PROJECT-TITLE

MATHEMATICAL MODELING OF TUMOR GROWTH

Department of Mathematics

Shahjalal University of Science and Technology, Sylhet

A project submitted to the Department of Mathematics

for the fulfillment of the requirement for Course No. MAT 433

(Course Title: Project in Mathematics and Relevant Fields)

in 4th Year 2nd Semester 2018 (Session 2014-15

for B.Sc. (Honours) degree in Mathematics

Supervised By

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Submitted By

Project Group No: 14

Students of 4th Year 2nd Semester

Session: 2014-15

DECLARATION

We the undersigned hereby declare that we have done this project, entitled 'Mathematical modeling of tumor growth', under the supervision of Professor Dr. Md. Aminul Haque, Department of Mathematics, Shahjalal University of Science and Technology, Sylhet, Bangladesh.

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Session: 2014-15

CERTIFICATION

I hereby certify that this project, entitled 'Mathematical modeling of tumor growth' submitted by the students **Tanjim-Ul-Anam (Reg. No. 2014133099)** and **Md. Arafat Dewan Rishad (Reg. No. 2014133020)**, conform to acceptable standards and is fully adequate in scope and quality to fulfill the requirements for Course No. MAT 433 (Course Title: Project in Mathematics and Relevant Fields) in 4th Year 2nd Semester 2018 (Session 2014-15) of B.Sc. (Honours) degree in Mathematics.

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ACKNOWLEDGEMENTS

All compliments to almighty Creator who has given us the energy and ability to complete this work successfully. We would like to express our deepest gratitude, appreciation, deepest sense of indebtedness and profound respect to our supervisor **Professor Dr. Md. Aminul Haque**, Department of mathematics, Shahjalal University of Science and Technology for his continuous proper and perfect guidance, valuable suggestions and affectionate encouragement at every stage of our best teacher whom we always have the privilege to learn from.

ABSTRACT

Using mathematical models to simulate the dynamics of biological processes has a long history. Over the past couple of decades or so, quantitative approaches have also made their way into cancer research. Tumors in general and cancers in particular are tissues growing under special conditions. Typically, the body is able to balance cell growth and division. In the case of tumors, cells grow abnormally and this abnormal growth of cells is known as tumor. An increasing number of mathematical, physical and computational techniques have been applied to various aspects of tumor growth, with the ultimate goal of understanding the response of the cancer population to clinical intervention. In this project, firstly tumor growth models considering uninfected and infected cells were discussed. Furthermore, we have also explored the dynamics of tumor growth considering uninfected, infected and free virus cells and figure out the response of cells on tumor growth. We have determined the equilibrium points and Jacobian matrix from the models. In the analysis, we have obtained the virus free state that is the nonzero equilibrium point is stable which means infected cells are cleared and tumor cannot develop in our body. On the contrary in the virus state the nonzero equilibrium point is stable virus cells remain and tumor can develop in our body. Furthermore, we have developed MATLAB code and performed the numerical simulations which are used to represent the result graphically.

Key words: Tumor growth, asymptotical stability, numerical solution, cancer, uninfected cells, infected cells, free virus cells.

CONTENTS

CHAPTER 1

GENERAL INTRODUCTION

1.1 Introduction:

The tumor modeling represents a complex multistep phenomenon which is highly discussed in the literature. To study the tumor evolution different ODE models have been presented and developed in the literature [1,2,3]. The growth of tumors can be represented by three basic stages (avascular, vascular and metastasis) and its modeling depends on these stages. The avascular stage, which can also be studied using both discrete or continuum models [5]. In order to grow, an angiogenesis process is added to the system considered implying blood vessel formation [4]. Finally, the metastasis stage is well known to be difficult to treat and is characterized by a propagation of tumor cells in different parts of the body. Basically, these different models are based on mass conservation laws and reaction diffusion processes.

Tumors in general and cancers in particular are tissues growing under special conditions. Typically, the body is able to balance cell growth and division. In the case of tumors, cells grow abnormally and this abnormal growth of cells is known as tumor. Cancer cells grow in the same manner. However, unlike the cells in benign tumors, cancerous cells can invade nearby tissue and spread to other parts of the body. During tumor growth, normal cellular pathways that prevent growth and protect genome integrity are often blocked due to mutations. Conversely, pro-growth pathways are usually hyper-activated, often by acquired and, in some cases, congenital mutations. As the tumor grows, hypoxia induces the expression of growth factors that stimulate blood vessel formation into and around the tumor, further promoting growth.

Tumor growth modeling is one of the most important topics in recent time and thousands of papers and journal article have been published. Herein we will give an introduction on how such models are derived and how they can be utilized to simulate tumor growth and treatment response. We will then discuss a number of different models and discuss their confirmative and predictive power for cancer biology.

1.2 Structure of this project:

The structure of this project as follows:

In Chapter:2, *we have discussed some definitions which will be needed in later sections*

In Chapter:3, *we have discussed tumor growth considering uninfected and infected cells.*

In Chapter:4, *we have discussed tumor growth considering uninfected, infected and free virus cells.*

In Chapter:5, *Discussions and General Conclusion*

Appendix:

References:

CHAPTER 2

PRELIMINARIES

2.1 Mathematical Modeling:

A mathematical model is an abstract model that uses mathematical language to describe the behavior of a system. Mathematical models are used particularly in the natural sciences and engineering disciplines (such as physics, biology, and electrical engineering) but also in the social sciences and business (such as economics, finance, sociology, and political science). However, physicists, engineers, computer scientists, and economists use mathematical models most extensively. Mathematical models can take many forms, including but not limited to dynamical systems, statistical models, differential equations, or game theoretic models. A differential equation that describes some physical process is often called a mathematical model for the process. It is a description of a system using mathematical concepts and language. The mathematical model is used in a different section of science and engineering. A model may help to explain a system and to study the effects of different components and to make predictions about the behavior [18].

2.2 Cell:

The cell is the basic structural, functional, and biological unit of all known living organisms. A cell is the smallest unit of life. Cells are often called “building blocks of life” [9].

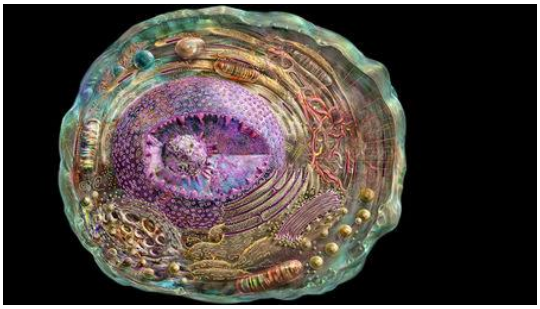


Fig-2.1: cell [13]

2.3 Cancer:

Cancer is a group of diseases involving abnormal cell growth with potential to invade or spread to the other parts of the body [7].

2.4 Tumor:

A tumor is an abnormal growth of cells that serves no purpose. Tumor can be solid or fluid. In general, tumors are divided in three groups [8].

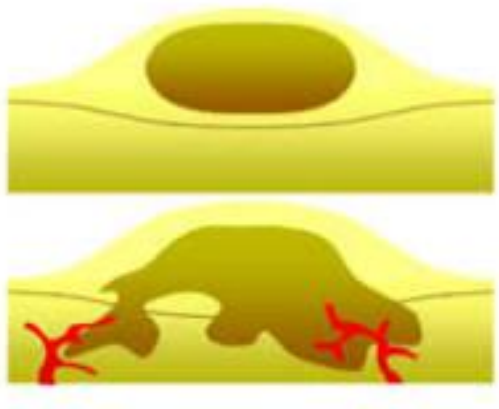


Fig-2.2: Tumor

2.5 Types of Tumor:

Benign:

These are not cancerous and cannot spread. A benign tumor will remain in its current form. They do not generally return after being removed. Most benign tumor are not harmful to human health. However, even though they are not cancerous, some may press against nerves and blood vessels and cause pain and other negative effects [14].

Example:

1.Adenomas

2.Fibroids

3.Hemangiomas

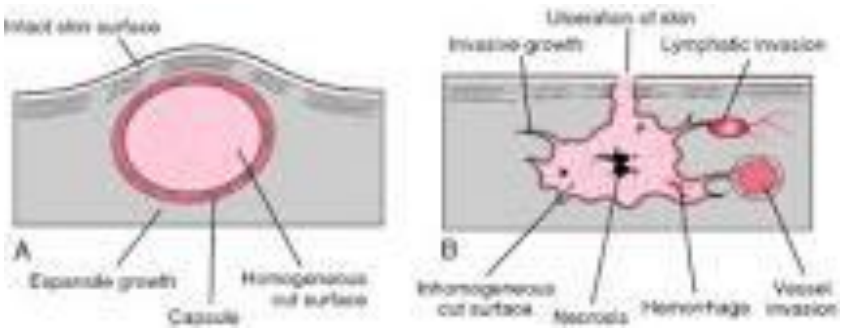


Fig-2.3: Benign Tumor [12]

Premalignant:

A premalignant tumor is not yet cancerous but appears to be developing the properties of cancer.

Example:

1. Actinic keratosis
2. Cervical dysplasia
3. Leukoplakia

Malignant:

Malignant tumor is cancerous. They grow first, spread and get worse.

Example:

1. Carcinoma
2. Sarcoma
3. Blastoma

2.6 Virus:

Viruses depend on the host cells that they infect to reproduce. When found outside of host cells, viruses exist as a protein coat or capsid, sometimes enclosed within a membrane. The capsid encloses either DNA or RNA which codes for the virus elements [10].

2.7 Immune system:

The immune system is the body's defense against infectious organisms and other invaders. Through a series of steps called the immune response, the immune system attacks organisms and substances that invade body systems and cause disease [11].

2.8 Angiogenesis:

Angiogenesis is the formation of new blood vessels. This process involves the migration, growth, and differentiation of endothelial cells, which line the inside wall of blood vessels [15].

2.9 Equilibrium point:

Equilibrium is a state of a system which does not change. If the dynamics of a system is described by a differential equation (or a system of differential equations), then equilibria can be estimated by setting a derivative (all derivatives) to zero. An equilibrium (or equilibrium point) of a dynamical system generated by an autonomous system of ordinary differential equations (ODEs) is a solution that does not change with time. For example, each motionless pendulum position corresponds to the equilibrium of the corresponding equations of motion, one is stable, the other one is not. Geometrically, equilibria are points in the system's phase space.

More precisely, the ODE, $x' = f(x)$ has an equilibrium solution $x(t) = xe, if\ f(xe) = 0$. Finding equilibria, i.e., solving the equation $f(x) = 0$ is easy only in a few special cases.

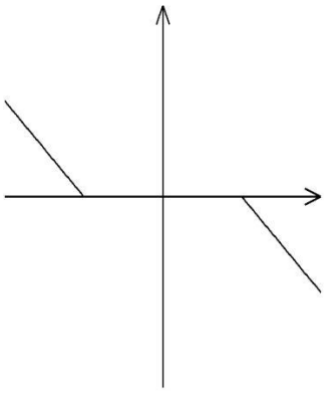
Equilibria are sometimes called fixed points or steady states. Most mathematicians refer to equilibria as time-independent solutions of ODEs, and to fixed points as time-independent solutions of iterated maps $x(t + 1) = f(x(t))$.

2.10 Stable:

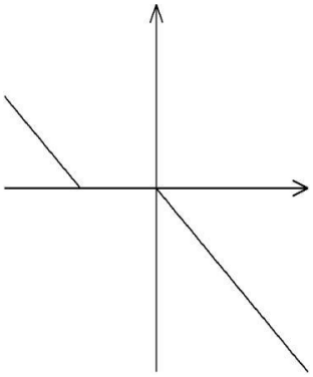
An equilibrium solution N = c is called stable if any solution N(t) that starts near N = c stays near it. The equilibrium N = c is called asymptotically stable if any solution N(t) that starts near N = c (Constant) actually converges to it -- that is,

$Lim\ t \to \infty N(t) = c$ (Constant)

The origin is stable if and only if x $f(x) \leq 0$ in some neighborhood of the origin.



Stable



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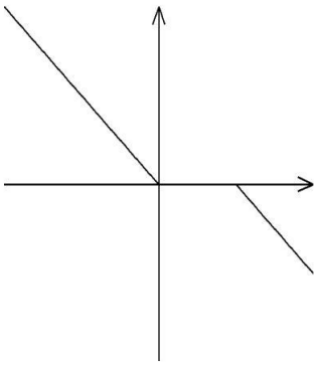


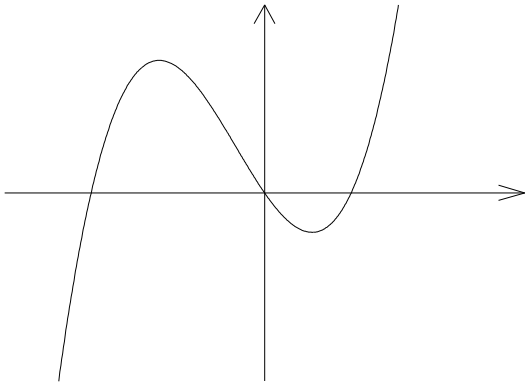
stable

2.11 Eigenvalue:

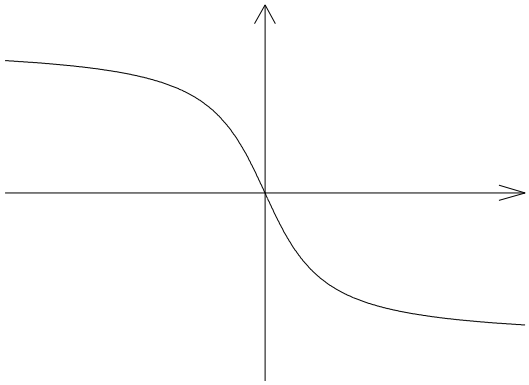
A scalar associated with a given linear transformation of a vector space and having the property that there is some nonzero vector which when multiplied by the scalar is equal to the vector obtained by letting the transformation operate on the vector especially**:** a root of the characteristic equation of a matrix.

2.12 Asymptotically Stable and Globally Asymptotically Stable:

The origin is asymptotically stable if and only if $x\, f(x) < 0$ in some neighborhood of the origin



Asymptotically Stable



Globally Asymptotically Stable

CHAPTER 3

Tumor growth models considering uninfected and infected cells

3.1 Introduction:

Modeling tumor-immune interaction has attracted much attention in the last decades. This interaction is very complex and mathematical models can help to shape our understanding the dynamics of this biological phenomenon. Tumor is formed by new cells that are mutated, we also said that they grow quicker than the healthy ones. But not all tumors cells grow up in the same way. If this happen, a cell cycle around 24 hours would make 10^6 tumor cells and after less than one month, there is a tumor of 10cm.That is the reason why we differentiate at least two types of cells uninfected and infected. In this chapter we have considered models for tumor growth considering uninfected and infected cells and drug therapy.

3.2 Mathematical Formulation:

In this model we have discuss about two types of cells uninfected and infected. We have considered the function $F(P)$ which represents the growth of uninfected cells. In our case we will take logistic power and Gompertz law.

Moreover, a tumor exhibits a layer of infected cells which are thought to arise as uninfected cells lose access to nutrients. In the same way, infected cells die after sufficient lack of nutrient, this is expressed $by - dI$ (d the death rate). In addition, it is known that infected cells may transform into uninfected cells again. So, there will be an exchange of uninfected and infected cells, this is expressed as $bU - cI$, where bU represents the cells that became infected and $-cI$ the ones that transform to uninfected $-cU$. It is considered a linear transition between U and I and I and U, whatever is the way of transferring from U to I or in reverse, it may be expressed as a Taylor series in U, and this expression has a linear leading term.

A system of differential equation represents the following tumor growth model (3.1) considering uninfected and infected cells.

$\frac{dU}{dt} = F(U) - bU + cI;$

(3.1)

$\frac{dI}{dt} = bU - cI - dI;$

The size of the tumor is defined by:

$N(t) = U(t) + I(t);$

3.3 Analysis of mathematical stability:

$\frac{dU}{dt} = U.R(U) - bU + cI$

$\frac{dI}{dt} = bU - cI - dI$

We consider,

F(U) = $U.R(U) = rU\left(1 - \frac{U}{K}\right)^a$

where $r > 0, K > 0, a > 0, b > 0, c > 0 \; and \; d \geq 0.$

For the equilibrium point, $\frac{dU}{dt} = \frac{dI}{dt} = 0$

$\frac{dU}{dt} = rU\left(1 - \frac{U}{K}\right)^a - bU + cI = 0$……(3.2)

$\frac{dI}{dt} = bU - cI - dI = 0$…… (3.3)

From (3.3),

$bU - cI - dI = 0$

$I = \frac{bU}{c+d}$

From (3.2),

$rU\left(1 - \frac{U}{K}\right)^a - bU + cI = 0$…… (3.4)

Pitting the value of I in (3.4) we get,

$U\left(r\left(1-\frac{U}{K}\right)^{a}-b+\frac{cb}{c+d}\right)=0$

So, $U=0$ or $r\left(1-\frac{U}{K}\right)^{a}-b+\frac{cb}{c+d}=0$

If we take $U=0$ then, $I=0$

so, $(0,0)$ is an equilibrium point.

Again if, $r\left(1-\frac{U}{K}\right)^{a}-b+\frac{cb}{c+d}=0$

then $U_1 = \mathrm{K}\sqrt[a]{1-\frac{bd}{r(c+d)}}$ and

$I_1 = \frac{bU}{c+d}U_1$

$(\overline{U_1},\overline{I_1})$ is another equilibrium point $\left(\mathrm{K}\sqrt[a]{1-\frac{bd}{r(c+d)}}\ ,\frac{bU}{c+d}\ \mathrm{U}_1\right)$

If we take the equilibrium point $(U,I)=(0,0)$

Now we check the stability for $\overline{E_1}$= (0 ,0),

let [J($\bar{E}_1$)] be the Jacobian matrix

$$[\mathrm{J}(\bar{E}_1)] = \begin{bmatrix} r\left(1-\frac{U}{K}\right)^{a}-\frac{rUa}{k}\left(1-\frac{U}{K}\right)^{a-1}-b & c \\ b & -c-d \end{bmatrix}$$

$$= \begin{bmatrix} r-b & c \\ b & -c-d \end{bmatrix}$$

$$det[M] = (r-b)(-c-b)-bc$$
$$= -rc-br+bc+bd-bc$$
$$= bd-cr-br<0$$

If $bd<r(b+c)$

$tr[M]=r-b-c-d<0$

If $r<b+c+d$

So, $det[M] < \frac{1}{4}\, tr[M]^2$

Therefore, we have two distinct real eigenvalues

$$\begin{vmatrix}\lambda & 0\\ 0 & \lambda\end{vmatrix} - \begin{bmatrix} r-b & c \\ b & -c-d\end{bmatrix} = 0$$

$$\begin{vmatrix}\lambda - r + b & c \\ b & \lambda + c + d\end{vmatrix} = 0$$

Characteristic equation is,

$$\lambda^2 - (-b-c-d\ +\ r)\lambda + (bd - cr - br) = 0$$

Therefore, the eigen values are:

$$\lambda_1 = \frac{1}{2}(-b-c-d+\ r\ -\ \sqrt{(-b-c-d+r)^2 - 4(bd-cr-dr)}\ )$$

$$\lambda_2 = \frac{1}{2}(-b-c-d\ \ +\ r + \sqrt{(-b-c-d+r)^2 - 4(bd-cr-dr)}\ )$$

Since, $bd - cr - dr < 0$

Then, $-4(bd-cr-dr) > 0$ and $\sqrt{(-b-c-d+r)^2 - 4(bd-cr-dr)} > 0$

So, eigenvalues are real and distinct. Therefore, the zero-equilibrium point is a node and the model is asymptotically stable.

If we take the equilibrium point $\overline{E}_2 = (\overline{U_1}, \overline{I_1})$ $= \left(\mathrm{K}\sqrt[a]{1 - \frac{bd}{r(c+d)}}, \frac{bU}{c+d}\ \mathrm{U}_1\right)$

Now we check the stability for $\bar{E}_2 = \left(\mathrm{K}\sqrt[a]{1 - \frac{bd}{r(c+d)}}, \frac{bU}{c+d}\ \mathrm{U}_1\right)$

let $[\mathrm{J}(\bar{E}_2)]$ be the Jacobian matrix

$$[\mathrm{J}(\bar{E}_2)] = \begin{bmatrix} r\left(1-\frac{U}{K}\right)^a - \frac{rUa}{k}\left(1-\frac{U}{K}\right)^{a-1} - b & c \\ b & -c-d\end{bmatrix}$$

$$= \begin{bmatrix} -ar + \frac{bd}{c+d}\left(1+a\right) - b & c \\ b & -c-d\end{bmatrix}$$

$$det[M] = \left(-ar + \frac{bd}{c+d}(1+a) - b\right)(-c-d) - bc$$

$$tr[M] = -ar + \frac{bd}{c+d}(1+a) - b - c - d$$

$det[M] < 0$ and $tr[M] < 0$

Since, $r > 0, b > 0, a > 0, c > 0$ *and* $d \geq 0$.

So, $det[M] < \frac{1}{4} tr[M]^2$

Therefore, we have two distinct real eigenvalues.

$$\begin{vmatrix} \lambda & 0 \\ 0 & \lambda \end{vmatrix} - \begin{bmatrix} -ar + \frac{bd}{c+d}(1+a) - b & c \\ b & -c-d \end{bmatrix} = 0$$

$$\begin{bmatrix} \lambda + ar - \frac{bd}{c+d}(1+a) + b & c \\ b & \lambda + c + d \end{bmatrix} = 0$$

So, the characteristic equation is: $\lambda^2 - (tr\ M)\ \lambda + det\ M$.

$\overline{\lambda}_1 = \frac{1}{2}\left(tr\ M + \sqrt{((tr\ M)^2 - 4 \det M)}\right)$

$\overline{\lambda}_2 = \frac{1}{2}\left(tr\ M - \sqrt{(tr\ M)^2 - 4 \det M)}\right)$

Since, $det[M] < 0$

Then, $-4 \det M > 0$ and so, $\sqrt{(tr\ M)^2 - 4 \det M)} > 0$

So, eigenvalues are real and distinct. Therefore, the nonzero-equilibrium point is a node and the model is asymptotically stable.

3.4 Numerical Analysis:

The system which we have discussed is a system of non- linear ODE and it is difficult to find the analytical solution of the model. Hence, we have executed the numerical analysis to find the numerical solution and visualize these solutions graphically through MATLAB program. To find the numerical solution, MATLAB code has been developed. We have also checked the stability condition of the model on both the equilibrium point. In order to support the theoretical result, we have developed the MATLAB code to show the stability numerically and graphically.

We have used the parameter values to perform our numerical analysis which is shown in the table below:

Table-3.4.1 Variables and parameter:

Parameters and variables:	Values
Variables:	
U = Uninfected cells density	10 mm^{-3}
I = Infected cells density	10 mm^{-3}
Parameters and constants:	
a = growth rate of uninfected cells	1 day^{-1}
b = rate of change to infected cells	1day^{-1}
d = death rate of infected cells	0.5 day^{-1}
c = rate of change to uninfected cells	0.2 day^{-1}
k = vasculature of the tumor	1 mm^{-3}

3.4.2 Numerical solutions of the model by using the values of parameters from (Table-3.4.1):

U	I
10.000000000000000	10.000000000000000
9.496433212205298	9.977568980644255
9.040760044318468	9.950644355086729
8.626525293044862	9.919722617790068
8.248381992610886	9.885235910725667
7.901863377781519	9.847562619008432
7.583208930785149	9.807035856979878
7.289230115831433	9.763950331566623
7.017205624032329	9.718567943218151
6.764798828754006	9.671122394492672
6.529992144772179	9.621823011098545
6.311034385810778	9.570857932387622
6.106398213312642	9.518396792851030
5.914745489380905	9.464592989598442
5.734898872285371	9.409585610680981
5.565818380498672	9.353501083734777
5.406581939976575	9.296454592555925
5.256369146550688	9.238551299987781
5.114447640056082	9.179887408265968
4.980161612853238	9.120551082252543
4.852922072575661	9.060623256447164
4.732198554404366	9.000178343026404
4.617512037193399	8.939284855233641
4.508428864234861	8.878005958069533
4.404555506258165	8.816399956300641
4.305534033586688	8.754520728221468
4.211038187876387	8.692418112303022
4.120769962793978	8.630138252784379
4.034456618322687	8.567723909369478
3.951848065857397	8.505214735445392
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3.5 Graphical representations:

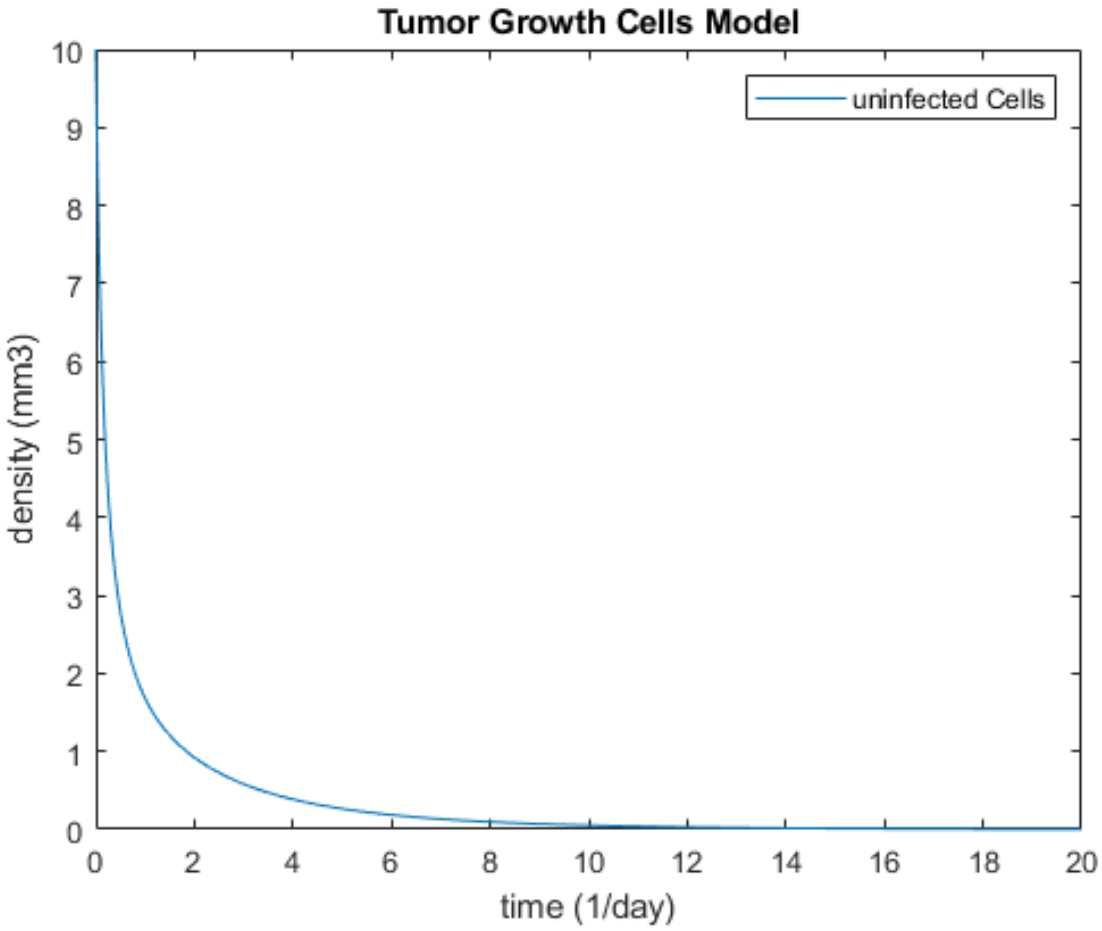

Fig-3.1: Shows the stability of uninfected cells

In this Fig-3.1 we have observed uninfected cells density with respect to time. It's density deceases with time and becomes a straight line approximately after 10 days. So, approximately after 10 days uninfected cells have reached to equilibrium when the initial density is $10mm^{-3}$.

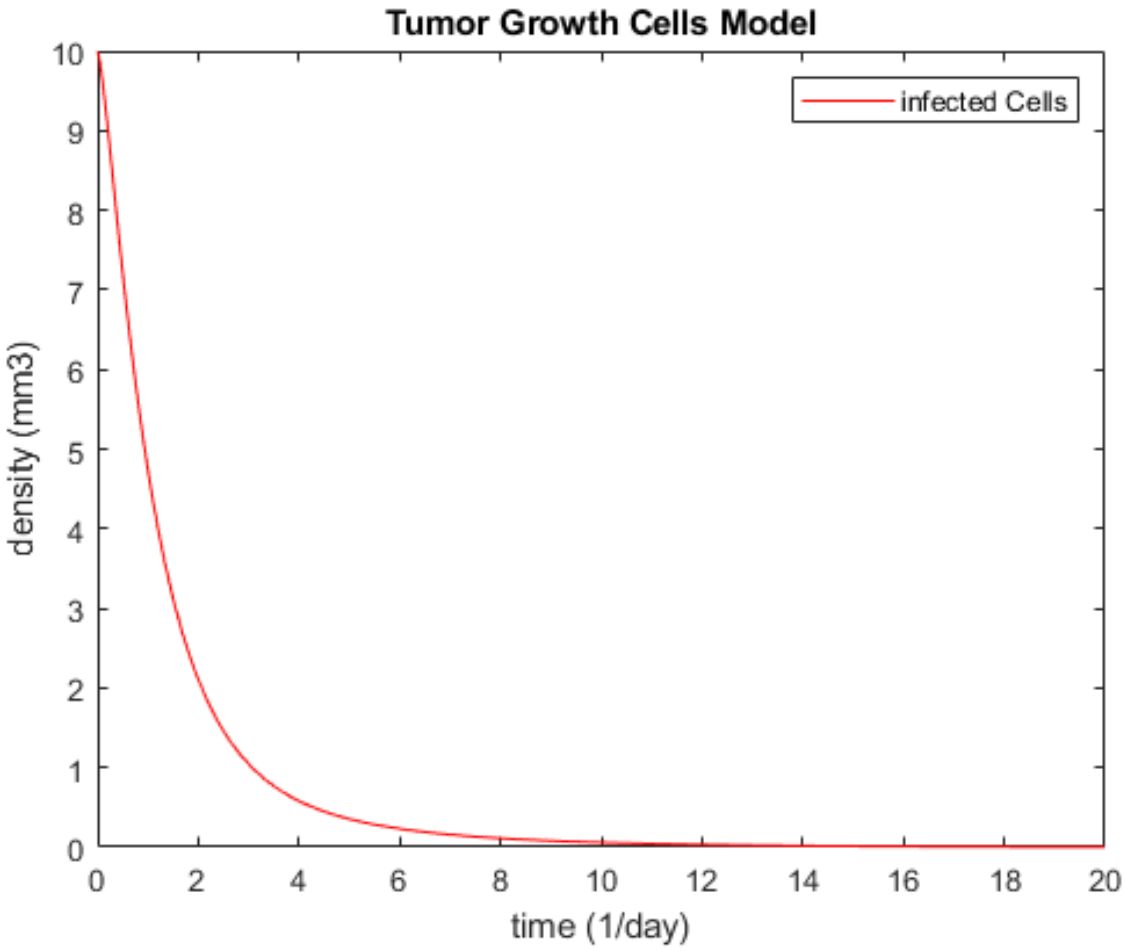

Fig-3.2: Shows the stability of infected Cells

In this Fig-3.2 we have observed infected cells density with respect to time. It's density deceases with the time and approximately after 10 days it has reached to zero and becomes a straight line. We have observed our body's immune system have removed infected cells approximately after 10 days when the initial density is 10 mm^{-3}. So, infected cells need approximately 10 days to reach equilibrium.

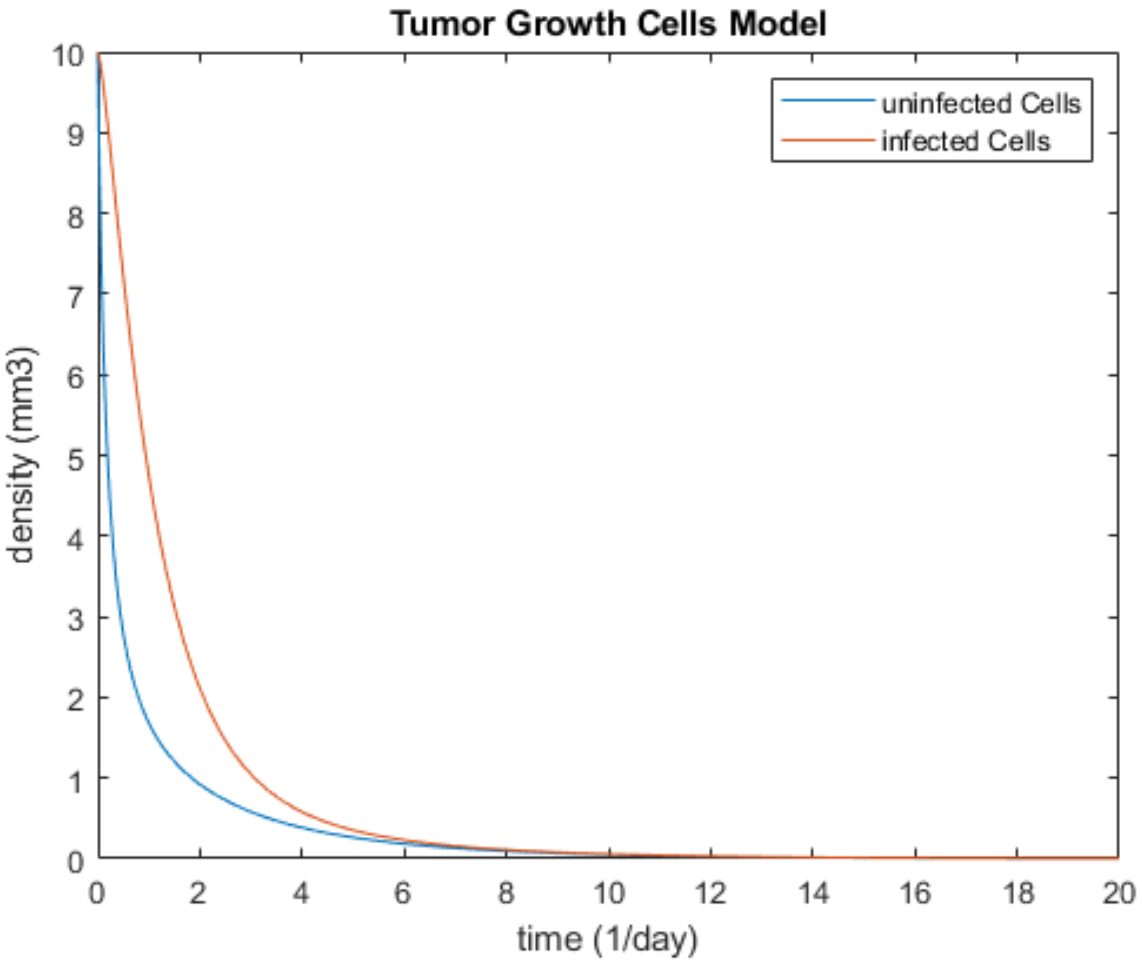

Fig-3.3: Shows the numerical solutions of the system (3.1)

In this Fig-3.3 we have observed uninfected and infected cells density with respect to time where uninfected cells density decreases faster than the infected cells density. We have observed that uninfected cells and infected cells both are decreasing but uninfected cells decreasing rapidly and both become straight line at the same point.

3.6 Tumor growth model considering uninfected and infected cells under cytotoxic and cytostatic drugs:

Cytotoxic and cytostatic drugs have a great effect on controlling or reducing tumor growth for uninfected or infected cells. Cytostatic drug controls the transition of uninfected cells to infected cells and cytotoxic drug kills the infected cells. Now we have presented a model which removes infected cells more rapidly due to the introduction of drugs. In this model we will discuss the effects of cytotoxic and cytostatic drugs on tumor growth considering uninfected and infected.

3.7 Mathematical Formulation:

Cytotoxic and cytostatic drugs are used for two purposes. They are given below:

1. The first way is controlling the transition of cells. If they stay in as uninfected cell they will not translate into infected cells. Proteins that block the translation of uninfected cells are cyclins, they are called cytostatic drugs and the concentration of this drug will be denoted as c_{stat} in the model.
2. The second way is by killing directly infected cells. This is target with cytotoxic drugs. The concentration of this drug is named as c_{tox} and they are called chemotherapies. Now a system of differential equation represents the effects of cytotoxic and cytostatic drugs on tumor growth model (3.2) considering uninfected and infected cells.

$$\frac{dU}{dt} = F(U) - (b + c_{stat})U + cI - c_{tox}\,U\,; \tag{3.5}$$

$$\frac{dI}{dt} = (b + c_{stat})U - cI - dI\,;$$

3.8 Analysis of mathematical stability:

Here we analyze the next model considering uninfected and infected cells:

$\frac{dU}{dt} = F(U) - (b + c_{stat})U + cI - c_{tox}\,U;$

$\frac{dI}{dt} = (b + c_{stat})U - cI - dI;$

where $r > 0, a > 0, K >, b > 0, c > 0, c_{stat} > 0, c_{tox}$ and $d \geq 0$.

To simplify the study of the model we will consider

$b_1 = b + c_{stat} + c_{tox} > 0$ and $b_2 = b + c_{stat} > 0$.

We consider,

F(U) = $U\,.R(U) = rU\left(1 - \frac{U}{K}\right)^a$

Putting the values $F(u)$

$\frac{dU}{dt} = rU\left(1 - \frac{U}{K}\right)^a - b_1U + cI$

$\frac{dI}{dt} = b_2U - cI - dI$

For the equilibrium point, $\frac{dU}{dt} = \frac{dI}{dt} = 0$

$\frac{dU}{dt} = rU\left(1 - \frac{U}{K}\right)^a - b_1U + cI = 0$……..(3.6)

$\frac{dI}{dt} = b_2U - cI - dI = 0$…….....(3.7)

From (3.7),

$b_2U - cI - dI = 0$

$I = \frac{b_2U}{c+d}$ …….. (3.8)

From (3.6),

$rU\left(1 - \frac{U}{K}\right)^a - b_1U + cI = 0$

Putting the value of I in (3.8) we get,

$U\left(r\left(1 - \frac{U}{K}\right)^a - b_1 + \frac{cb_2}{c+d}\right) = 0$

$U = 0$ or $r\left(1 - \frac{U}{K}\right)^a - b_1 + \frac{cb_2}{c+d} = 0$

If $U = 0$ then $I = 0$

So, (0,0) is an equilibrium point.

If $r\left(1 - \frac{U}{K}\right)^a - b_1 + \frac{cb_2}{c+d} = 0$

Then, $\overline{U_1} = \left(K\sqrt[a]{1 + \frac{-b_1 d + c(b_2 - b_1)}{r(c+d)}}\right)$

We can write $\overline{U_1} = \overline{U}$

and $\overline{I_1} = \frac{b_2 \overline{U}}{c+d}$

So, we have another equilibrium point $\left(\overline{U}, \frac{b_2 \overline{U}}{c+d}\right)$

If we take the equilibrium point $(U, I) = (0,0)$

Now we check the stability for $\bar{E}_1 = (0, 0)$,

let [J($\bar{E}_1$)] be the Jacobian matrix

$$[J(\bar{E}_1)] = \begin{bmatrix} r\left(1 - \frac{U}{K}\right)^a - \frac{rUa}{k}\left(1 - \frac{U}{K}\right)^{a-1} - b_1 & c \\ b_2 & -c - d \end{bmatrix}$$

$$= \begin{bmatrix} r - b_1 & c \\ b_2 & -c - d \end{bmatrix}$$

$\det[M] = (r - b_1)(-c - d) - b_2 c < 0$

$tr[M] = r - b_1 - c - d < 0$

Since, $r > 0, b > 0, a > 0, c > 0$ *and* $d \geq 0$.

So, $det[M] < \frac{1}{4}\, tr[M]^2$

Therefore, we have two distinct real eigenvalues.

So, the characteristic polynomial is $\lambda^2 - (-b_1 - c - d + r)\,\lambda + (r - b_1)(-c - d) - b_2 c$

Therefore, the eigen values are:

$\lambda_1 = \frac{1}{2}(-b_1 - c - d + r) - \sqrt{(-b_1 - c - d + r)^2 - 4[(r - b_1)(-c - d) - b_2 c]}$

$\lambda_2 = \frac{1}{2}(-b_1 - c - d + r + \sqrt{(-b_1 - c - d + r)^2 - 4[(r - b_1)(-c - d) - b_2 c]}$

Since, $(r - b_1)(-c - d) - b_2 c < 0$

Then, $4\big((r - b_1)(-c - d) - b_2 c\big) > 0$

And so, $\sqrt{(-b_1 - c - d + r)^2 - 4[(r - b_1)(-c - d) - b_2 c]} > 0$

So, eigenvalues are real and distinct. Therefore, the zero-equilibrium point is a node and the model is asymptotically stable.

If we take the equilibrium point $\overline{E}_2 = (\overline{U_1}, \overline{I_1}) = \left(\overline{U}, \frac{b_2 \overline{U}}{c+d}\right)$

Now we check the stability for $\bar{E}_2 = \left(\overline{U}, \frac{b_2\overline{U}}{c+d}\right)$

let $[J(\bar{E}_2)]$ be the Jacobian matrix

$$[J(\bar{E}_1)] = \begin{bmatrix} r\left(1-\frac{U}{K}\right)^a - \frac{rUa}{k}\left(1-\frac{U}{K}\right)^{a-1} - b_1 & c \\ b_2 & -c-d \end{bmatrix}$$

$$= \begin{bmatrix} -ar + \frac{b_1 d + (b_2 - b_1)c}{c+d}(1+a) - b_1 & c \\ b_2 & -c-d \end{bmatrix}$$

$$tr\ M\ = -ar + \frac{b_1 d + (b_2 - b_1)c}{c+d}(1+a) - b_1 - \ c - d$$

$$\det M = \left(-ar + \frac{b_1 d + (b_2 - b_1)c}{c+d}(1+a) - b_1\right)(-c-d) - cb_2$$

Since, $r > 0, b > 0, a > 0, c > 0\ and\ d \geq 0.$

So, $det[M] < \frac{1}{4}\ tr[M]^2$

Therefore, we have two distinct real eigenvalues.

So, the characteristic equation is: $\lambda^2 - (tr\ M)\ \lambda\ + det\ M.$

$$\overline{\lambda}_1 = \frac{1}{2}\left(tr\ M + \sqrt{((tr\ M)^2 - 4\det M)}\right)$$

$$\overline{\lambda}_2 = \frac{1}{2}\left(tr\ M - \sqrt{(tr\ M)^2 - 4\det M)}\right)$$

Since, $det[M] < 0$

Then, $-4\det M > 0$ and so, $\sqrt{(tr\ M)^2 - 4\det M)} > 0$

So, eigenvalues are real and distinct. Therefore, the nonzero-equilibrium point is a node and the model is asymptotically stable.

3.9 Numerical Analysis:

The system which we have discussed is a system of non- linear ODE and it is difficult to find the analytical solution of the model. We have also checked the stability condition of the model on both the equilibrium point. In order to support the theoretical result, we have showed the stability of numerically and graphically.

We have used the parameter values to perform our numerical analysis which is shown in the table below:

Table-3.9.1 Variables and parameters:

Parameters and variables:	Values
Variables:	
U = Uninfected cells density	$10\ mm^{-3}$
I = Infected cells density	$10\ mm^{-3}$
Parameters and constants:	
a = growth rate of uninfected cells	$1\ day^{-1}$
b = rate of change to infected cells	$1\ day^{-1}$
d = death rate	$1\ day^{-1}$
c = rate of change to uninfected cells	$1\ day^{-1}$
k = vasculature of the tumor	$1\ mm^{-3}$

3.9.2 Numerical solutions of the model by using the values of parameters from (Table-3.9.1):

U	I
10.000000000000000	10.000000000000000
3.506304552437836	9.965827021692219
2.884774680024008	9.929577884562770
2.517401116437920	9.884245371840162
2.270235018031878	9.833382800887618
2.091018584390579	9.778843204942312
1.954557918200731	9.721736295032125
1.847007416436319	9.662787681014278
1.760040957494682	9.602501426717858
1.688309883794878	9.541243446489315
1.628200108999316	9.479288340584420
1.577170062428426	9.416847562339793
1.533373646308775	9.354087294047110
1.495433648154364	9.291140294907375
1.462299409736114	9.228114039995408
1.433154042271984	9.165096481882413
1.407351999348561	9.102160234986052
1.384375915186532	9.039365682105442
1.363806045819014	8.976763325360546
1.345298176490369	8.914395595436543
1.328567351057838	8.852298264732250
1.313375689213298	8.790501565742829
1.299523127872277	8.729031086607158
1.286840289736878	8.667908495795329
1.275182922980408	8.607152134100295
1.264427517543199	8.546777502367414
1.254467813829822	8.486797666429862
1.245211996174292	8.427223595657114
1.236580417419195	8.368064447797307
1.228503739541944	8.309327810016056

3.10 Graphical representations:

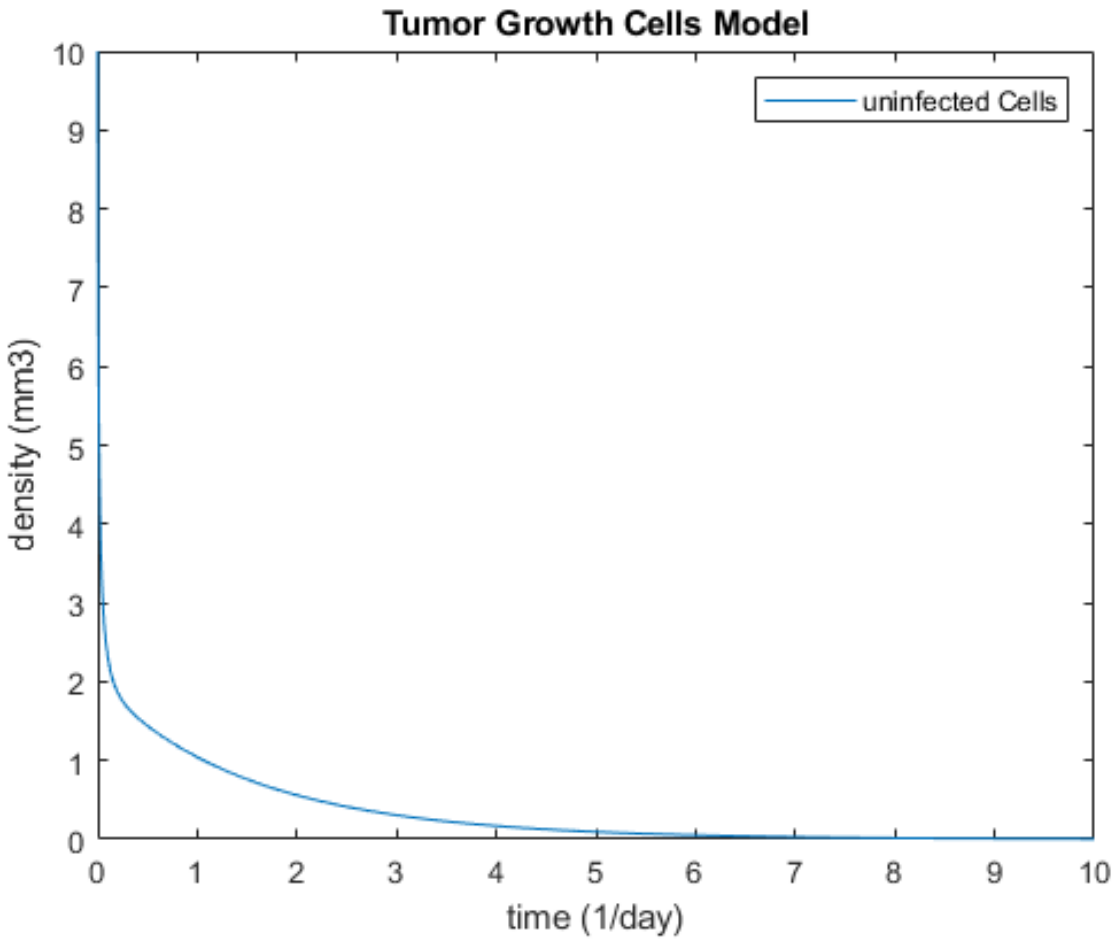

Fig-3.4: Shows the stability uninfected Cells

In this Fig-3.4 we have observed uninfected cells density with respect to time when we have used cytotoxic and cytostatic drugs. It's density deceases with time and approximately after 6 days it has reached to zero and becomes a straight line. Under the effect of cytotoxic and cytostatic drugs uninfected cells take around approximately 6 days to reach equilibrium when the initial density is $10mm^{-3}$.

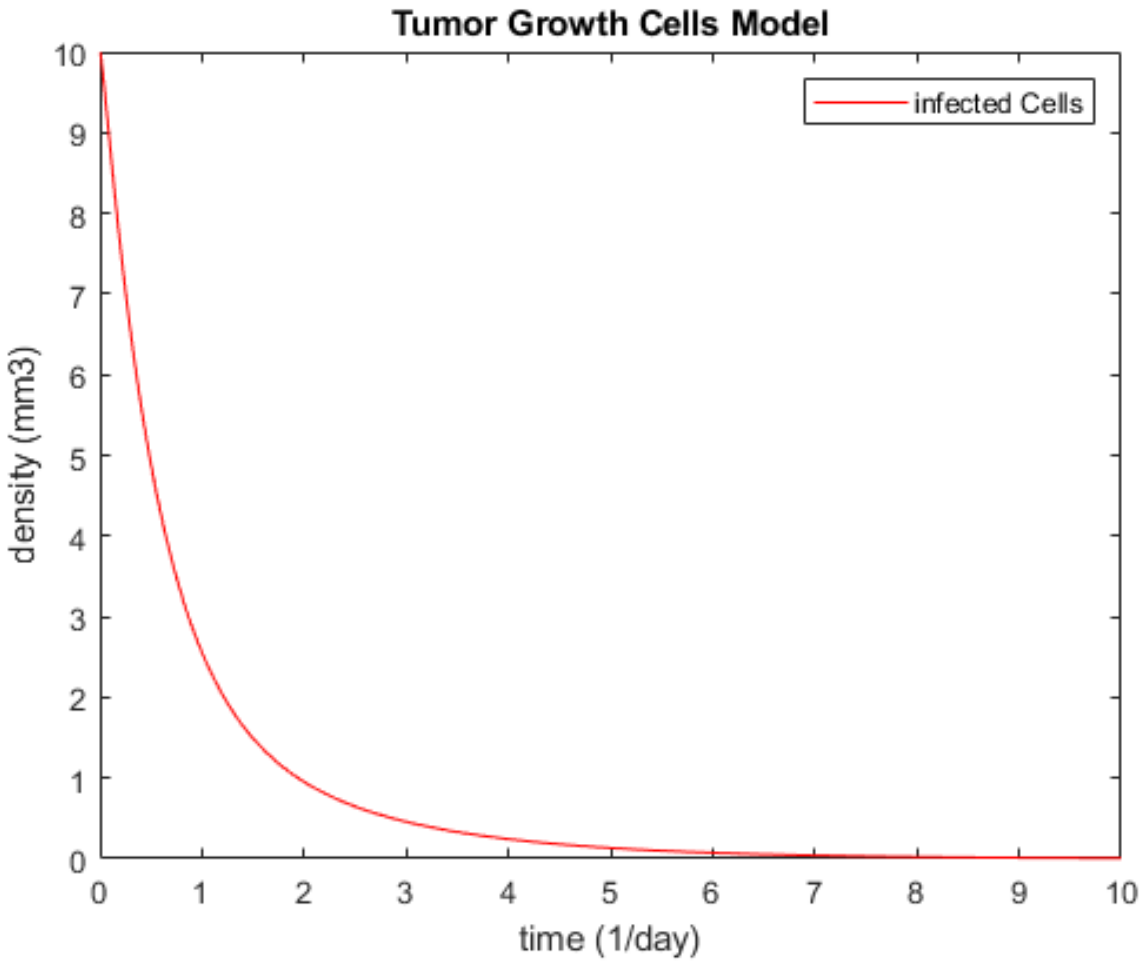

Fig-3.5: Shows the stability Quiescent Cells

In this Fig-3.5 we have observed infected cells density with respect to time when we have used cytotoxic and cytostatic drugs. It's density deceases with time and approximately after 6.5 days it has reached to zero and becomes a straight line. So, under the effect of cytotoxic and cytostatic drugs infected cells have removed infected cells from our body approximately after 6.5 days when the initial density is 10 mm^{-3}. Therefore, infected cells need around 6.5 days to reach equilibrium.

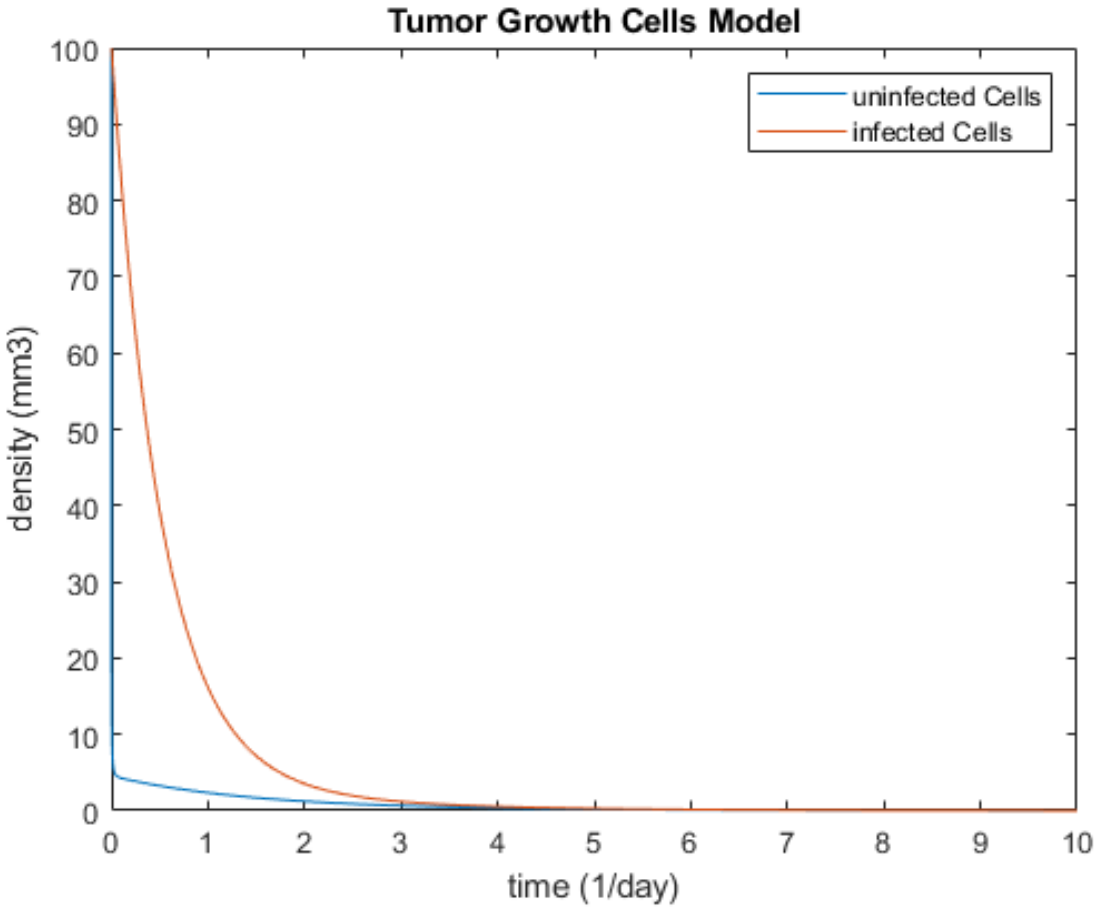

Fig-3.6: Shows the numerical solutions of the system by using the parameter's values from Table (3.7.2)

In this Fig-3.6 we have observed uninfected and infected cells density with respect to time when we have used cytotoxic and cytostatic drugs. Uninfected cells density decreases rapidly than infected cells density. Uninfected cells need around 6 days where infected cells need around 6.5 days to achieve stability under the effects of cytotoxic and cytostatic drugs.

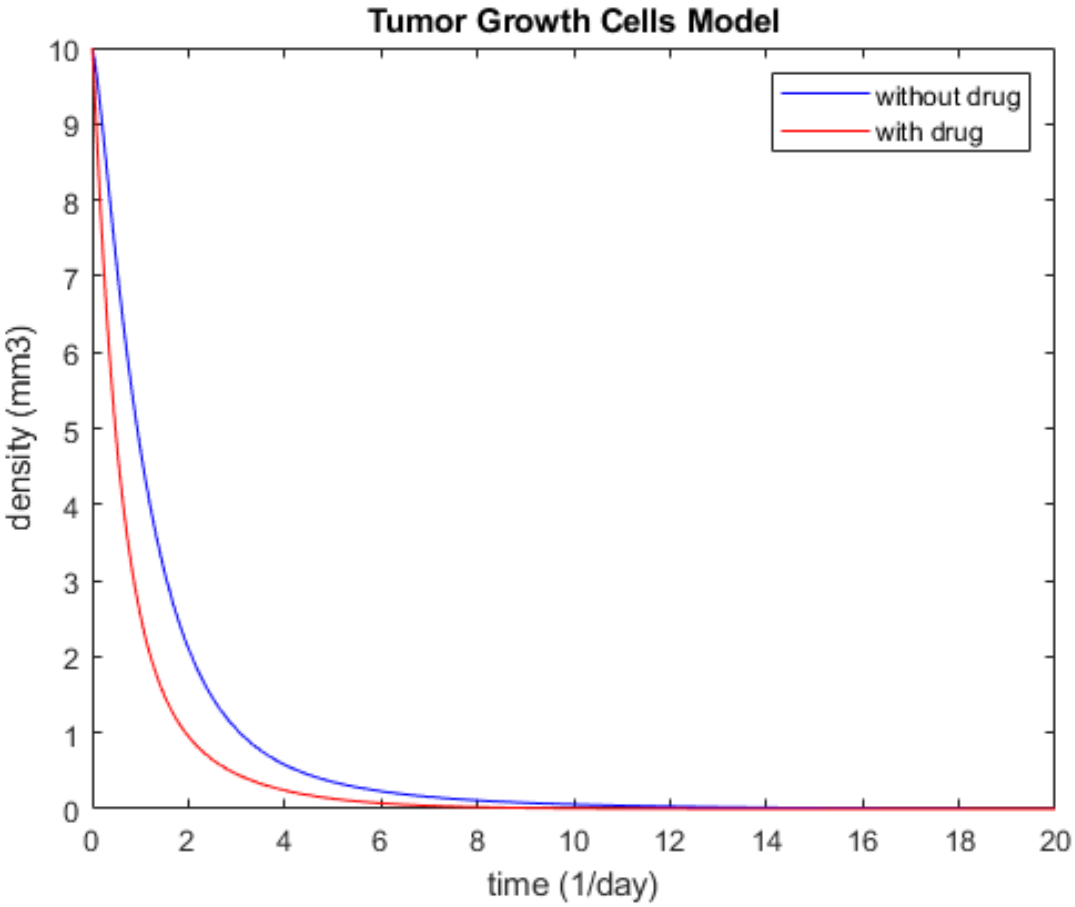

Fig-3.8: Shows the comparison of infected cells before and after using cytotoxic and cytostatic drugs

In this Fig-3.8 we have observed the density of infected cells before and after the use of cytotoxic and cytostatic drugs. We have observed that in both cases infected cells are decreasing but when we have used cytotoxic and cytostatic drugs infected cells density decrease faster. Normally infected cells need around 10 days to reach to zero but when we have used cytotoxic and cytostatic drugs it need around 6.5 days to reach zero. So, when drugs are used infected cells have removed faster from our body.

3.11 Conclusion:

In this chapter we have discussed tumor growth considering uninfected and infected cells. In first model the effects of infected and uninfected cells on tumor growth under the normal circumstances have been discussed, on the other hand, in the second model we have discussed tumor growth considering uninfected and infected cells under the cytotoxic and cytostatic drugs.

We have observed that in the first model, the zero-equilibrium state and the nonzero equilibrium state both are asymptotically stable. In the second model, the zero-equilibrium state and the nonzero equilibrium state both are also asymptotically stable. The first model take time to control the infected cells as we have not used any drug. So, we have discussed another model in this chapter where cytotoxic and cytostatic drugs are used to control the tumor growth. In the second model we have observed that under the effects of cytotoxic and cytostatic drugs infected cells removed much faster than our previous model. The first model where we do not use any kind of drugs, the immune system of our body controls the amounts of infected cells but it takes time to remove the infected cells. But in the second model we have used cytotoxic and cytostatic drugs where the infected cells removed much faster than the previous model. We also compare the infected cells density before and after use of cytotoxic and cytostatic drugs for a certain time. In this comparison we have observe that when we used cytotoxic and cytostatic drugs infected cells density decrease more rapidly than when we did not use any drug. It means cytotoxic and cytostatic drugs remove infected cells faster than immune system of our body. But in this chapter, we do not consider the free virus cells which play an important role in tumor growth. Free virus cells cannot be controlled only by the immune system of our body. So, in the next chapter, we will discuss tumor growth considering uninfected, infected and free virus cells.

CHAPTER 4

Tumor growth models considering uninfected, infected and free virus cells.

4.1 Introduction:

Tumors possess mechanisms that suppress antitumor activity such as ligands which block natural killer cells and cytotoxic tumor infiltrating cell functions. Greatly because of this, successful cancer treatment often requires a combination of treatment regimens. In the previous models, we have discussed tumor growth considering uninfected and infected cells. In this chapter we will discuss tumor growth considering uninfected, infected and free virus cells.

4.2 Mathematical Formulation:

Time-dependent cell concentrations of uninfected tumor cells $U(t)$, infected tumor cells $I(t)$, a free virus population $V(t)$, and a chemotherapeutic drug $C(t)$ in an avascular tumor localization are considered. The uninfected tumor grows logistically at an intrinsic rate α per day, and the total tumor carrying capacity is K cells in a tumor nodule. The infected tumor cells die off at a rate δ per day. Virus multiplication in the tumor is represented by the function $\beta U(t)V(t)$, where β is the virus replication rate measured per day per 10^6 cells or viruses. The response of the drug to the uninfected and infected tumor is, respectively, modelled by the functions $\delta_0 U(t)C(t)$ and $\delta_1 I(t)C(t)$ where δ_0 and δ_1 are induced lysis rates caused by the chemotherapeutic drug measured per day per cell. Virus lifespan is taken to be $1/c$ and its production is considered to be $b\delta I$ where b is the virus burst size, measured in number of viruses per day per cell, and δ is the infected tumor cells death rate measured per day. Chemotherapeutic drug infusion into the body is modelled with a function $g(t)$ and that the drug gets depleted from body tissue at a rate λ per day.

Drug infusion into the body is simulated using (a) a constant rate $g(t) = q$, (b) an exponential $g(t) = q\ exp(-at)$, and (c) a sinusoidal function $g(t)=q$ sin2(at), where q is the rate of drug infusion. The constant a determines the exponential drug decay and period for the sinusoidal infusion. Constant drug infusion may relate to a situation where a patient is put on an intravenous injection or a protracted venous infusion and the drug is constantly pumped into the body [22, 23]. The exponential drug infusion may relate a situation where a cancer patient is given a single bolus and the drug exponentially decays in the body tissue. This form of infusion is not common although it is now used for some drugs, for example, a single dose of carboplatin can be given to patients with testicular germ cell tumors and breast cancer [24, 25]. The third scenario is possible when a cancer patient makes several visits to a health facility and is given injections or anticancer drugs periodically [26, 27]. The assumptions above lead to the following system of nonlinear first-order differential equations (also similarly derived in [28, 29, 30]:

$$\frac{dU}{dt} = \alpha\, U(t)(1 - U(t) + I(t)) - \beta U(t)V(t) - \delta_0 U(t)C(t);$$

$$\frac{dI}{dt} = \beta\, U(t)V(t) - \delta I(t) - \delta_1 I(t)C(t); \qquad (4.1)$$

$$\frac{dV}{dt} = b\delta I(t) - \beta\, U(t)V(t) - \Upsilon V(t)$$

$$\frac{dC}{dt} = g(t) - \lambda C(t)$$

Subject to initial concentrations

$$U(0) = U_0$$

$$I(0) = I_0 \qquad (4.2)$$

$$V(0) = V_0$$

$$C(0) = C_0$$

For the analysis, the variables in system (4.1) are first rescaled by setting $t = \delta t$, $U = KU$, $I = KI$, $V = V_0 V$, and $C = C_0 C$. Taking $V_0 = K$, the parameters are renamed to become

$$\overline{\alpha} = \frac{\alpha}{\delta}, \overline{\beta} = \frac{\beta V_0}{\delta}, \overline{\delta} = \frac{\delta_0 C_0}{\delta}, \overline{\delta_1} = \frac{\delta_1 C_0}{\delta}, \ \overline{b} = \frac{bk}{V_0}, \overline{\Upsilon} = \frac{\Upsilon}{\delta}, \Phi = \frac{q}{\delta C_0}, \Psi = \frac{\lambda}{\delta}, \overline{a} = \frac{a}{\delta} \qquad (4.3)$$

For simplicity, we drop the bars and equation (4.1) becomes

$$\frac{dU}{dt} = \alpha\, U(t)(1 - U(t) + I(t)) - \beta U(t)V(t) - \delta_0 U(t)C(t);$$

$$\frac{dI}{dt} = \beta\, U(t)V(t) - \delta I(t) - \delta_1 I(t)C(t);$$

$$\frac{dV}{dt} = b\delta I(t) - \beta\, U(t)V(t) - \Upsilon V(t) \qquad (4.4)$$
$$\frac{dC}{dt} = g(t) - \lambda C(t)$$

$\xi(t) = \phi, \xi(t) = \phi\, exp(-at)$, and $\phi\, sin^2(at)$, respectively, are the constant, exponential, and sinusoidal infusion functions. For this model to be biologically meaningful, its solutions should be positive and bounded because they represent concentrations.

Without chemotherapy, equation (4.4) is reduced to

$$\frac{dU}{dt} = \alpha\, U(t)(1 - U(t) + I(t)) - \beta U(t)V(t);$$
$$\frac{dI}{dt} = \beta\, U(t)V(t) - I(t); \qquad (4.5)$$
$$\frac{dV}{dt} = b\, I(t) - \beta\, U(t)V(t) - \Upsilon V(t)$$

4.3 Analysis of mathematical stability of the model (4.5):

For equilibrium point $\frac{dP}{dt} = \frac{dQ}{dt} = \frac{dV}{dt} = 0$,

we obtain from (4.1)

$$\frac{dU}{dt} = \alpha\, U(t)(1 - U(t) + I(t)) - \beta U(t)V(t) = 0 \quad \text{.....(4.6)}$$
$$\frac{dI}{dt} = \beta U(t)V(t) - I(t) = 0 \quad \text{.....(4.7)}$$
$$\frac{dV}{dt} = b\, I(t) - \beta\, U(t)V(t) - \Upsilon V(t) = 0 \quad \text{.....(4.8)}$$

Now, we consider equilibrium point $\overline{E_1} = (U, I, V)$

From (4.7) we obtain

$$\beta\, U(t)V(t) - I(t) = 0$$
$$I(t) = \beta\, U(t)V(t) \quad \text{.....(4.9)}$$

From (4.9) we obtain

$$b\, I(t) - \beta\, U(t)V(t) - \Upsilon V(t) = 0$$
$$V(t) = \frac{b\, I(t)}{\beta\, U(t) - \Upsilon} \quad \text{.....(4.10)}$$

From (4.6) we obtain

$$\alpha\, U(t)(1 - U(t) + I(t)) - \beta U(t)V(t) = 0$$

$U(t)\left(\alpha\left(1-U(t)+I(t)\right)-\beta V(t)\right)=0$

if $U(t)=0$ then $\left(\alpha\left(1-U(t)+I(t)\right)-\beta V(t)\right)\neq 0$

So, if $U(t)=0$ then from (4.10)

$I(t)=0$

From (5)

$V(t)=0$

Therefore, the equilibrium points,

$\overline{E}_1=(U,I,V)=(0,0,0)$

Now we check the stability for

$\overline{E}_1$ = (0 ,0 ,0)

let $\left[J(\overline{E_1})\right]$ be the Jacobian matrix of (3.1) then,

$$\left[J(\overline{E_1})\right]=\begin{bmatrix}\alpha\left(1-U(t)+I(t)\right)-\beta V(t) & \alpha U(t) & -\beta U(t)\\ \beta V(t) & -1 & \beta U(t)\\ -\beta V(t) & b & -\beta U(t)-\Upsilon\end{bmatrix}$$

$$=\begin{bmatrix}\alpha & 0 & 0\\ 0 & -1 & 0\\ 0 & b & -\Upsilon\end{bmatrix}$$

$$det\left(\left[J(\overline{E_1})\right]\right)=\alpha\begin{bmatrix}-1 & 0\\ b & -\Upsilon\end{bmatrix}$$

Let, $A=\begin{bmatrix}-1 & 0\\ b & -\Upsilon\end{bmatrix}$

$det([A])=\Upsilon>0$

$tr([A])=-1-\Upsilon$

$=-(1+\Upsilon)<0$

If $0<\frac{tr([A])^2}{4}$

But $\frac{tr([A])^2}{4}>det([A])$

So, we have two distinct real eigenvalues.

Let λ be the eigenvalue and $J\left(\overline{E_1}\right)$ be the Jacobian matrix then,

$\left|\lambda I-J\left(\overline{E_1}\right)\right|=0$

$$\left|\begin{bmatrix}\lambda & 0 & 0\\ 0 & \lambda & 0\\ 0 & 0 & \lambda\end{bmatrix}-\begin{bmatrix}\alpha & 0 & 0\\ 0 & -1 & 0\\ 0 & b & -\Upsilon\end{bmatrix}\right| = 0$$

$$\begin{bmatrix}\lambda-\alpha & 0 & 0\\ 0 & \lambda+1 & 0\\ 0 & -b & \lambda+\Upsilon\end{bmatrix} = 0$$

$$(\lambda-\alpha)(\lambda^2+(\Upsilon+1)\lambda+\Upsilon) = 0$$

The eigenvalues are

$\lambda = \alpha$ or $\lambda = \frac{-(\Upsilon+1)\pm\sqrt{(\Upsilon+1)^2-4(\Upsilon+1)\Upsilon}}{2}$

Here, we have observed the one eigenvalue is real which is positive. If $(\Upsilon+1)\Upsilon > 0$ the other two eigen value are real and distinct. So, zero equilibrium point is node and the model is asymptotically stable [20].

Consider equilibrium points,

$\overline{E}_2 = (U, I, V)$

From (6)

If $U(t) \neq 0$ then $\left(\alpha\left(1-U(t)+I(t)\right)-\beta V(t)\right) = 0$

So, $U(t) = I(t) - \frac{\beta V(t)}{\alpha} - 1$

From (4)

$$I(t) = \beta\left(I(t) - \frac{\beta V(t)}{\alpha} - 1\right)V(t)$$

$$= \beta I(t)V(t) - \frac{\beta^2\left(V(t)\right)^2}{\alpha} - \beta V(t)$$

From (5)

$$V(t) = \frac{bI(t)}{\beta I(t) - \frac{\beta^2 V(t)}{\alpha} - \beta - \Upsilon}$$

$$\left[J(\overline{E_1})\right] = \begin{bmatrix}\alpha\left(1-U(t)+I(t)\right)-\beta V(t) & \alpha U(t) & -\beta U(t)\\ \beta V(t) & -1 & \beta U(t)\\ \beta V(t) & b & -\beta U(t)-\Upsilon\end{bmatrix}$$

$$det\left[J(\overline{E_2})\right] = \left[\alpha\left(1 - U(t) + I(t)\right) - \beta V(t)\right]\left(\beta U(t) + \Upsilon - bBU(t)\right) + \alpha U(t)[-\beta^2 U(t)V(t) + \beta^2 U(t)V(t) + \Upsilon\beta V(t)] - \beta V(t)[b\beta V(t) - \beta V(t)]$$

$$det\left[J(\overline{E_2})\right] = \left[\alpha\left(1 - U(t) + I(t)\right) - \beta V(t)\right]\left(\beta U(t) + \Upsilon - bBU(t)\right) + \alpha U(t)\Upsilon\beta V(t) - \beta V(t)[b\beta V(t) - \beta V(t)]$$

$$tr\left[J(\overline{E_2})\right] = \alpha\left(1 - U(t) + I(t)\right) - \beta V(t) - 1 - \beta V(t) - \Upsilon$$

$$= \alpha - \alpha\, U(t) - \alpha\, I(t) - \beta\, V(t) - 1 - \beta V(t) - \Upsilon$$

$tr\left[J(\overline{E_2})\right] < 0$ if $\alpha > 0$

If $det\left[J(\overline{E_2})\right] < 0$

Then $tr\left[J(\overline{E_2})\right] < -4det\left[J(\overline{E_2})\right]$

So, we have two complex eigenvalues and these eigenvalues are complex conjugate. So, the nonzero equilibrium point is spiral and model is stable [20].

4.4 Numerical Analysis:

Numerical analysis is the branch of mathematics which deals with the development and use of numerical methods. The system (4.1) is a system of non- linear ODE and it is difficult to find the analytical solution of this model. Therefore, we have performed here the numerical analysis to find the numerical solution and visualize these solutions graphically through MATLAB programming. We have developed the Matlab code to find the numerical solution. To support the theoretical result, we have developed the MATLAB code to show the stability of numerically and graphically. We have used the parameter values to perform our numerical analysis which is shown in the table below:

Table-4.4.1 Variables and parameters:

Parameters and variables:	Values
Variables:	
U(t) = Uninfected cells density	10 mm^{-3}
I(t) = Infected cells density	10 mm^{-3}
V(t) = Free virus cells density	1 mm^{-3}
Parameters and constants:	
$\alpha =$ Intrinsic rate	0.206 day^{-1}
$b =$ Virus burst size	10 day^{-1}
$\beta =$ Virus replication rate	0.005 day^{-1}
$\Upsilon =$ Virus lifespan	0.005 day^{-1}

4.4.2 Numerical solutions of the model by using the values of parameters from (Table-4.4.1):

U	I	V
10.0000	10.0000	1.0000
9.6208	9.9006	1.9949
9.2648	9.8024	2.9797
8.9300	9.7051	3.9548
8.6147	9.6090	4.9200
8.3173	9.5138	5.8756
8.0365	9.4197	6.8217
7.7710	9.3265	7.7584
7.5196	9.2343	8.6857
7.2813	9.1431	9.6038
7.0552	9.0529	10.5128
6.8404	8.9635	11.4127
6.6361	8.8751	12.3037
6.4418	8.7877	13.1859
6.2566	8.7011	14.0593
6.0800	8.6154	14.9241
5.9115	8.5306	15.7803
5.7506	8.4467	16.6281
5.5968	8.3636	17.4674
5.4497	8.2813	18.2985
5.3088	8.1999	19.1214
5.1739	8.1194	19.9361
5.0446	8.0396	20.7428
4.9206	7.9607	21.5415
4.8015	7.8825	22.3324
4.6872	7.8051	23.1155
4.5774	7.7286	23.8908
4.4717	7.6528	24.6586
4.3701	7.5777	25.4187
4.2723	7.5034	26.1714

4.5 Graphical representations:

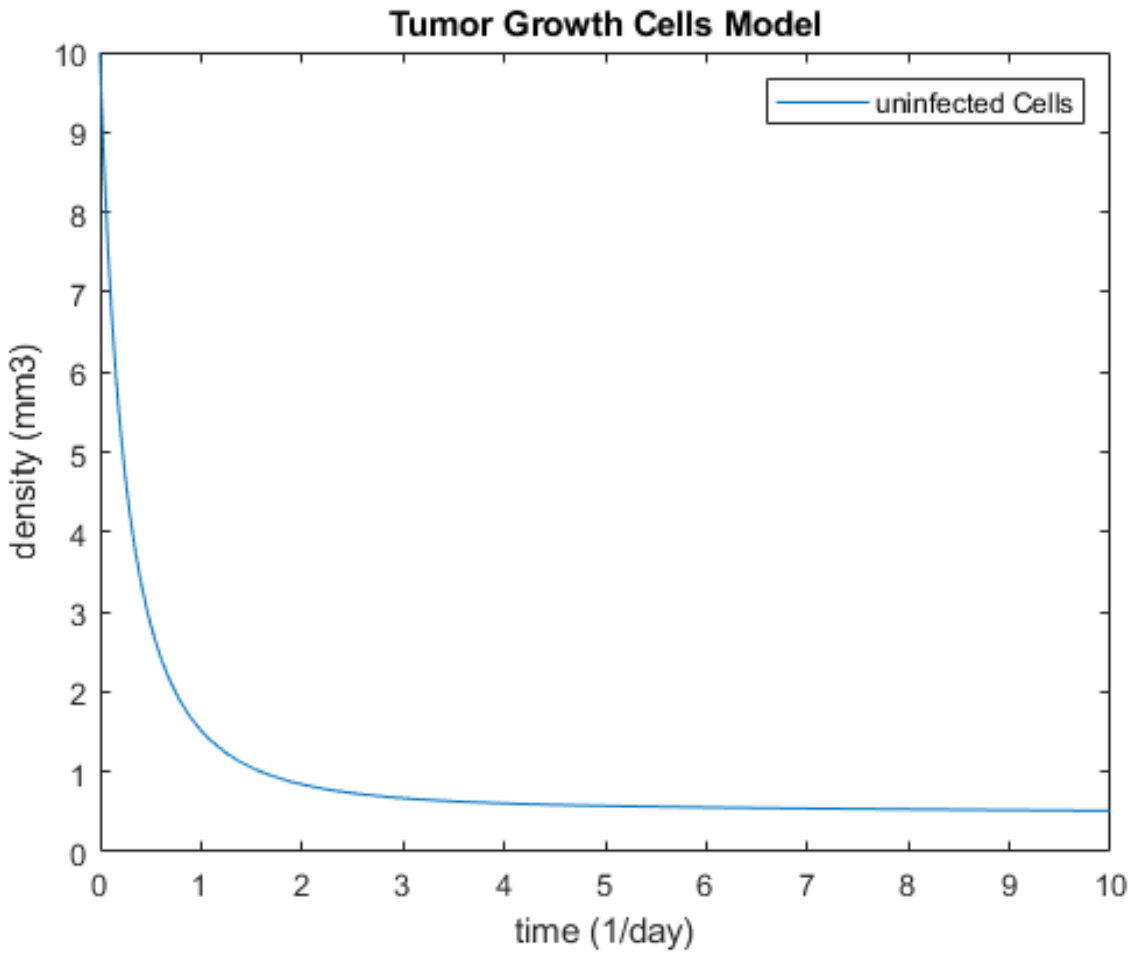

Fig-4.1: Shows the stability of uninfected Cells

In this Fig-4.1 we have observed uninfected cells density with respect to time. It's density deceases with time and approximately after 4 days it becomes straight line when the initial density is 10 mm^{-3}. So, uninfected cells need approximately 4 days to reach equilibrium when we have considered virus cells in this tumor growth model.

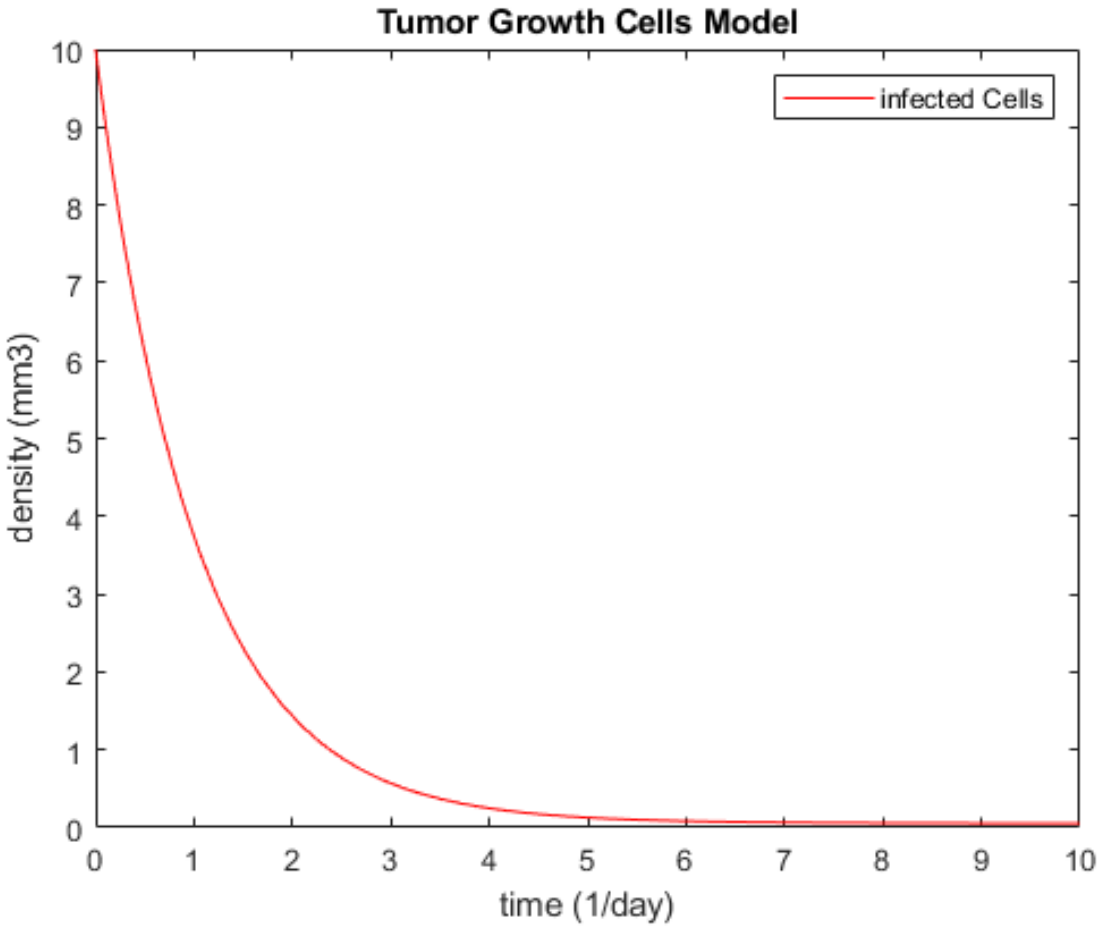

Fig-4.2: Shows the stability of infected Cells

In this Fig-4.2 we have observed infected cells density with respect to time. It's density deceases with the time and approximately after 7.5 days when the initial density is 10 mm^{-3} and it becomes straight line. Infected cells have removed due to the immune system of our body. So, infected cells need approximately 7.5 days to reach equilibrium when we have considered virus cells in this tumor growth model.

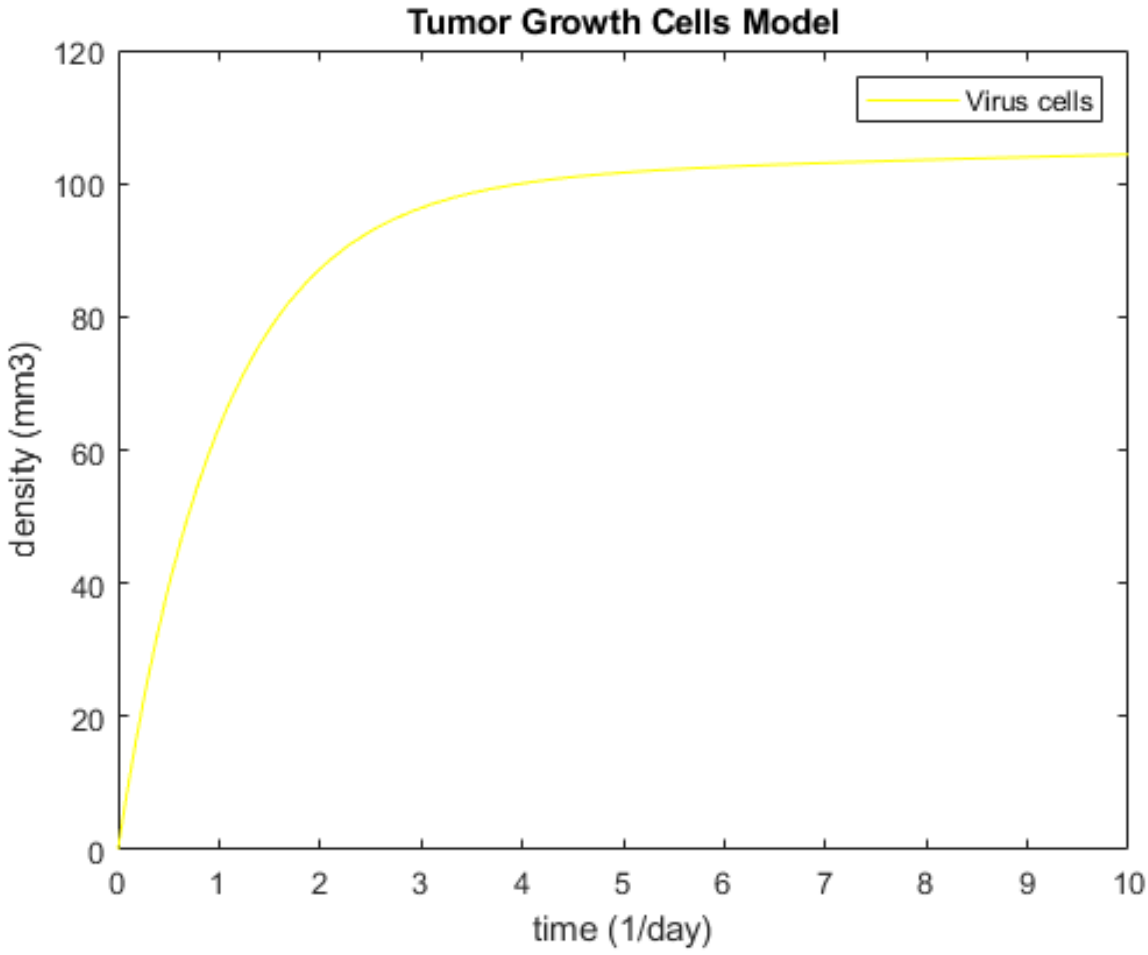

Fig-4.3: Shows the stability of free virus Cells

In this Fig-4.3 we have observed free virus cells density with respect to time. Its density rapidly increases with respect to time and after approximately 4 days free virus cells reach to equilibrium. Since we do not use any drug or chemotherapy our body's immune system cannot control the growth of free virus cells. Thus, free virus cells increase rapidly with time.

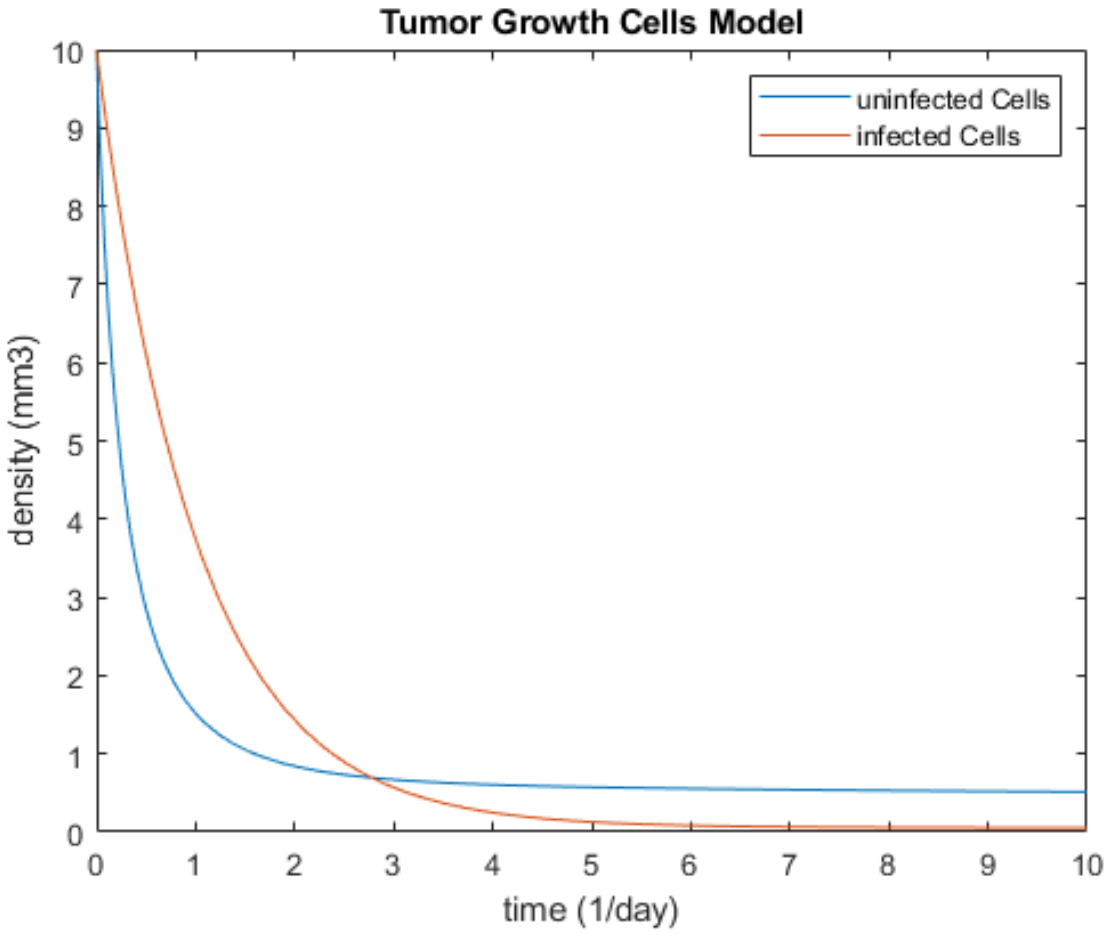

Fig-4.4: Shows the stability of uninfected cells and infected cells

In this Fig-4.4 we have observed uninfected, infected cells density with respect to time. Uninfected, infected cells density deceases with time and after some time they reach to equilibrium position. We have also observed that infected cells density decreases faster than uninfected cells density but uninfected cells reaches to equilibrium approximately after 4 days where infected cells need approximately 7.5 days to reach equilibrium. So, uninfected cells need less days to reach equilibrium.

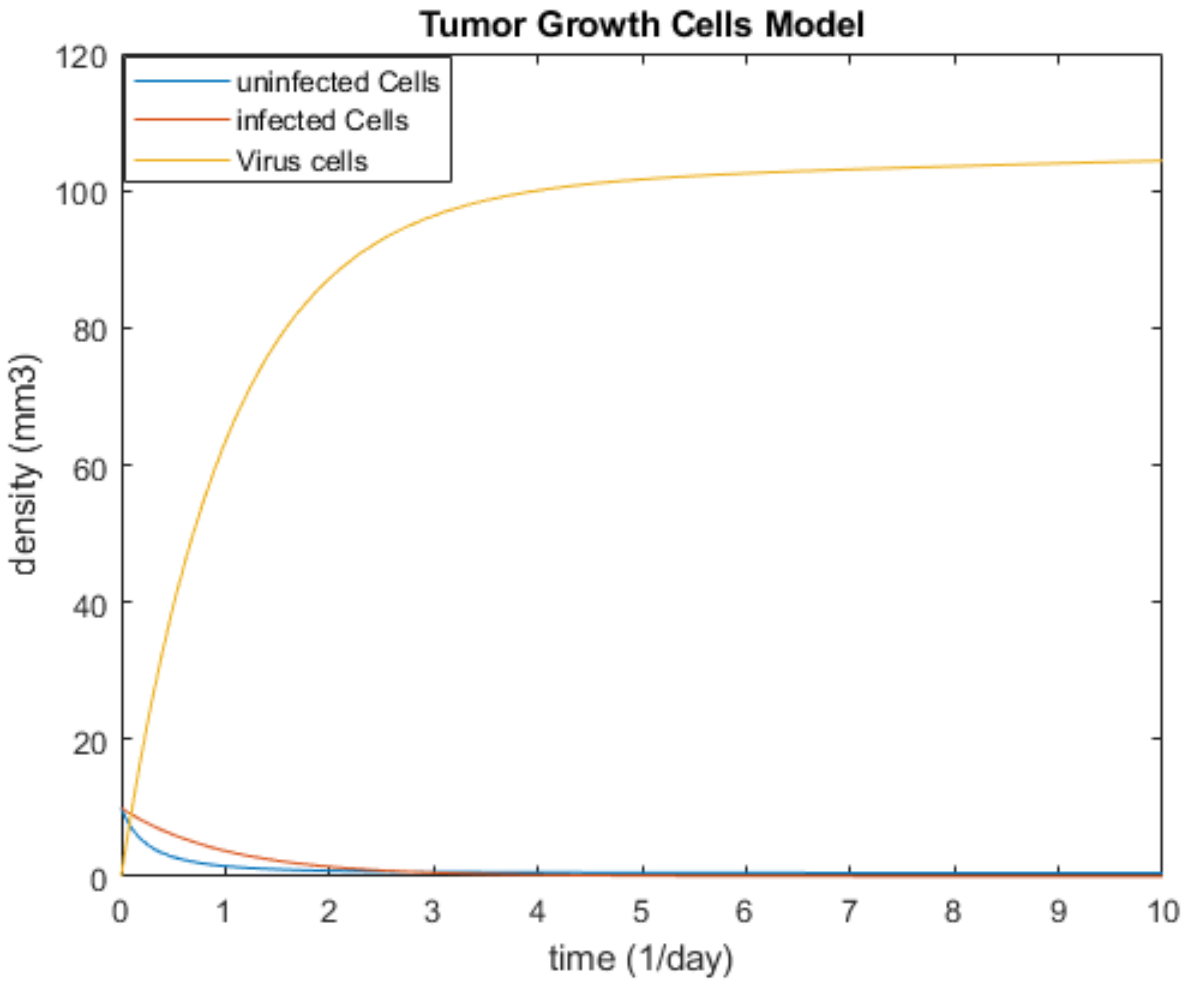

Fig-4.5: Shows the numerical solutions of the system by using the parameter's values from Table (4.3.2)

In this Fig-4.5 we have observed uninfected, infected and free virus cells density with respect to time where infected and free cells density deceases with time but free virus cells density increases rapidly with time. Since we have not used any drug or chemotherapy our body's immune system can control the growth of infected cells for certain time, however. it cannot control the growth of free virus cells.

4.6 Conclusion:

In this chapter, we have discussed tumor growth considering uninfected, infected and free virus cells. We have modified our ODE model by adding an extra variable which is free virus cells. We have observed that in this model, the zero-equilibrium state and the nonzero equilibrium state both are stable. We have observed that the immune system of our body decreases the density of infected cells but it cannot control the density of free virus cells. So, the population of free virus cells increase rapidly since no drug or chemotherapy is used. This means virus cells have remained in our body and since the immune system of our body cannot control this, the population of virus cells increase. This will infect more uninfected cells and after a certain time infected cells population will reach a position where the immune system of our body cannot control it without the help of chemotherapy or drug. Thus, tumor will grow in our body.

The difference between the chapter 3 and chapter 4 is that we added free virus cells in chapter 4 which has a major impact in tumor growth. Between these two chapter if we want to compare the model of chapter four is more appropriate since in this chapter, we also considered free virus cells which has a great impact in tumor growth.

CHAPTER 5

DISCUSSION AND GENERAL CONCLUSION

Tumor is the cause of abnormal growth of cells. Some nutrients control the growth of cells in our body, when these nutrients are blocked body cannot control the cells growth. Thus, tumor grow in our body which may cause cancer. In this project, we have discussed some mathematical model which helps us to understand tumor growth. In the first model of chapter three, tumor growth considering uninfected and infected cells is discussed and this model is asymptotically stable. In the second model of chapter three tumor growth considering uninfected and infected cells under cytotoxic and cytostatic drugs is discussed and this model is also asymptotically stable. The model in chapter four is tumor growth considering uninfected, infected and free virus cells and the model is stable. The main difference between these models is that in the first two models we have considered uninfected and infected cells and in the last model we have considered uninfected and infected and free virus cells. In the first model of chapter three, infected cells take approximately 10 days to reach their stability when initial density is 10 mm^{-3}. Here the immune system of our body controls the population level of infected cells since we have not used any kind of drug. But in the second model cytotoxic and cytostatic drugs has been used to control the infected cells and it take approximately 6.5 days for infected cells to reach their stability when initial density is 10 mm^{-3}. In chapter four, we have modified our model with extra cells called virus cells and have not used any kind of drugs or chemotherapy. In this model infected cells take approximately 7.5 days to reach stability when initial density is 10 mm^{-3}. So, we have observed that in the third chapter infected cells have been removed by the immune system of our body or cytotoxic and cytostatic drugs. But in the fourth chapter we have observed that the immune system of our body has removed the infected cells but cannot control the population growth of virus cells which means virus cells will remain in our body and it will infect the uninfected cells. Thus, tumor can grow in our body.

Therefore, we have observed that virus cells play an important role in the tumor growth model since it increases the population level of infected cells which eventually helps tumor to grow in our body. However, due to the shortness of time we cannot discuss the effects of chemotherapy or drugs considering uninfected, infected or virus cells on tumor growth. If we use drug, we will get better result for this model. Since, we have observed in chapter 3, when we use drug, infected cells

remove faster from our body. To get the better results further study is needed to investigate about the effects of chemotherapy or drugs in the model of chapter 4.

Appendix

Function (3.1):

```
function rk = odes13(t,y,T,FT)

format long

FT = interp1(T,FT,t);
r=0.5; a=1; b=1; c=0.2; k=1; d=1;
rk(1) = r*y(1)*(1-(y(1)/k).^a)-b*y(1)+c*y(2);
rk(2) = b*y(1)-c*y(2)-d*y(2);
rk = rk(:);
end
```

Function (3.2):

```
function rk = odes14(t,y,T,FT

format long

FT = interp1(T,FT,t);

r=1; s=1; b=1; c=1; t=1; d=1;

rk(1) = r*y(1)*(1-y(1).^2)-(b+s+t)*y(1)+c*y(2);
rk(2) = (b+s)*y(1)-c*y(2)-d*y(2);
rk = rk(:);
end
```

Function (4.1):

```
function rk = odes16(t,y,T,FT)

format long
FT = interp1(T,FT,t);
alpha=0.206; beta=0.001; b=10; lambda=0.001;
rk(1) = alpha*y(1)*(1-y(1)-y(2))-beta*y(1)*y(3);
rk(2) = beta*y(1)*y(3)-y(2);
```

```
rk(3) = b*y(2)-beta*y(1)*y(3)-lambda*y(3);
rk = rk(:);
end
```

Figure (3.1 and 3.4):

```
timerange = [0 20];
IC = [10; 10];
T = linspace(0,1,5);
FT = linspace(0,1,5);
[t, y] = ode45(@(t, y) odes13(t,y,T,FT),timerange,IC);
plot(t,y(:,1));
title('Tumor Growth Cells Model');
xlabel('time (1/day)');
ylabel('density (mm3)');
legend('uninfected Cells')
```

Figure (3.2 and 3.5):

```
timerange = [0 20];
IC = [10; 10];
T = linspace(0,1,5);
FT = linspace(0,1,5);
[t, y] = ode45(@(t, y) odes13(t,y,T,FT),timerange,IC);
plot(t,y(:,2),'r');
title('Tumor Growth Cells Model');
xlabel('time (1/day)');
ylabel('density (mm3)');
legend('infected Cells')
```

Figure (3.3 and 3.6):

```
timerange = [0 20];
IC = [10; 10];
T = linspace(0,1,5);
FT = linspace(0,1,5);
[t, y] = ode45(@(t, y) odes13(t,y,T,FT),timerange,IC);
plot(t,y(:,1), t,y(:,2));
title('Tumor Growth Cells Model');
xlabel('time (1/day)');
```

```
ylabel('density (mm3)');
legend('uninfected Cells','infected Cells')
```

Figure (3.7):

```
timerange = [0 20];
IC = [10; 10];
T = linspace(0,1,5);
FT = linspace(0,1,5);
[t, y] = ode45(@(t, y) odes13(t,y,T,FT),timerange,IC);
plot(t,y(:,1));
hold on
[t, y] = ode45(@(t, y) odes14(t,y,T,FT),timerange,IC);
plot(t,y(:,1));
title('Tumor Growth Cells Model');
xlabel('time (1/day)');
ylabel('density (mm3)');
legend('without drug','with drug')
```

Figure (3.8):

```
timerange = [0 20];
IC = [10; 10];
T = linspace(0,1,5);
FT = linspace(0,1,5);
[t, y] = ode45(@(t, y) odes13(t,y,T,FT),timerange,IC);
plot(t,y(:,2),'b');
hold on
[t, y] = ode45(@(t, y) odes14(t,y,T,FT),timerange,IC);
plot(t,y(:,2),'r');
title('Tumor Growth Cells Model');
xlabel('time (1/day)');
ylabel('density (mm3)');
legend('without drug','with drug')
```

Figure (4.1):

```
timerange = [0 10];
IC = [10;10;0];
T = linspace(0,1,10);
```

```
FT = linspace(0,1,10);
[t, y] = ode45(@(t, y) odes16(t,y,T,FT),timerange,IC);
plot(t,y(:,1));
title('Tumor Growth Cells Model');
xlabel('time (1/day)');
ylabel('density (mm3)');
legend('uninfected Cells');
```

Figure (4.2):

```
timerange = [0 10];
IC = [10;10;0];
T = linspace(0,1,10);
FT = linspace(0,1,10);
[t, y] = ode45(@(t, y) odes16(t,y,T,FT),timerange,IC);
plot(t,y(:,2),'r');
title('Tumor Growth Cells Model');
xlabel('time (1/day)');
ylabel('density (mm3)');
legend('infected Cells');
```

Figure (4.3):

```
timerange = [0 10];
IC = [10;10;0];
T = linspace(0,1,10);
FT = linspace(0,1,10);
[t, y] = ode45(@(t, y) odes16(t,y,T,FT),timerange,IC);
plot(t,y(:,3),'y');
title('Tumor Growth Cells Model');
xlabel('time (1/day)');
ylabel('density (mm3)');
legend('Virus cells');
```

Figure (4.4):

```
timerange = [0 10];
IC = [10; 10; 0];
T = linspace(0,1,10);
FT = linspace(0,1,10);
[t, y] = ode45(@(t, y) odes16(t,y,T,FT),timerange,IC);
plot(t,y(:,1), t,y(:,2));
title('Tumor Growth Cells Model');
xlabel('time (1/day)');
ylabel('density (mm3)');
legend('uninfected Cells', 'infected Cells');
```

Figure (4.5):

```
timerange = [0 10];
IC = [10; 10; 0];
T = linspace(0,1,10);
FT = linspace(0,1,10);
[t, y] = ode45(@(t, y) odes16(t,y,T,FT),timerange,IC);
plot(t,y(:,1), t,y(:,2), t,y(:,3));
title('Tumor Growth Cells Model');
xlabel('time (1/day)');
ylabel('density (mm3)');
legend('Proliferative Cells', 'Quiescent Cells', 'Virus cells');
```

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