# EFFECTS OF INCUBATION AND CHEMOTHERAPY ON THE DYNAMICS OF TUMOR GROWTH USING MATHEMATICAL MODELING APPROACH

**Abstract**The application of Mathematical models in simulating processes that are biological in nature has been in effect for a long time. A great number of Mathematical, Computational, Engineering and Physical approaches have been administered to several aspects of development of Tumor, with a view of appreciating how cancer cell population responds to medical intervention. This research therefore considered a Mathematical model for the consequences of incubation and Chemotherapy on Tumor growth dynamics by formulating a deterministic S (susceptible), E (exposed), I (infectious), R (recovered) model using Delay differential equations. The Delay in this case accounted for the duration between the subjection of a cell to cancer virus and the onset of symptomatic disease. Reproduction number ($R_0$) of the model was ascertained using next generation matrix approach. The stability analysis of Cancer Free Equilibrium Point (CFEP) of the model were investigated. MATLAB computer program was used for numerical simulations to validate the analytic results. The investigation and analysis of the consequences of incubation and Chemotherapy on the stability of the equilibrium point was also done. This study of Tumor growth dynamics is significant in that it shall help establish the stage and the extent of cancer spread within the body cells. It shall also help develop a better drug administration procedure as well as provide mechanistic insights. Parameter values used were mostly estimated values. From the numerical findings it was found that $R_0$ at CFEP was obtained at 0.6667 was stable.
**Keywords:**Tumor growth,Reproduction Number,Delay,Stability,Cancer FreeEquilibrium,Chemotherapy

## 1.Introduction

Mathematical modeling of biological processes especially on cancer has in recent times received much attention. Mathematical models of Biological processes and the associated numerical simulation has reduced the complicated and costly experimental procedures [2, 8, 11, 22]. It has been adopted by several epidemiologists as one of the approaches to study non-communicable diseases. Worldwide, including Africa, cancer is rated second as a main cause of mortality behind heart diseases; this is according to World Health Organization (2018). Cancerous tumor growth, spread to the adjacent tissues and treatment have been explained by various Mathematical models in the past. Terminal illnesses or diseases are conditions which cannot be cured hence leads to the death of the affected person. Examples of terminal diseases are Liver disease, HIV, Lung disease, advanced heart disease, advanced cancer among others. [6, 7, 13, 23]
According to World Health Organization (WHO), 2020, breast, lung, colon, rectum and prostate cancers are the most common ones. In this study we examine how Mathematical models can be used to imitate Tumor growth as well as cancer medication.
Tumor is an abnormal mass of tissue which may be solid inside or filled with fluid. There are three Tumor types, namely benign, premalignant and malignant Tumors. When the development of Tumor cells are restricted to thelocation of emergence, does not spread to other sites of the body, grows slowly and have distinct borders, then they are said to be benign Tumors. Such tumors are non-cancerous. Premalignant tumors are those in which cells are not yet cancerous but have the potential of becoming cancerous. Finally, when the cells are unusual, growrapidly and can proliferate to other sections of the body, then they are referred to as malignant tumors or cancerous cells. Toestablish if a tumor is cancerous or benign, a fragment of the cells is taken through a biopsy procedure by a doctor and then examined. A pathologist then analyzes thebiopsy under a microscope. On the other hand, cancer is a genetic malady caused by changes to genes that control the way the body cells function, how they grow and how they fractionate. Cancer cells diverge from the other cells in different ways. For example, their growth takes place even in the absence of the signal initiating the growth, continues growing despite the signals stopping their growth. They also attack the surrounding cells of the body among others. [4, 19, 21]. Cancer is regarded as one of the most exhausting illness to treat and hence leads to more deaths than most diseases. It's also noted that combating cancer is crucial for public health, [1, 3, 16, 24]. Over the years several methods of cancer treatment have been used, these include hormone therapy, surgery, radiotherapy, immune therapy and chemotherapy among others. Mathematical epidemiology has contributed to a more in-depth understanding of cancerous Tumor growth as a terminal ailment, its effect and possible future forecast about its spread in the body and the mechanism of its control and treatment.
Advanced mathematical model for cancer analysis considering time delay was done [3, 5, 9, 25]. The changing characteristic of the nonlinear mathematical model which was initially fronted by introducing the delay component in the relationship between the tumor cell itself and the body's defense system. This was done in an effort to ensure that the model is more practical. The investigation of the Mathematical model showed that, the elimination of the tumor cells entailed a joint effort of both normal cells and the immune system without the drug administration. However it was also shown that the immune system of the body does not acknowledge the tumor cells immediately so as to give enough feedback time (i.e., the delay term is prolonged), the growth rate of the tumor increases hence the system's immune stability is lost and finally drifts away from the tumor-free steady point. As a consequence, the immune–normal cell fails to effect the destruction of the tumor burden.
According to [11, 14, 17] they investigated a mathematical model for chemo-immunotherapy, which is a combination of chemotherapy and immunotherapy for brain cancer. The system of equations used included nonlinear first-order ODEs. The mathematical model considered the interaction of immune system cells with cancer cells and the treatment. The dynamic variables of the system are immature dendritic cells, immunogenic dendritic cells, tolerogenic dendritic cells, naive $T$-cells, cytotoxic $T$-cells, proliferating cytotoxic $T$-cells, cancer cells, and chemotherapy medicine. They proposed a new treatment

protocol, which was essentially a new analytical function that depended on the time interval between treatment and dosage. To investigate the stability of the equilibrium points, it was necessary to solve the nonlinear algebraic equation related to the mathematical model, which, in this case, was impossible analytically. Hence, they applied the SPVF algorithm to transfer the mathematical model to a new coordinate with an explicit hierarchy and divided it into fast and slow subsystems. This procedure enabled them to investigate only the fast subsystem, without losing the biological information of the original model. They determined all equilibrium points of the model in the new coordinates and their stability. The equilibrium points had no biological meaning in the new coordinates; hence, they inversely transformed only the stable equilibrium points into the original coordinates of the model. They investigated the mathematical model with our proposed treatment protocol, with constant dosage and different time intervals between treatments, that is, 7, 14, 28, and 56 days. Thereafter, they compared their analysis results with experimental (clinical) data. The optimal treatment was found to correspond to the protocol with a 7day interval between treatments. The next step involved the application of the protocol with different dosages and time intervals simultaneously. They examined the behaviour of cancer cells when the initial conditions were changed. All results were identified to reach a state of equilibrium at approximately the same time. Indeed, this was dependent on the treatment, which had been determined to vary in terms of dosage and time.

A model with random noise on the dynamical behaviour of the Tumor and the immune system was developed. The study assimilated the consequence of noise into a model for Tumor-immune system with Holling type III response functions to cater for the alterations in cell dynamics. It made use of a stochastic Lyapunov function together withIto's formula, to provide enough constrain for establishing the existing stationary distribution results, weak persistence, and elimination of Tumor cells. The stochastic model for Tumor- immune interaction was used. The research also showed that the growth of tumor can be reduced by increasing the intensity of the noise as a fundamental factor in the existence of immune effectors. [15, 18, 20,27]

According to [4,10,12, 26] they considered the analysis of a cancer Mathematical model which included the time-delay in the interactivity amidst the Tumor cells and the immune system of the body and their stimulation processes. It analyzed and observed the model dynamics together with changes of crucial restrictions and the effect of time delay on anti -Tumor immune reaction. The delay term was included in the model. As a consequence, the modified model demonstrated that the system was able to bring about varying responses even with the delay term included. In addition, it demonstrated that the oscillations were continuous and couldn't be eliminated through the addition of the delay term. The numerical simulations and bifurcation analysis indicated that a "careful" consideration of the model's framework has to be determined so that the fixed-state becomes less stable. It was shown that the time delay was not a requirement to originate oscillations since such oscillations could be generated even in the absence of the delay term.

Inthispaper,we have formulated a SEIR deterministic mathematical model with delay differential equations (DDE) for the investigation of the effects of incubation and chemotherapy on Tumor growth dynamics. In a SEIR model the individuals in a population are divided into four sub-populations or compartments. These compartments are the susceptible **(S)**, which refers to the healthy Cells which have not yet come into contact with the cancer cells. The exposed **(E)** are the Cells which have come into contact with the Cancer cells but are not yet infective or infectious. The infective **(I)** are those that have become infected with the cancer cells and are infectious and the recovered **(R)** are those that have recovered or removed from the cell population.The method is suitable for all infectious diseases such as Diabetes, Measles, Tuberculosis, HIV, and COVID-19 virus disease among others.

**2.MethodsofSolution**

ThestabilityofthemodelhasbeenapproachedfromJacobianmatrixmethodofcheckingstabilityofCancerFreeEquilibrium Point(CFEP)andnumericalsimulationshavebeendoneusingMATLABtovalidatetheanalyticresults.

**2.1.ModelEquations**

From the flow chart, the parameters and the model assumptions the tumor dynamics can be modeled using the following delay differential equations.

$$\frac{dS}{dt} = \Lambda - \gamma SI_{\tau} - \mu_1 S \qquad (2.1)$$

$$\frac{dE}{dt} = \gamma SI_{\tau} - \mu_2 E - \sigma E - (1-\sigma)\beta E_{\tau} \qquad (2.2)$$

$$\frac{dI}{dt} = (1-\sigma)\beta E_{\tau} - \mu_3 I - (\alpha+\eta)I_{\tau} \qquad (2.3)$$

$$\frac{dR}{dt} = (\alpha+\eta)I_{\tau} + \sigma E - \mu_4 R \qquad (2.4)$$

The total cell population N, is given as$N = S + E + I + R$ .

**2.2 Model preliminary Analysis**

The preliminary analysis of the formulated model is given in this section. The analysis includes positivity and boundedness of the model solution, calculation of the basic reproductive number, determination and the stability analysis of the equilibrium points. Finally, the sensitivity analysis of the basic reproductive number is also done.

Positivity and boundedness are therefore essential features of an epidemiological study.

**2.2.1 Positivity of the solution of the model**

The model monitors the cell population in Tumor dynamics, so all its associated parameters must be non-negative. Positivity of the solution is one of the important features of an epidemiological model. It is therefore important to prove that all state variables are non-negative for all time $t \geq 0$. Further any solution with positive initial values will remain positive for all the time $t \geq 0$. Biologically, positivity implies that the population will survive a long time. Therefore to check how biologically

valid the proposed model is, the positivity of the proposed model must be shown.

**Theorem 1**

Let $S(0) \geq 0, E(0) \geq 0, I(0) \geq 0$ and $R(0) \geq 0$, then it implies that all the variables of the model $S(t), E(t), I(t)$ and $R(t)$ will all remain positive for all solutions of the model equations for $t > 0$

The closed region $\sum = \left\{(S, E, I, R) \in \mathbb{R}_+^4; \text{such that } 0 < N \leq \frac{\Lambda}{\mu_1}\right\}$ is positively invariant set for the model equations (2.1), (2.2), (2.3) and (2.4)

**Proof**

From the model equation (2.1)

$$\frac{dS}{dt} = \Lambda - (\gamma I_\tau + \mu_1)S$$

$$\frac{dS}{dt} + (\gamma I_\tau + \mu_1)S = \Lambda$$

Letting $(\gamma I_\tau + \mu_1)$ =A, the equation above becomes

$$\frac{dS}{dt} + AS = \Lambda$$

The integrating factor for the above Ordinary Differential Equation is given as $e^{\int A dt} = e^{At}$

$$e^{At}\frac{dS}{dt} + ASe^{At} = \Lambda e^{At}$$

$$\frac{d}{dt}(Se^{At}) = \Lambda e^{At}$$

Integrating the above equation and substituting the limits yields

$$S(t)e^{At} - S(0)e^{A(0)} = \Lambda e^{At} - \Lambda e^{A(0)}$$

$$S(t) = S(0)e^{-(\gamma I_\tau + \mu_1)t} + \Lambda - \Lambda e^{-(\gamma I_\tau + \mu_1)t} \qquad (2.5)$$

as $t \to \infty, S(t) = \Lambda > 0$ implying that S(t) is positive

From equation (2.2), (2.3) and (2.4) we can similarly show respectively that

$$E(t) = E(0)e^{-\int_0^t (\mu_2+\sigma)+(1-\sigma)\beta E(k-\tau)d\xi} + \int_0^t (\gamma S I_\tau)e^{-\int_\omega^t (\mu_2+\sigma)+(1-\sigma)\beta E(k-\tau)d\xi} d\omega \quad (2.6)$$

$$I(t) = I(0)e^{-\int_0^t \mu_3+(\alpha+\eta)I(k-\tau)]d\xi} + \int_0^t [(1-\sigma)\beta E(k-\tau)]\, e^{-\int_\omega^t [\mu_3+(\alpha+\eta)I(k-\tau)]d\xi} d\omega \qquad (2.7)$$

$$R(t) = R(0)e^{-\int_0^t \mu_4 d\xi} + \int_0^t [(\alpha+\eta)I(k-\tau) + \sigma E]\, e^{-\int_0^t \mu_4 d\xi} d\omega \qquad (2.8)$$

From the equations (2.5), (2.6), (2.7) and (2.8), since $S(t) > 0, E(t) > 0, I(t) > 0$ and R (t) > 0, it implies that the region $\sum$ is positively invariant and so it is sufficient to consider solution of the model equations.

**2.2.2 Boundedness of the solution of the model**

This subsection seeks to prove the boundedness of the solutions of the model equations. Since the model deals with the cell population, it follows that at any time, $t$ the sum of the cell population of all the compartments must be greater than the whole cell population.

**Theorem 2**

Let the closed region $\sum = \left\{(S, E, I, R) \in \mathbb{R}_+^4; \text{such that } 0 \leq N \leq \frac{\Lambda}{\mu_1}\right\}$ is bounded for the model equations (2.1), (2.2), (2.3) and (2.4)

**Proof**

Let $N(t) = S(t) + E(t) + I(t) + R(t)$ (2.9)

Differentiating (2.9) with respect to $t$ gives

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dE}{dt} + \frac{dI}{dt} + \frac{dR}{dt} \qquad (2.10)$$

Substituting (2.1), (2.2), (2.3) and (2.4) into (2.10) yields

$$\frac{dN}{dt} = \Lambda - \gamma SI_\tau - \mu_1 S + \gamma SI_\tau - \mu_2 E - \sigma E - \beta E_\tau + \sigma\beta E_\tau + \beta E_\tau - \sigma\beta E_\tau - \mu_3 I - \alpha I_\tau - \eta I_\tau + \alpha I_\tau + \eta I_\tau + \sigma E - \mu_4 R$$

$$= \Lambda - \mu_1 S - \mu_2 E - \mu_3 I - \mu_4 R$$

$$\frac{dN}{dt} \leq \Lambda - (S + E + I + R) \text{Where} \mu = \text{is the minimum of } \mu_1, \mu_2, \mu_3 \text{and } \mu_4$$

Letting $N = S + E + I + R$ yields

$$\frac{dN}{dt} \leq \Lambda - \mu N \qquad (2.11)$$

$$\frac{dN}{\mu N - \Lambda} \leq -dt \qquad (2.12)$$

Integrating equation (2.11) gives

$$\int_{N_0}^{N} \frac{dN}{\mu N - \Lambda} \leq \int_{t_0}^{t} -dt$$

$\ln(\mu N - \Lambda) - \ln(\mu N_0 - \Lambda) \leq -t - (-t_0)$

$\ln\left(\frac{\mu N - \Lambda}{\mu N_0 - \Lambda}\right) \leq t_0 - t$

$$N(t) \leq \frac{\Lambda}{\mu} + \frac{(\mu N_0 - \Lambda)e^{t_0}e^{-t}}{\mu} \qquad (2.13)$$

$$\lim_{t\to\infty} N(t) \leq \lim_{t\to\infty} \frac{(\mu N_0 - \Lambda)e^{t_0}e^{-t}}{\mu} \leq \frac{\Lambda}{\mu}$$

Hence $N(t) \leq \frac{\Lambda}{\mu}$

Which implies that $0 \leq N(t) \leq \frac{\Lambda}{\mu}$, $N(t)$ is bounded and so are $S(t)$,$E(t)$,$I(t)$ and $R(t)$of the model are also bounded in the region$\Sigma$

**2.3 Equilibrium points of the Model and their Stability Analysis.**

In epidemiology, there are usually two points of equilibrium, points where there is no change in the state of the system. The two points are the disease free equilibrium point and the endemic equilibrium point. For this study, the two points are Cancer Free Equilibrium Point (CFEP). The Cancer Free Equilibrium Point occurs when there is absence of cancer while at the Cancer Endemic Equilibrium Point there is presence of cancer within the cells. The equilibrium points are obtained by equating the model Equations 2.3, 2.4, 2.5 and 2.6 to zero then solving. The stability of the model is then studied around the equilibrium points. A system is said to be stable if all the eigenvalues obtained becomes linear around the fixed points.

**2.3.1 Cancer Free Equilibrium Point**

The Cancer Free Equilibrium Point $\mathcal{E}_o = (S_0, E_0, I_0, R_0)$ occurs when the infective class is absent and consequently the recoveries. It is found by equating the model equations to zero then evaluating.

At the Cancer Free Equilibrium$\frac{\mathrm{dS(t)}}{\mathrm{dt}} = \frac{\mathrm{dE(t)}}{\mathrm{dt}} = \frac{\mathrm{dI(t)}}{\mathrm{dt}} = \frac{\mathrm{dR(t)}}{\mathrm{dt}} = 0$ (2.14)

By substituting Equation (2.14) into the model equations (2.1), (2.2), (2.3) and (2.4) gives

$$\Lambda - \gamma\,\mathrm{SI}_\tau - \mu_1 \mathrm{S} = 0 \qquad (2.15)$$

$$\gamma\,\mathrm{SI}_\tau - \mu_2 \mathrm{E} - \sigma\mathrm{E} - (1-\sigma)\beta\mathrm{E}_\tau = 0 \qquad (2.16)$$

$$(1-\sigma)\beta\mathrm{E}_\tau - \mu_3 \mathrm{I} - (\alpha+\eta)\mathrm{I}_\tau = 0 \qquad (2.17)$$

$$(\alpha+\eta)\mathrm{I}_\tau + \sigma\mathrm{E} - \mu_4 \mathrm{R} = 0 \qquad (2.18)$$

If we let $\mathrm{I}_\tau = 0$ ,Equation (2.15) becomes $\Lambda - \mu_1 \mathrm{S} = 0$ and so

$$S = \frac{\Lambda}{\mu_1} \qquad (2.19)$$

Equations (2.16), (2.17) and (2.18) reduces to zero since all the infectious, exposed and the recovered sub populations are all equal zero i.e. $\mathrm{I} = \mathrm{E} = \mathrm{R} = 0$

Therefore, the Cancer Free Equilibrium Point of the SEIR model is then given by

$$\mathcal{E}_o = (S_0, E_0, I_0, R_0) = \left(\frac{\Lambda}{\mu_1}, 0, 0, 0\right)$$

**2.4 Determination of the basic reproductive number**

The basic reproduction number denoted by $\boldsymbol{R_0}$ is the most significant quantity in disease modeling. It is defined as the number of new infection incidences emanating from one infection known as the primary infection case in a completely vulnerable population. The reproduction number provides an overall measure of the potential for the spread of an infection within a completely susceptible population. Reproduction number also gives an elementary and explicit elucidation for the growth and decomposition of an endemic disease. The parameter is dependent not only on the transmission coefficient but also on the average duration of infectiousness of the disease. A higher value of the reproduction number ( $\boldsymbol{R_0}$) may be interpreted to mean a higher therapeutic intervention needed. Such intervention is to reduce the advancement and in the long run do away with the disease from the population under study. When $R_0 < 1$ the spread of cancer within the cells will reduce and finally die off while when$R_0 > 1$ the infection will persist.

To determine the reproductive number, the dominant or maximum eigenvalue of the next generation matrix is computed. The spectral radius of the matrix$\mathrm{FV}^{-1}$ gives the reproduction number that is,$R_0 = \rho(\mathrm{FV}^{-1})$ where $\boldsymbol{\rho}$ is the spectral radius of the next generation matrix, F is the matrix for the new cancer cells while V is the matrix of the transfers of infections from one compartment to another.

The vectors for the infected class and the uninfected class are then identified. The infected classes are E and Iwhich are represented by $\mathrm{X} = [\mathrm{E}, \mathrm{I}]^{\mathrm{T}}$while the uninfected class are represented by vector $\mathrm{Y} = [\mathrm{S}, \mathrm{R}]^{\mathrm{T}}$

The vector for the new infection rate $\mathcal{F} = \begin{bmatrix} \gamma\,\mathrm{SI}_\tau \\ 0 \end{bmatrix}$.This is the vector for new infections from the susceptible sub-population into the exposed sub-population.

The vector for other infections from compartment to another is given as

$$\mathcal{V} = \begin{bmatrix} (\mu_2+\sigma)\mathrm{E} + (1-\sigma)\beta\mathrm{E}_\tau \\ -(1-\sigma)\beta\mathrm{E}_\tau + \mu_3\mathrm{I} + (\alpha+\eta)\mathrm{I}_\tau \end{bmatrix}$$

The product of F and $\mathrm{V}^{-1}$ gives the next generation matrix

The matrix $\mathrm{F} = \left(\frac{\partial\mathcal{F}}{\partial \mathrm{X}}\Big|_{\mathcal{E}_0}\right)$ is the matrix formed by partial derivative of the vector of new infection rates evaluated at the Cancer

Free Equilibrium Point while the matrix $V = \left(\frac{\partial \mathcal{V}}{\partial X}\Big|_{\mathcal{E}_0}\right)$ is the matrix formed from the partial derivative of the vector of other rates which are not new infections evaluated at the Cancer Free Equilibrium Point. Therefore

$$F = \begin{bmatrix} \frac{\partial \mathcal{F}}{\partial E} & \frac{\partial \mathcal{F}}{\partial I} \\ \frac{\partial \mathcal{F}}{\partial E} & \frac{\partial \mathcal{F}}{\partial I} \end{bmatrix} \text{and} V = \begin{bmatrix} \frac{\partial \mathcal{V}}{\partial E} & \frac{\partial \mathcal{V}}{\partial I} \\ \frac{\partial \mathcal{V}}{\partial E} & \frac{\partial \mathcal{V}}{\partial I} \end{bmatrix}$$

Hence

$$F = \begin{bmatrix} 0 & \gamma S e^{-\lambda_\tau} \\ 0 & 0 \end{bmatrix} \text{and} V = \begin{bmatrix} (\mu_2 + \sigma) + (1-\sigma)\beta e^{-\lambda_\tau} & 0 \\ -(1-\sigma)\beta e^{-\lambda_\tau} & (\mu_3 + (\alpha + \eta)e^{-\lambda_\tau}) \end{bmatrix}$$

The inverse $V^{-1}$ of V is given as

$$= \frac{1}{(\mu_2 + \sigma + \beta e^{-\lambda_\tau} - \sigma\beta e^{-\lambda_\tau})(\mu_3 + \alpha e^{-\lambda_\tau} + \eta e^{-\lambda_\tau})} \begin{bmatrix} (\mu_3 + \alpha e^{-\lambda_\tau} + \eta e^{-\lambda_\tau}) & 0 \\ \beta e^{-\lambda_\tau} - \sigma\beta e^{-\lambda_\tau} & \mu_2 + \sigma + \beta e^{-\lambda_\tau} - \sigma\beta e^{-\lambda_\tau} \end{bmatrix}$$

$$= \begin{bmatrix} \frac{1}{\mu_2 + \sigma + \beta e^{-\lambda_\tau} - \sigma\beta e^{-\lambda_\tau}} & 0 \\ \frac{\beta e^{-\lambda_\tau} - \sigma\beta e^{-\lambda_\tau}}{(\mu_2 + \sigma + \beta e^{-\lambda_\tau} - \sigma\beta e^{-\lambda_\tau})(\mu_3 + \alpha e^{-\lambda_\tau} + \eta e^{-\lambda_\tau})} & \frac{1}{(\mu_3 + \alpha e^{-\lambda_\tau} + \eta e^{-\lambda_\tau})} \end{bmatrix}$$

Therefore $FV^{-1}$ reduces to

$$= \begin{bmatrix} 0 & \gamma S e^{-\lambda_\tau} \\ 0 & 0 \end{bmatrix} \begin{bmatrix} \frac{1}{\mu_2 + \sigma + \beta e^{-\lambda_\tau} - \sigma\beta e^{-\lambda_\tau}} & 0 \\ \frac{\beta e^{-\lambda_\tau} - \sigma\beta e^{-\lambda_\tau}}{(\mu_2 + \sigma + \beta e^{-\lambda_\tau} - \sigma\beta e^{-\lambda_\tau})(\mu_3 + \alpha e^{-\lambda_\tau} + \eta e^{-\lambda_\tau})} & \frac{1}{(\mu_3 + \alpha e^{-\lambda_\tau} + \eta e^{-\lambda_\tau})} \end{bmatrix}$$

$$= \begin{bmatrix} \frac{\gamma S e^{-\lambda_\tau}(\beta e^{-\lambda_\tau} - \sigma\beta e^{-\lambda_\tau})}{(\mu_2 + \sigma + \beta e^{-\lambda_\tau} - \sigma\beta e^{-\lambda_\tau})(\mu_3 + \alpha e^{-\lambda_\tau} + \eta e^{-\lambda_\tau})} & \frac{\gamma S e^{-\lambda_\tau}}{(\mu_3 + \alpha e^{-\lambda_\tau} + \eta e^{-\lambda_\tau})} \\ 0 & 0 \end{bmatrix}$$

And so

$$R_0 = \frac{\gamma S e^{-\lambda_\tau}(\beta e^{-\lambda_\tau} - \sigma\beta e^{-\lambda_\tau})}{(\mu_2 + \sigma + \beta e^{-\lambda_\tau} - \sigma\beta e^{-\lambda_\tau})(\mu_3 + \alpha e^{-\lambda_\tau} + \eta e^{-\lambda_\tau})} \qquad (2.20)$$

From (2.19), Equation (2.20) becomes

$$R_0 = \frac{\beta\Lambda\gamma e^{-2\lambda_\tau}(1-\sigma)}{\mu_1(\mu_2 + \sigma + \beta e^{-\lambda_\tau} - \sigma\beta e^{-\lambda_\tau})(\mu_3 + \alpha e^{-\lambda_\tau} + \eta e^{-\lambda_\tau})}$$

**2.5 Determination of the Stability of the Equilibrium Points**

The study of the stability of the equilibrium points consider the linearization of the model Equations about both the Cancer Free Equilibrium by taking the Jacobian Matrix the model equations

**2.5.1 Local Stability of the Cancer Free Equilibrium Points**

The local stability of the Cancer Free Equilibrium Point being the point where if the system is put somewhere nearby the equilibrium point, then it will move itself to the equilibrium point in some time.

**Theorem 3**

The Cancer Free Equilibrium Point $\mathcal{E}_0$ is locally stable if $R_0 < 1$ whereas $\mathcal{E}_0$ is unstable if $R_0 > 1$.

**Proof**

The Jacobian matrix at the Cancer Free Equilibrium Point is computed by differentiating each of the equations (2.1), (2.2), (2.3) and (2.4) with respect to S, E, I and R and letting $E = I = R = 0$. The matrix is defined as,

$$J_{\mathcal{E}_0} = \begin{bmatrix} -\mu_1 & 0 & -\gamma S e^{-\lambda_\tau} & 0 \\ 0 & -(\mu_2 + \sigma + \beta e^{-\lambda_\tau} - \sigma\beta e^{-\lambda_\tau}) & \gamma S e^{-\lambda_\tau} & 0 \\ 0 & \beta e^{-\lambda_\tau} - \sigma\beta e^{-\lambda_\tau} & -(\mu_3 + \alpha e^{-\lambda_\tau} + \eta e^{-\lambda_\tau}) & 0 \\ 0 & \sigma & \alpha e^{-\lambda_\tau} + \eta e^{-\lambda_\tau} & -\mu_4 \end{bmatrix} \qquad (2.21)$$

And the associated polynomial is given as $|J_{\mathcal{E}_0} - \lambda I| = 0$ and at the Cancer Free Equilibrium Point. Applying (2.19) in (2.21) we get

$$\begin{vmatrix} -\mu_1 - \lambda & 0 & \frac{-\gamma\Lambda e^{-\lambda_\tau}}{\mu_1} & 0 \\ 0 & -(\mu_2 + \sigma + \beta e^{-\lambda_\tau} - \sigma\beta e^{-\lambda_\tau}) - \lambda & \frac{\gamma\Lambda e^{-\lambda_\tau}}{\mu_1} & 0 \\ 0 & \beta e^{-\lambda_\tau} - \sigma\beta e^{-\lambda_\tau} & -(\mu_3 + \alpha e^{-\lambda_\tau} + \eta e^{-\lambda_\tau}) - \lambda & 0 \\ 0 & \sigma & \alpha e^{-\lambda_\tau} + \eta e^{-\lambda_\tau} & -\mu_4 - \lambda \end{vmatrix} = 0 \qquad (2.22)$$

Letting $A = -\mu_1, B = \frac{-\gamma\Lambda e^{-\lambda_\tau}}{\mu_1}, C = -(\mu_2 + \sigma + \beta e^{-\lambda_\tau} - \sigma\beta e^{-\lambda_\tau}), D = \frac{\gamma\Lambda e^{-\lambda_\tau}}{\mu_1}, Y = \beta e^{-\lambda_\tau} - \sigma\beta e^{-\lambda_\tau}, F = -(\mu_3 + \alpha e^{-\lambda_\tau} + \eta e^{-\lambda_\tau}), G = \sigma, H = \alpha e^{-\lambda_\tau} + \eta e^{-\lambda_\tau}$, and $Z = -\mu_4$

Equation (2.22) reduces to,

$$\begin{vmatrix} A-\lambda & 0 & B & 0 \\ 0 & C-\lambda & D & 0 \\ 0 & Y & F-\lambda & 0 \\ 0 & G & H & Z-\lambda \end{vmatrix} = 0$$

On solving we obtain the values of $\lambda_1, \lambda_2, \lambda_3$ and $\lambda_4$ as follows

$\lambda_1 = A, \lambda_2 = Z$

$$\lambda_3 = \frac{(C+F) + \sqrt{C^2 + F^2 - 2CF + 4DY}}{2}$$

and

$$\lambda_4 = \frac{(C+F) - \sqrt{C^2 + F^2 - 2CF + 4DY}}{2}$$

The Cancer Free Equilibrium point $\mathcal{E}_0$ in the model equations is asymptotically stable if $\lambda_1, \lambda_2, \lambda_3, \lambda_4 < 0$ and unstable if at least one of the $\lambda_1, \lambda_2, \lambda_3, \lambda_4$ is greater than zero for all $\mu_1, \mu_2, \mu_3, \mu_4, \sigma, \beta, \eta, \alpha, \Lambda$ and $\gamma$ being positive. The first two eigenvalues $\lambda_1 = -\mu_1$ and $\lambda_2 = -\mu_4$, which are real negative values, a sufficient condition for local stability. It is also clear that $\lambda_4$ is less dominant to $\lambda_3$. $\lambda_3$ is therefore the most dormant Eigen value.

$$\frac{(C+F) + \sqrt{C^2 + F^2 - 2CF + 4DY}}{2} < 0$$

for the stability of the Cancer Free Equilibrium point

$DY < CF$

$$\left(\frac{\gamma\Lambda e^{-\lambda_\tau}}{\mu_1}\right)\left(\beta e^{-\lambda_\tau} - \sigma\beta e^{-\lambda_\tau}\right) < (\mu_2 + \sigma + \beta e^{-\lambda_\tau} - \sigma\beta e^{-\lambda_\tau})(\mu_3 + \alpha e^{-\lambda_\tau} + \eta e^{-\lambda_\tau})$$

$$\frac{\Lambda\gamma e^{-\lambda_\tau}\left(\beta e^{-\lambda_\tau} - \sigma\beta e^{-\lambda_\tau}\right)}{\mu_1(\mu_2 + \sigma + \beta e^{-\lambda_\tau} - \sigma\beta e^{-\lambda_\tau})(\mu_3 + \alpha e^{-\lambda_\tau} + \eta e^{-\lambda_\tau})} < 1$$

$R_0 < 1$ hence the Cancer Free Equilibrium is stable

### 3.MainResults

The numerical simulations of the equations of the model were determined using the following parameters and their estimated values.

**Table 1**: Table of parameters and their values

| **Parameter** | **Description** | **Value** |
|---|---|---|
| S(0) | Initial Susceptible population | 1000(estimated) |
| E(0) | Initial Exposed population | 500(estimated) |
| I(0) | Initial Infected population | 400(estimated) |
| R(0) | Initial Recovered population | 300(estimated) |
| N(0) | Initial Total population | 2200(estimated) |
| γ | Rate at which Susceptible cells become exposed by one infectious cell per contact time | 0.5 (estimated) |
| **β** | Rate at which the exposed cells become infectious | 0.02 (estimated) |
| σ | Recovery rate of exposed cells due to autoimmunity | 0.03 (estimated) |
| η | Recovery rate of symptomatic cells due to chemotherapy | 0.01 (estimated) |
| ∧ | Constant influx rate of new susceptible cells | 0.02 (estimated) |
| $\mu_1$ | Coefficient of Natural mortality rate of Susceptible cells | 0.005(estimated) |
| $\mu_2$ | Natural mortality rate of | 0.020(estimated) |

| | | |
|---|---|---|
| | Exposed cells | |
| $\mu_3$ | Natural mortality rate of Infective cells | 0.050(estimated) |
| $\mu_4$ | Rate of mortality of the recovered sick cells | 0.010(estimated) |
| $\alpha$ | Natural recovery rate of symptomatic infected cells | 0.02(estimated) |
| $\tau$ | Time Delay | To be determined |

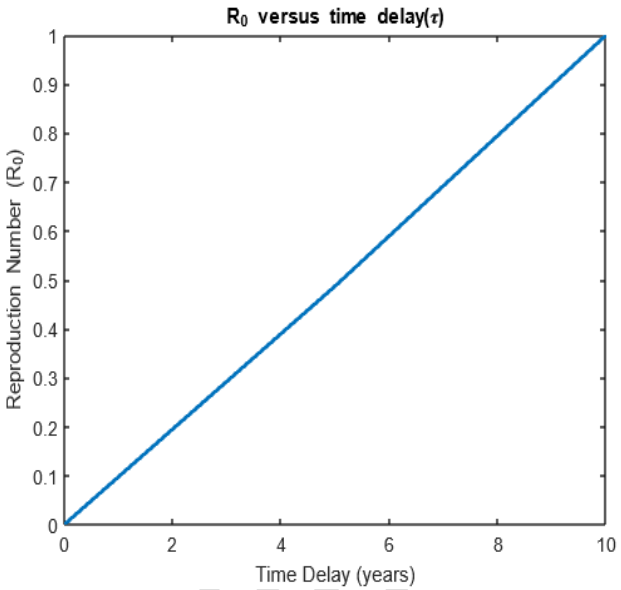


**Figure 1**: A plot of Reproduction number ($R_o$) against Time Delay (years) ($\tau$)

**Figure 1** shows a plot of the Reproduction number ($R_0$) against the Time delay ($\tau$) in days. From the graph it's clear that as the Time delay increases the amount of tumor cells also increases while the amount of tumor cells are lower when the delay time is shorter.

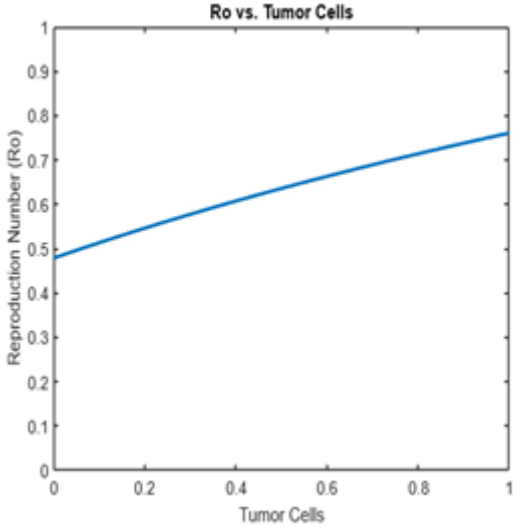


**Figure 2**: A plot of Reproduction number ($R_0$) against the Number of Tumor Cells

**Figure 2** shows a plot of the Reproduction number ($R_0$) against the Number of Tumor Cells. From the graph it can be seen clearly that there is an increase in the amount of Tumor cells as the Reproduction Number increases. Also at low replication rate the Number of Tumor cells are lower.

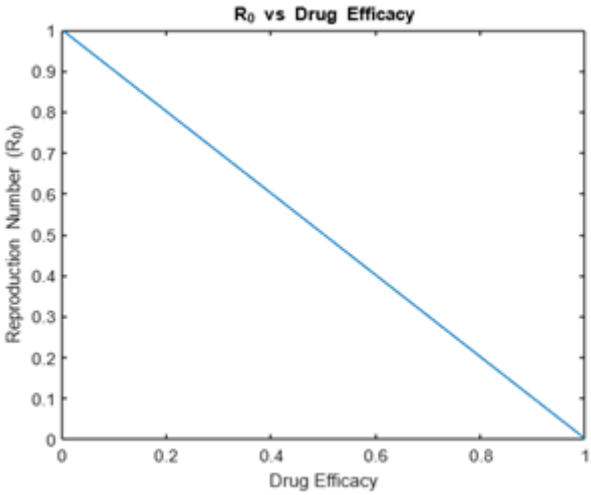


**Figure 3**: A plot of Reproduction number ($R_0$) against the Drug Efficacy

**Figure 3** shows a plot of the Reproduction number ($R_0$) against the Drug Efficacy. It shows that as the drug efficacy increases, the reproduction number decreases. This therefore depicts that chemotherapy plays an important role in reducing the tumor replication for stability to be attained at $R_0 < 1$

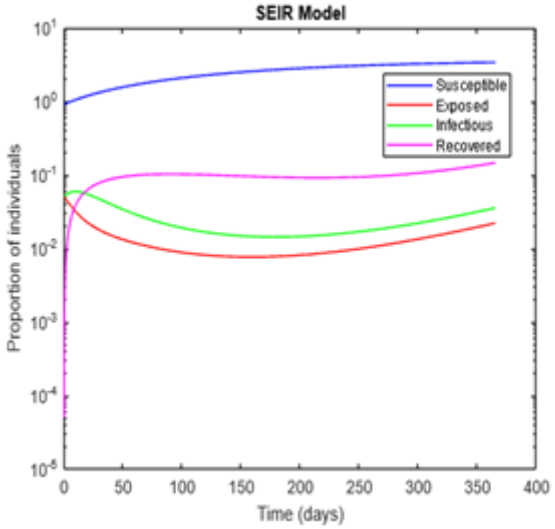


**Figure 4**: A plot of Proportion of individuals against the Time (days).

**Figure 4** shows a plot of the Proportion of individuals against the Time in days. It gives the dynamics of the various compartments of the SEIR model with time. From the graph it's clear that the number of the susceptible cells are more than the infected cells.

## 4. Summary, Conclusion and Recommendations

### 4.1 Introduction

The chapter outlines in summary the effects of incubation and chemotherapy on both the Cancer Free Equilibrium Point (CFEP)

### 4.2 Summary of the three sections of this research paper.

The major aim of this research was to formulate a SEIR model for the Tumor dynamics using delay differential equations and then study the effects of time delay and the effects of chemotherapy or drug efficacy on the stability of both the Cancer Free Equilibrium Point (CFEP). These effects are analyzed analytically and numerically using MATLAB DDE23 solver and assumed parameter values. In Chapter One, an introduction of the thesis is given. Starting with background information of the research is discussed by highlighting cancer modeling, definition of cancer and types of Tumors are illustrated including a summary discussion on cancer statistics and its methods of treatment. The definition of Delay Differential Equations, types of Delay Differential Equations, simulations of delay differential equations and their analytic solutions are also discussed. Finally, the problem statement for the research, the objectives of the research and the significance of the research are also given attention in this chapter. Chapter Two outlines a brief literature cancer modeling, methods used, findings and limitations of such studies. Here the research gaps were identified which formed the basis of this study. Chapter three, outlines the methodology of the research. The SEIR model for the Tumor dynamics, its assumptions and the model equations. The model preliminary analysis, the determination of the basic reproductive number, computation of the Cancer Free Equilibrium Point

and Cancer Endemic Equilibrium Point and the stability analysis of the equilibrium points both local and global were also discussed in this chapter. In Chapter Four, numerical simulations were obtained using MATLAB DDE23 and analytic results derived in Chapter Three were verified.

### 4.3 Conclusions

The research was a formulation of a Delay Differential Equation of SEIR Tumor growth dynamics model. The CFEP was attained when$R_0 < 1$. Numerical simulation of the model was carried out to validate the analytic results. It was found out that, $R_0$ was 0.6667 at CFEP. The reproduction number is critical in minimizing the growth of Tumor. The increased educational awareness for early screening also helps in early detection for ease of management.

### 4.4 Recommendations

This research has not exhausted all the scientific studies on Tumor growth dynamics and treatment. The effects of immune response to Tumor growth dynamics were not considered. The model can be extended to include reaction-diffusion effects on the Tumor growth dynamics. Public knowledge through education on pre-disposing factors and early screening are also possible insights for further research work on Tumor growth dynamics. An advancement for a vaccine therapy against the Tumor development and growth should also be considered in future studies.

### 4.5 Suggestions for Further Research

The research recommends future work should consider inclusion of reaction –diffusion model and the effect of the immune response and chemotherapy. This is because of possible spread of Tumor to other parts of the body hence reaction-diffusion.

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