/10.2991/assehr.k.210421.111

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