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Solution of Modified Kuznetsov Model with Mixed Therapy

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Abstract

In this paper two modifications on Kuznetsov model namely on growth rate law and fractional cell kill term are given. Laplace Adomian decomposition method is used to get the solution (volume of the tumor) as a function of time .Stability analysis is applied. For lung cancer the tumor will continue in growing in spite of the treatment.

Keywords: Cancer, Dynamical systems, Tumor therapy, Laplace Adomian Decomposition method.

1. INTRODUCTION

Cancer is one of the most dangerous diseases in the history of pathology. It is explained as an uncontrolled growth of abnormal cells inside the body [11]. Cells are the basic units of the body building and cancer grows from normal cells. The origin of the word cancer is credited to the Greek physician Hippocrates (460-370 BC), who is considered the "Father of Medicine". Hippocrates used the terms carcinos and carcinoma to describe non-ulcer forming and ulcer-forming tumors.

In Greek, these words refer to a crab, most likely applied to the disease because the finger-like spreading projections from a cancer called to mind the shape of a crab [2]. There are five main cancer groups, including Carcinomas, Sarcomas, Lymphomas, Leukemias, and Brain tumors [4].

Cancer has many causes that have been documented to date, such as exposure to chemicals, drinking alcohol, smoking, excessive sunlight exposure, and genetic differences [17]. According to the reports of the Cancer Research Institute, about 1,252,000 cases were diagnosed, with 547,000 deaths in 1995 in the United States alone [5]. The International Agency for Research on Cancer reported that 12.7 million new cancer cases were detected in 2008 [11]. Today, there are new techniques for the detection of cancer and this will increase the chances of survival to more than 50%. Cancer treatment is applied in many different ways, including treatment that aims to

- Kill or remove cancer cells (basic treatment)
- Destroy the remaining cancer cells (helper treatment)
- Treat the side effects caused by cancer and its treatment (supportive treatment).

There are several treatment techniques which are used to treat cancer, such as surgery, chemotherapy, radiotherapy, immunotherapy, transplant bone marrow and stem cells, hormone therapy, drug therapy, and clinical trials. Scientists are still looking for alternative ways to deal with cancer.

Mathematics was always serving other science and the past century witnessed many contributions of mathematicians in all fields of life. Mathematicians used mathematical modeling as a tool to describe vital phenomena and problems that face the world. The idea of using the qualitative theory of ordinary differential equations reaches back to the twenties of the past century when Lotka and Volterra formulated a simple mathematical model in population dynamics theory **(*)**[17]. They described the interaction between the predator and the prey in a model called predator-prey model which is a very important problem in ecology.

In 1973, Bell proposed a mathematical model consisting of two equations based on the predator-prey model [13]. De Boer and Hogeweg (1986) introduced a complex model of 10 ODEs and 3 additional equations describing several players of immune response. This model also covers all the phenomena from uncontrolled tumor growth to tumor regression due to immune system response [15]. Kuznetsov (1992 and 1994) presented a mathematical model of CTL (Cytotoxic T Lymphocytes i.e. cells with antitumor activity) cells response to the growth of immunogenic tumor, and he explained a number of phenomena, including sneaking through, dormant state of the tumor, and immunostimulation [10].

Adam and Bellomo (1997) published a good summary on the tumor-immune dynamics, and it was based on Kuznetsov's work [1]. Kirschner and Panetta (1998) described the dynamics between tumor cells, effector cells, and the cytokine

(*) *This is a part of MSc. thesis by Fatima Ahmed under supervision of Prof. Dr. Saad Naji.*

interleukine-2 (IL-2) by a mathematical model, which is considered as a modulator of the immune stimulus [9]. de Pillis and Radunskaya (2001 and 2006) proposed detailed models about the immune response differentiating between Natural Killer cells (NK-cells), CD8+ cytotoxic T-cells, and other lymphocytes [6][7].

Sotolongo-Costa et al. (2003) introduced a model of periodical immunotherapy with cytokines, and this work was based on kuznetsov's model also. In the same year, Szymanska presented a detailed model of immune response considering the interaction between cancer cells, NK-cells, lymphokine-activated killer cells, Cytotoxic T-cells, helper-cells, and B-cells [15]. Page and Uhr (2005) proposed different mathematical models of the interaction between tumor and antibody for the murine BCL1 lymphoma and illustrated how this interaction leads to dormancy of the tumor [12].

2. ANALYSIS OF KUZNETSOV MODEL

In 1994, the Russian mathematician Kuznetsov formulated a mathematical model describing the conflict between the immune cells and the tumor cells. This model involves two equations with variables E and T, where E represents the number of CTL cells and T represents the number of tumor cells [10]. The model is in the form:

$$\frac{dE}{dt} = s + \frac{\rho ET}{\alpha+T} - c_1 ET - d_1 E$$

$$\frac{dT}{dt} = rT(1 - bT) - c_2 ET \qquad (1)$$

Where $s, \rho, \alpha, c_1, d_1, r, b, c_2$ are positive parameters.

Some mathematicians used chemotherapy in addition to immunotherapy in Kuznetsov's model to get more powerful and influential model [13]. Kuznetsov model became a mix of two therapies as follows:

$$\frac{dE}{dt} = s + \frac{\rho ET}{\alpha+T} - c_1 ET - d_1 E - \alpha_1(1 - e^{-C})E$$

$$\frac{dT}{dt} = rT(1 - bT) - c_2 ET - \alpha_2(1 - e^{-C})\,T$$

$$\frac{dC}{dt} = -d_2 C \qquad (2)$$

Where $\alpha_1, \alpha_2, d_2 > 0$ and C represents the concentration of the chemotherapy drug in the blood.

Kuznetsov assumed that the tumor grows logistically in the absence of treatment, and he used the logistic growth form r T (1-bT) to represent the growth of the tumor cells. The two parameters r and b represent the maximal growth rate and the inverse

of tumor carrying capacity respectively. The tumor grows logistical means that the tumor will reach a maximum value which is the carrying capacity, then either it will keep growing in the same volume or it will decay, but the tumor growth will not exceed the carrying capacity. Figure (1) explains the logistic growth of the tumor.

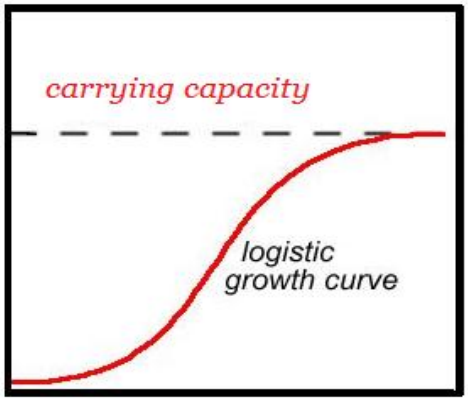
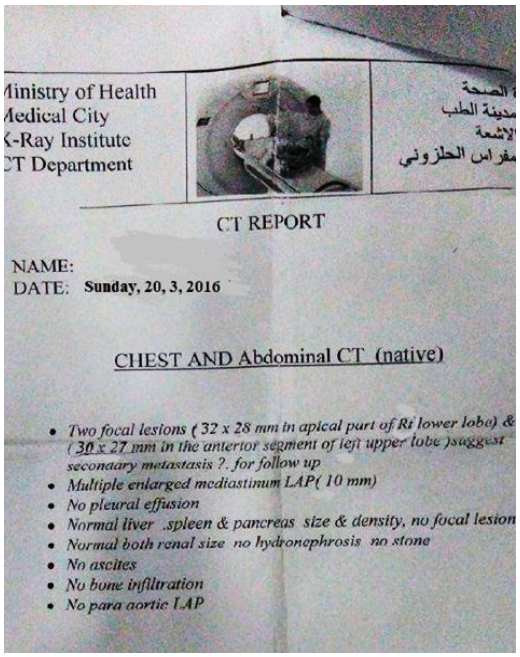


Figure (1)

But this is not the fact. The following three CT images show that the tumor decreased and increased uncontrollably for the same patient.

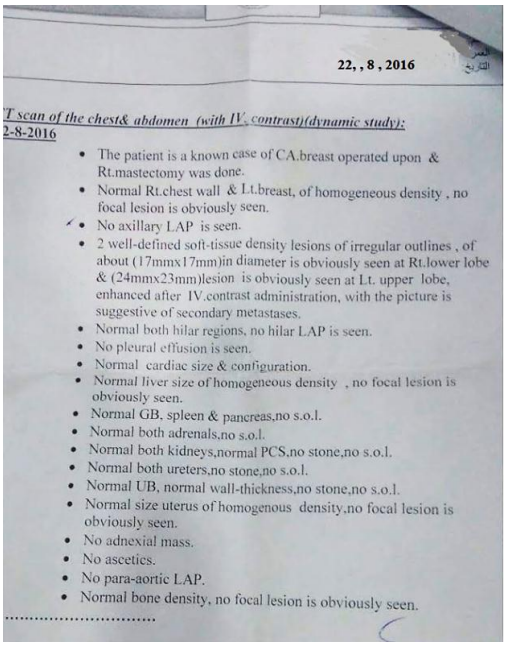

Ministry of Health
Medical City
X-Ray Institute
CT Department

CT REPORT

NAME:
DATE: **Sunday, 20, 3, 2016**

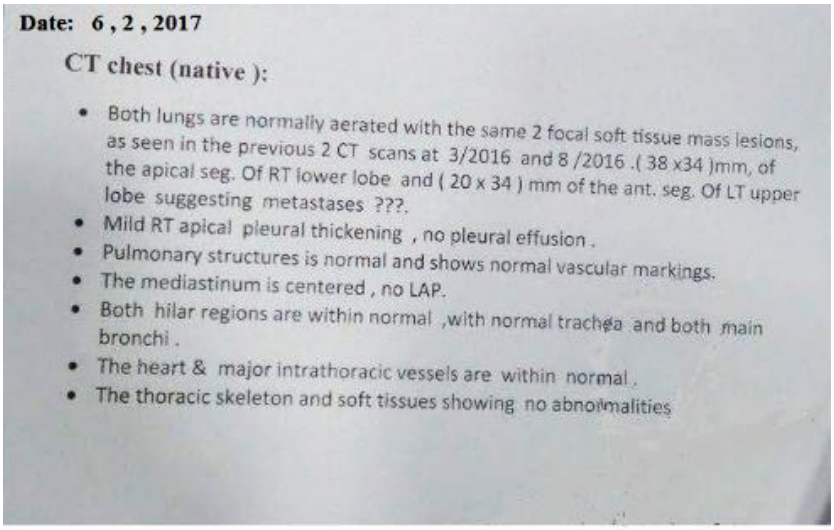
CHEST AND Abdominal CT (native)

- *Two focal lesions (32 x 28 mm in apical part of Rt lower lobe) & (30 x 27 mm in the antertor segment of left upper lobe)suggest seconaary metastasis ?. for follow up*
- *Multiple enlarged mediastinum LAP(10 mm)*
- *No pleural effusion*
- *Normal liver .spleen & pancreas size & density, no focal lesion*
- *Normal both renal size no hydronephrosis no stone*
- *No ascites*
- *No bone infiltration*
- *No para aortic LAP*


22, , 8 , 2016

T scan of the chest& abdomen (with IV. contrast)(dynamic study):
2-8-2016

- The patient is a known case of CA.breast operated upon & Rt.mastectomy was done.
- Normal Rt.chest wall & Lt.breast, of homogeneous density , no focal lesion is obviously seen.
- No axillary LAP is seen.
- 2 well-defined soft-tissue density lesions of irregular outlines , of about (17mmx17mm)in diameter is obviously seen at Rt.lower lobe & (24mmx23mm)lesion is obviously seen at Lt. upper lobe, enhanced after IV.contrast administration, with the picture is suggestive of secondary metastases.
- Normal both hilar regions, no hilar LAP is seen.
- No pleural effusion is seen.
- Normal cardiac size & configuration.
- Normal liver size of homogeneous density , no focal lesion is obviously seen.
- Normal GB, spleen & pancreas,no s.o.l.
- Normal both adrenals,no s.o.l.
- Normal both kidneys,normal PCS,no stone,no s.o.l.
- Normal both ureters,no stone,no s.o.l.
- Normal UB, normal wall-thickness,no stone,no s.o.l.
- Normal size uterus of homogenous density,no focal lesion is obviously seen.
- No adnexial mass.
- No ascetics.
- No para-aortic LAP.
- Normal bone density, no focal lesion is obviously seen.



Date: 6 , 2 , 2017

CT chest (native):

- Both lungs are normally aerated with the same 2 focal soft tissue mass lesions, as seen in the previous 2 CT scans at 3/2016 and 8 /2016 .(38 x34)mm, of the apical seg. Of RT lower lobe and (20 x 34) mm of the ant. seg. Of LT upper lobe suggesting metastases ???.
- Mild RT apical pleural thickening , no pleural effusion .
- Pulmonary structures is normal and shows normal vascular markings.
- The mediastinum is centered , no LAP.
- Both hilar regions are within normal ,with normal trachea and both main bronchi .
- The heart & major intrathoracic vessels are within normal .
- The thoracic skeleton and soft tissues showing no abnormalities

According to the medical researches, the tumor cells will metastasize (spread) to other parts of the body in the absence of treatment. This means that the tumor will not continue to grow with the same size, but it will spread in all directions through tissues and lymphatic system. From this result we can say that the logistic growth form which assumed by Kuznetsov is not accurate enough to describe the growth of the tumor, and this is a weak point in model (2).

The second weak point in model (2) is the fractional cell kill term $(1 - e^{-C})$ in the first and second equation which represents the effect of chemotherapy on the immune cells and the tumor cells.

$$(1 - e^{-C}) = 1 - [1 - C + \frac{C^2}{2!} - \frac{C^3}{3!} + \cdots]$$

$$= C - \frac{C^2}{2!} + \frac{C^3}{3!} + \cdots$$

This term must be positive for all values of C in order to control the growth of the tumor cells, but when C takes values larger than 4 we notice that this term becomes oscillating between positive and negative. This instability of the fractional cell kill term does not guarantee the decreasing of the tumor growth rate. So we suggest the form $(e^C - 1)$ to be the new fractional cell kill term.

3. Modified Kuznetsov Model

In the previous section we studied the weak points of model (2) and their effect on the performance of the model. Now, we will introduce two modifications to replace the weak parts in the model.

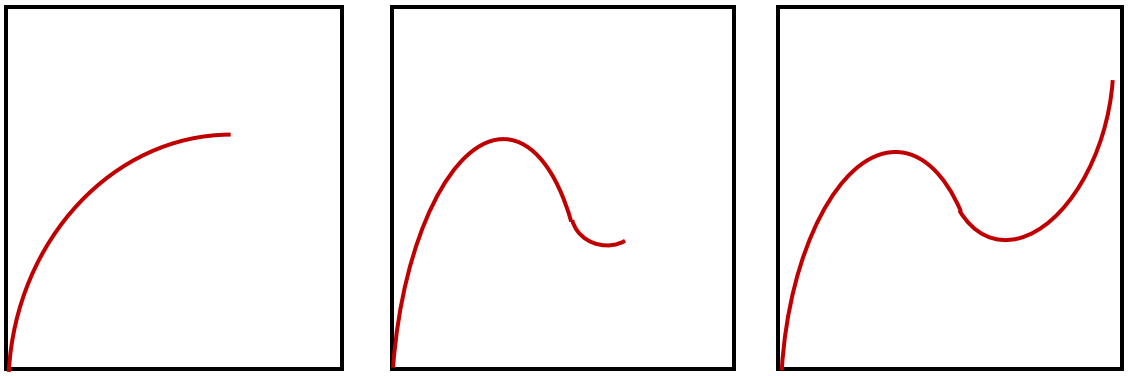
3.1 On the Birth Rate

For the birth rate of the tumor cells we suggested two modifications to replace the logistic growth form r T (1-bT) in model (2).

i. $\mathbf{B(T) = T\left(\frac{T^3}{3} - \frac{(a+b)T^2}{2} + abT\right),} \qquad \mathbf{0 < a < \frac{b}{3}}$

Where the term $-\frac{(a+b)T^2}{2}$ stands for the intraspecific competition.

When some part of the body is affected with cancer, the tumor cells will start to divide rapidly until it reaches a serious level (see Figure (2a)). This rapid growth of abnormal cells will alert the immune system about an existing risk in a specific part of the body. The immune cells will interact with the tumor cells and this interaction will cause a decreasing in number of tumor cells in the tumor site (see Figure (2b)). After a struggle with the tumor cells, the immune cells will become inactive and it will lose its ability to fight cancer. The tumor will grow again after defeating the immune cells and it will be very difficult to cure (see Figure (2c)).



(a) **(b)** **(c)**

Figure (2)

ii. $\mathbf{B(T) = r\,T\left(\frac{T^2}{2} - T + 2\right),} \qquad \mathbf{r > 0}$

This is the second suggestion for the tumor growth rate. It describes the tumor growth after detection by the immune system and as we can see in Figure (3) that the tumor will regrow after interacting with the immune cells.

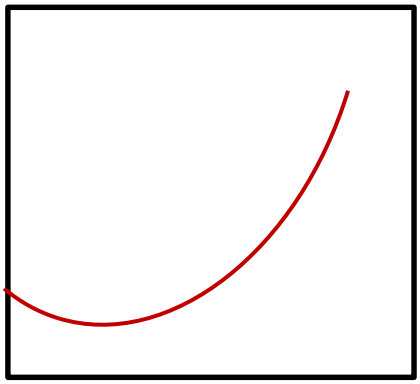


Figure (3)

3.2 On the Fractional Cell Kill Term

As mentioned in the previous section, the new form of the fractional cell kill term is

$F(C) = e^{C} - 1$

This form will enhance the effectiveness of chemotherapy to destroy the tumor cells.

After clarifying the new modifications, model (2) will be in the following two forms:

$$\frac{dE}{dt} = s + \frac{\rho ET}{\alpha+T} - c_1 ET - d_1 E - \alpha_1(e^{C} - 1)E$$

$$\frac{dT}{dt} = \left(\frac{T^4}{3} - \frac{(a+b)T^3}{2} + abT^2\right) - c_2 ET - \alpha_2(e^{C} - 1)T$$

$$\frac{dC}{dt} = -d_2 C \qquad (3)$$

And

$$\frac{dE}{dt} = s + \frac{\rho ET}{\alpha+T} - c_1 ET - d_1 E - \alpha_1(e^{C} - 1)E$$

$$\frac{dT}{dt} = r\,T\left(\frac{T^2}{2} - T + 2\right) - c_2 ET - \alpha_2(e^{C} - 1)T$$

$$\frac{dC}{dt} = -d_2 C \qquad (4)$$

Also the initial conditions of both models are $E(0) = \mu_1$, $T(0) = \tau$, and $C(0) = \mu_2$.

4. THE SOLUTION OF THE MODIFIED MODEL

In this section, a Laplace Adomian decomposition algorithm is used for the solution of models (3) and (4), and we will explain this method through the solution. At first we solve model (3) and then we use the same procedure with model (4).

Remember that

$$\frac{1}{\alpha+T} = \frac{1}{\alpha}\left[\frac{1}{1+\frac{T}{\alpha}}\right] = \frac{1}{\alpha}\left[1-\frac{T}{\alpha}+\frac{T^2}{\alpha^2}-\frac{T^3}{\alpha^3}+\cdots\right]$$

$$(e^C - 1) = \left[C+\frac{C^2}{2!}+\frac{C^3}{3!}+\cdots\right]$$

Now, let s = ℓ (to avoid the symbol s used in Laplace transform) in model (3)

$$\frac{dE}{dt} = \ell + \frac{\rho ET}{\alpha}\left[1-\frac{T}{\alpha}+\frac{T^2}{\alpha^2}\right] - c_1 ET - d_1 E - \alpha_1\left[C+\frac{C^2}{2!}\right]E$$

$$\frac{dT}{dt} = \frac{T^4}{3} - \frac{(a+b)T^3}{2} + abT^2 - c_2 ET - \alpha_2\left[C+\frac{C^2}{2!}\right]T$$

$$\frac{dC}{dt} = -d_2 C$$

Then model (3) will be:

$$\frac{dE}{dt} = \ell - d_1 E + \left(\frac{\rho}{\alpha}-c_1\right)ET - \alpha_1 EC - \frac{\alpha_1}{2}EC^2 - \frac{\rho}{\alpha^2}ET^2 + \frac{\rho}{\alpha^3}ET^3$$

$$\frac{dT}{dt} = \frac{T^4}{3} - \frac{(a+b)T^3}{2} + abT^2 - c_2 ET - \alpha_2 TC - \frac{\alpha_2}{2}TC^2$$

$$\frac{dC}{dt} = -d_2 C \qquad (5)$$

With initial conditions E (0)= μ_1,T(0)= τ, and C(0)= μ_2 .

The Laplace Adomian decomposition method consists first of applying the Laplace transform (denoted throughout this paper by $\mathcal{L}$) to both sides of (5), hence

$$\mathcal{L}\left[\frac{dE}{dt}\right] = \mathcal{L}[\ell] - \mathcal{L}[d_1 E] + \mathcal{L}\left[\left(\frac{\rho}{\alpha}-c_1\right)ET\right] - \mathcal{L}[\alpha_1 EC] - \frac{1}{2}\mathcal{L}[\alpha_1 EC^2] - \mathcal{L}\left[\frac{\rho}{\alpha^2}ET^2\right] + \mathcal{L}\left[\frac{\rho}{\alpha^3}ET^3\right]$$

$$\mathcal{L}\left[\frac{dT}{dt}\right] = \frac{1}{3}\mathcal{L}[T^4] - \frac{1}{2}\mathcal{L}[(a+b)T^3] + \mathcal{L}[abT^2] - \mathcal{L}[c_2 ET] - \mathcal{L}[\alpha_2 TC] - \mathcal{L}\left[\frac{\alpha_2}{2}TC^2\right]$$

$$\mathcal{L}\left[\frac{dC}{dt}\right] = -\mathcal{L}[d_2 C] \qquad (6)$$

Applying the initial conditions on (6), we get

$$\mathcal{L}[E] = \frac{\mu_1}{s} + \frac{\ell}{s^2} - \frac{d_1}{s}\mathcal{L}[E] + \frac{1}{s}\left(\frac{\rho}{\alpha}-c_1\right)\mathcal{L}[ET] - \frac{\alpha_1}{s}\mathcal{L}[EC] - \frac{\alpha_1}{2s}\mathcal{L}[EC^2] - \frac{\rho}{\alpha^2 s}\mathcal{L}[ET^2] + \frac{\rho}{\alpha^3 s}\mathcal{L}[ET^3]$$

$$\mathcal{L}[T] = \frac{\tau}{s} + \frac{1}{3s}\mathcal{L}[T^4] - \frac{(a+b)}{2s}\mathcal{L}[T^3] + \frac{ab}{s}\mathcal{L}[T^2] - \frac{c_2}{s}\mathcal{L}[ET] - \frac{\alpha_2}{s}\mathcal{L}[TC] - \frac{\alpha_2}{2s}\mathcal{L}[TC^2]$$

$$\mathcal{L}[C] = \frac{\mu_2}{s} - \frac{d_2}{s}\mathcal{L}[C] \quad (7)$$

The Laplace Adomian decomposition technique consists next of representing the solution as an infinite series, namely,

$$E = \sum_{n=0}^{\infty} E_n \ , \quad T = \sum_{n=0}^{\infty} T_n \ , \text{and } C = \sum_{n=0}^{\infty} C_n \quad (8)$$

Where the terms E_n, T_n, and C_n are to be recursively computed. Also the nonlinear terms in the system are represented as follows:

$A = ET$, $B = EC$, $D = EC^2$, $F = ET^2$, $G = ET^3$, $H = T^4$, $I = T^3$, $P = T^2$, $Q = TC$, and $R = TC^2$

The nonlinear operators A, B, D, F, G, H, I, P, Q, and R will be decomposed as follows:

$$A = \sum_{n=0}^{\infty} A_n \ , \quad B = \sum_{n=0}^{\infty} B_n \ , \quad D = \sum_{n=0}^{\infty} D_n \ , \quad F = \sum_{n=0}^{\infty} F_n \ ,$$

$$G = \sum_{n=0}^{\infty} G_n \ , \quad H = \sum_{n=0}^{\infty} H_n \ ,$$

$$I = \sum_{n=0}^{\infty} I_n \ , \quad P = \sum_{n=0}^{\infty} P_n \ , \quad Q = \sum_{n=0}^{\infty} Q_n \ , \text{ and } R = \sum_{n=0}^{\infty} R_n \quad (9)$$

Where A_n, $B_n, D_n, F_n, G_n, H_n, I_n, P_n$, Q_n, and R_n are called the Adomian polynomials and we will expand them as follows

$$A_0 = E_0T_0 \qquad B_0 = E_0C_0$$

$$A_1 = E_0T_1 + E_1T_0 \qquad B_1 = E_0C_1 + E_1C_0$$

$$A_2 = E_0T_2 + E_1T_1 + E_2T_0 \qquad B_2 = E_0C_2 + E_1C_1 + E_2C_0$$

$$\vdots \qquad \vdots$$

$$D_0 = E_0C_0^2 \qquad F_0 = E_0T_0^2$$

$$D_1 = E_1C_0^2 + 2E_0C_0C_1 \qquad F_1 = E_1T_0^2 + 2E_0T_0T_1$$

$D_2 = E_2C_0^2 + 2E_0C_0C_2 + E_0C_1^2 + 2E_1C_0C_1$ $F_2 = E_2T_0^2 + 2E_0T_0T_2 + E_0T_1^2 + 2E_1T_0T_1$

$\vdots$ $\vdots$

$G_0 = E_0T_0^3$ $H_0 = T_0^4$

$G_1 = E_1T_0^3 + 3E_0T_0^2T_1$ $H_1 = 4T_1T_0^3$

$G_2 = E_2T_0^3 + 3E_0T_0^2T_2 + 3E_0T_0T_1^2 + 3E_1T_0^2T_1$ $H_2 = 4T_2T_0^3 + 6T_0^2T_1^2$

$\vdots$ $\vdots$

$I_0 = T_0^3$

$I_1 = 3T_1T_0^2$

$I_2 = 3T_2T_0^2 + 3T_0T_1^2$

$\vdots$

And we use the same procedure with P_n, Q_n, and R_n . Now, Substituting (8) and (9) into (7) results

$$\mathcal{L}\left[\sum_{n=0}^{\infty} E_n\right] = \frac{\mu_1}{s} + \frac{\ell}{s^2} - \frac{d_1}{s}\mathcal{L}\left[\sum_{n=0}^{\infty} E_n\right] + \frac{1}{s}\left(\frac{\rho}{\alpha} - c_1\right)\mathcal{L}\left[\sum_{n=0}^{\infty} A_n\right] - \frac{\alpha_1}{s}\mathcal{L}\left[\sum_{n=0}^{\infty} B_n\right] - \frac{\alpha_1}{2s}\mathcal{L}\left[\sum_{n=0}^{\infty} D_n\right] - \frac{\rho}{\alpha^2 s}\mathcal{L}\left[\sum_{n=0}^{\infty} F_n\right] + \frac{\rho}{\alpha^3 s}\mathcal{L}\left[\sum_{n=0}^{\infty} G_n\right]$$

$$\mathcal{L}\left[\sum_{n=0}^{\infty} T_n\right] = \frac{\tau}{s} + \frac{1}{3s}\mathcal{L}\left[\sum_{n=0}^{\infty} H_n\right] - \frac{(a+b)}{2s}\mathcal{L}\left[\sum_{n=0}^{\infty} I_n\right] + \frac{ab}{s}\mathcal{L}\left[\sum_{n=0}^{\infty} P_n\right] - \frac{c_2}{s}\mathcal{L}\left[\sum_{n=0}^{\infty} A_n\right] - \frac{\alpha_2}{s}\mathcal{L}\left[\sum_{n=0}^{\infty} Q_n\right] - \frac{\alpha_2}{2s}\mathcal{L}\left[\sum_{n=0}^{\infty} R_n\right]$$

$$\mathcal{L}\left[\sum_{n=0}^{\infty} C_n\right] = \frac{\mu_2}{s} - \frac{d_2}{s}\mathcal{L}\left[\sum_{n=0}^{\infty} C_n\right] \quad (10)$$

When n=0

$$\mathcal{L}[E_0] = \frac{\mu_1}{s} + \frac{\ell}{s^2}$$

$$\mathcal{L}[T_0] = \frac{\tau}{s}$$

$$\mathcal{L}[C_0] = \frac{\mu_2}{s} \quad (11)$$

Then applying the inverse Laplace transform on (11), we obtain the values of E_0, T_0, and C_0

$$E_0 = \mu_1 + \ell t$$

$$T_0 = \tau$$

$$C_0 = \mu_2 \quad (12)$$

And when n= 1

$$\mathcal{L}[E_1] = -\frac{d_1}{s}\mathcal{L}[E_0] + \frac{1}{s}\left(\frac{\rho}{\alpha} - c_1\right)\mathcal{L}[A_0] - \frac{\alpha_1}{s}\mathcal{L}[B_0] - \frac{\alpha_1}{2s}\mathcal{L}[D_0] - \frac{\rho}{\alpha^2 s}\mathcal{L}[F_0] + \frac{\rho}{\alpha^3 s}\mathcal{L}[G_0]$$

$$\mathcal{L}[T_1] = \frac{1}{3s}\mathcal{L}[H_0] - \frac{(a+b)}{2s}\mathcal{L}[I_0] + \frac{ab}{s}\mathcal{L}[P_0] - \frac{c_2}{s}\mathcal{L}[A_0] - \frac{\alpha_2}{s}\mathcal{L}[Q_0] - \frac{\alpha_2}{2s}\mathcal{L}[R_0]$$

$$\mathcal{L}[C_1] = -\frac{d_2}{s}\mathcal{L}[C_0] \qquad (13)$$

Substituting (12) into (13), we get

$$\mathcal{L}[E_1] = -\frac{d_1}{s}\mathcal{L}[\mu_1 + \ell t] + \frac{1}{s}\left(\frac{\rho}{\alpha} - c_1\right)\mathcal{L}[(\mu_1 + \ell t)\tau] - \frac{\alpha_1}{s}\mathcal{L}[(\mu_1 + \ell t)\mu_2] - \frac{\alpha_1}{2s}\mathcal{L}[(\mu_1 + \ell t)\mu_2^2] - \frac{\rho}{\alpha^2 s}\mathcal{L}[(\mu_1 + \ell t)\tau^2] + \frac{\rho}{\alpha^3 s}\mathcal{L}[(\mu_1 + \ell t)\tau^3]$$

$$\mathcal{L}[T_1] = \frac{1}{3s}\mathcal{L}[\tau^4] - \frac{(a+b)}{2s}\mathcal{L}[\tau^3] + \frac{ab}{s}\mathcal{L}[\tau^2] - \frac{c_2}{s}\mathcal{L}[(\mu_1 + \ell t)\tau] - \frac{\alpha_2}{s}\mathcal{L}[\tau\mu_2] - \frac{\alpha_2}{2s}\mathcal{L}[\tau\mu_2^2]$$

$$\mathcal{L}[C_1] = -\frac{d_2}{s}\mathcal{L}[\mu_2] \qquad (14)$$

After simplifying the terms inside the brackets and applying the inverse Laplace transform, we obtain

$$E_1 = \mu_1\left(-d_1 + \tau\left(\frac{\rho}{\alpha} - c_1\right) - \alpha_1\mu_2 - \frac{\alpha_1\mu_2^2}{2} - \frac{\rho\tau^2}{\alpha^2} + \frac{\rho\tau^3}{\alpha^3}\right)t + \ell\left(-d_1 + \tau\left(\frac{\rho}{\alpha} - c_1\right) - \alpha_1\mu_2 - \frac{\alpha_1\mu_2^2}{2} - \frac{\rho\tau^2}{\alpha^2} + \frac{\rho\tau^3}{\alpha^3}\right)\frac{t^2}{2}$$

$$T_1 = \left(\frac{\tau^4}{3} - \frac{(a+b)\tau^3}{2} + ab\tau^2 - c_2\tau\mu_1 - \alpha_2\tau\mu_2 - \frac{\alpha_2\tau\mu_2^2}{2}\right)t - \frac{c_2\tau\ell}{2}t^2$$

$$C_1 = -\mu_2 d_2 t \qquad (15)$$

Because of the uniform convergence property, few terms of each series of E, T, and C are enough for good accuracy [14].

$$E(t) = E_0 + E_1 + E_2$$

$$E(t) = \mu_1 + \left[s + \mu_1\left(-d_1 + \tau\left(\frac{\rho}{\alpha} - c_1\right) - \alpha_1\mu_2 - \frac{\alpha_1\mu_2^2}{2} - \frac{\rho\tau^2}{\alpha^2} + \frac{\rho\tau^3}{\alpha^3}\right)\right]t + \left[\mu_2\alpha_1\mu_1 d_2(1+\mu_2) + s\left(-d_1 + \tau\left(\frac{\rho}{\alpha} - c_1\right) - \alpha_1\mu_2 - \frac{\alpha_1\mu_2^2}{2} - \frac{\rho\tau^2}{\alpha^2} + \frac{\rho\tau^3}{\alpha^3}\right) + \mu_1\left(-d_1 + \tau\left(\frac{\rho}{\alpha} - c_1\right) - \alpha_1\mu_2 - \frac{\alpha_1\mu_2^2}{2} - \frac{\rho\tau^2}{\alpha^2} + \frac{\rho\tau^3}{\alpha^3}\right)^2 + \mu_1\left(\frac{\tau^3}{3} - \frac{(a+b)\tau^2}{2} + ab\tau - c_2\mu_1 - \alpha_2\mu_2 - \frac{\alpha_2\mu_2^2}{2}\right)\left(\tau\left(\frac{\rho}{\alpha} - c_1\right) - \frac{2\rho\tau^2}{\alpha^2} + \frac{3\rho\tau^3}{\alpha^3}\right)\right]\frac{t^2}{2} + \left[\mu_2\alpha_1 s d_2(1+\mu_2) - c_2\mu_1\frac{s}{2}\left(\tau\left(\frac{\rho}{\alpha} - c_1\right) - \frac{2\rho\tau^2}{\alpha^2} + \frac{3\rho\tau^3}{\alpha^3}\right) + \frac{s}{2}\left(-d_1 + \tau\left(\frac{\rho}{\alpha} - c_1\right) - \alpha_1\mu_2 - \frac{\alpha_1\mu_2^2}{2} - \frac{\rho\tau^2}{\alpha^2} + \frac{\rho\tau^3}{\alpha^3}\right)^2 + s\left(\frac{\tau^3}{3} - \frac{(a+b)\tau^2}{2} + ab\tau - c_2\mu_1 - \alpha_2\mu_2 - \frac{\alpha_2\mu_2^2}{2}\right)\left(\tau\left(\frac{\rho}{\alpha} - c_1\right) - \frac{2\rho\tau^2}{\alpha^2} + \frac{3\rho\tau^3}{\alpha^3}\right)\right]\frac{t^3}{3} - \frac{c_2 s^2}{2}\left(\tau\left(\frac{\rho}{\alpha}\right.\right.$$

$-c_1) - \frac{2\rho\tau^2}{\alpha^2} + \frac{3\rho\tau^3}{\alpha^3}) \frac{t^4}{4}$

(16)

$T(t) = T_0 + T_1 + T_2$

$T(t) = \tau + [\frac{\tau^4}{3} - \frac{(a+b)\tau^3}{2} + ab\tau^2 - c_2\tau\mu_1 - \alpha_2\tau\mu_2 - \frac{\alpha_2\tau\mu_2^2}{2}]\, t + [\alpha_2\mu_2\tau d_2(1+\mu_2) - c_2\tau s + (\frac{\tau^3}{3} - \frac{(a+b)\tau^2}{2} + ab\tau - c_2\mu_1 - \alpha_2\mu_2 - \frac{\alpha_2\mu_2^2}{2})(\frac{4\tau^4}{3} - \frac{3(a+b)\tau^3}{2} + 2ab\tau^2 - c_2\tau\mu_1 - \alpha_2\tau\mu_2 - \frac{\alpha_2\tau\mu_2^2}{2}) - c_2\tau\mu_1(-d_1 + \tau(\frac{\rho}{\alpha} - c_1) - \alpha_1\mu_2 - \frac{\alpha_1\mu_2^2}{2} - \frac{\rho\tau^2}{\alpha^2} + \frac{\rho\tau^3}{\alpha^3})]\, \frac{t^2}{2} + [-c_2\tau\frac{s}{2}(-d_1 + \tau(\frac{\rho}{\alpha} - c_1) - \alpha_1\mu_2 - \frac{\alpha_1\mu_2^2}{2} - \frac{\rho\tau^2}{\alpha^2} + \frac{\rho\tau^3}{\alpha^3}) - c_2\frac{s}{2}(\frac{4\tau^4}{3} - \frac{3(a+b)\tau^3}{2} + 2ab\tau^2 - c_2\tau\mu_1 - \alpha_2\tau\mu_2 - \frac{\alpha_2\tau\mu_2^2}{2}) - c_2 s(\frac{\tau^4}{3} - \frac{(a+b)\tau^3}{2} + ab\tau^2 - c_2\tau\mu_1 - \alpha_2\tau\mu_2 - \frac{\alpha_2\tau\mu_2^2}{2})]\, \frac{t^3}{3} + \frac{c_2^2 s^2\tau}{2}\, \frac{t^4}{4}$ (17)

$C(t) = C_0 + C_1 + C_2$

$C(t) = \mu_2 - \mu_2 d_2\, t + \mu_2 \frac{d_2^2 t^2}{2}$ (18)

To draw the function T(t) we have to determine the values of a and b. These values of a and b will be determined from the data of patients representing the tumor size vs. the period of therapy.

As mentioned before that the same procedure and steps will be used to solve model (4). Presenting the model and the initial conditions as follows

$\frac{dE}{dt} = s + \frac{\rho ET}{\alpha+T} - c_1 ET - d_1 E - \alpha_1(e^C - 1)E$

$\frac{dT}{dt} = r\, T\, (\frac{T^2}{2} - T + 2) - c_2 ET - \alpha_2(e^C - 1)T$

$\frac{dC}{dt} = -d_2 C$

$E(0) = \mu_1$, $T(0) = \tau$, and $C(0) = \mu_2$

After applying the steps of the Laplace Adomian decomposition method, the solution of the above model:

$E(t) = E_0 + E_1 + E_2$

$E(t) = \mu_1 + [s + \mu_1(-d_1 + \tau(\frac{\rho}{\alpha} - c_1) - \alpha_1\mu_2 - \frac{\alpha_1\mu_2^2}{2} - \frac{\rho\tau^2}{\alpha^2} + \frac{\rho\tau^3}{\alpha^3})]\, t + [\mu_2\alpha_1\mu_1 d_2(1+\mu_2) + s(-d_1 + \tau(\frac{\rho}{\alpha} - c_1) - \alpha_1\mu_2 - \frac{\alpha_1\mu_2^2}{2} - \frac{\rho\tau^2}{\alpha^2} + \frac{\rho\tau^3}{\alpha^3}) + \mu_1(-d_1 + \tau(\frac{\rho}{\alpha} - c_1) - \alpha_1\mu_2 - \frac{\alpha_1\mu_2^2}{2} - \frac{\rho\tau^2}{\alpha^2} + \frac{\rho\tau^3}{\alpha^3})^2 + \mu_1(\frac{r\tau^2}{2} - r\tau + 2r - c_2\mu_1 - \alpha_2\mu_2 - \frac{\alpha_2\mu_2^2}{2})(\tau(\frac{\rho}{\alpha} - c_1) - \frac{2\rho\tau^2}{\alpha^2} + \frac{3\rho\tau^3}{\alpha^3})]\, \frac{t^2}{2} + [\alpha_1 s\mu_2 d_2(1+\mu_2) + \frac{s}{2}(-d_1 + \tau(\frac{\rho}{\alpha}$

$$- c_1) - \alpha_1\mu_2 - \frac{\alpha_1\mu_2^2}{2} - \frac{\rho\tau^2}{\alpha^2} + \frac{\rho\tau^3}{\alpha^3})^2 - c_2\mu_1\frac{s}{2}(\tau(\frac{\rho}{\alpha} - c_1) - \frac{2\rho\tau^2}{\alpha^2} + \frac{3\rho\tau^3}{\alpha^3}) + s(\frac{r\tau^2}{2} - r\tau + 2r - c_2\mu_1 - \alpha_2\mu_2 - \frac{\alpha_2\mu_2^2}{2})(\tau(\frac{\rho}{\alpha} - c_1) - \frac{2\rho\tau^2}{\alpha^2} + \frac{3\rho\tau^3}{\alpha^3})]\frac{t^3}{3} - \frac{c_2s^2}{2}(\tau(\frac{\rho}{\alpha} - c_1) - \frac{2\rho\tau^2}{\alpha^2} + \frac{3\rho\tau^3}{\alpha^3})\frac{t^4}{4}$$

(19)

$$T(t) = \tau + [\frac{r\tau^3}{2} - r\tau^2 + 2r\tau - c_2\tau\mu_1 - \alpha_2\tau\mu_2 - \frac{\alpha_2\tau\mu_2^2}{2}]t + [\alpha_2\mu_2\tau d_2(1+\mu_2) - c_2\tau s + (\frac{3r\tau^3}{2} - 2r\tau^2 + 2r\tau - c_2\tau\mu_1 - \alpha_2\tau\mu_2 - \frac{\alpha_2\tau\mu_2^2}{2})(\frac{r\tau^2}{2} - r\tau + 2r - c_2\mu_1 - \alpha_2\mu_2 - \frac{\alpha_2\mu_2^2}{2}) - c_2\tau\mu_1(-d_1 + \tau(\frac{\rho}{\alpha} - c_1) - \alpha_1\mu_2 - \frac{\alpha_1\mu_2^2}{2} - \frac{\rho\tau^2}{\alpha^2} + \frac{\rho\tau^3}{\alpha^3})]\frac{t^2}{2} + [-c_2\frac{s}{2}(\frac{3r\tau^3}{2} - 2r\tau^2 + 2r\tau - c_2\tau\mu_1 - \alpha_2\tau\mu_2 - \frac{\alpha_2\tau\mu_2^2}{2}) - c_2s\tau(\frac{r\tau^2}{2} - r\tau + 2r - c_2\mu_1 - \alpha_2\mu_2 - \frac{\alpha_2\mu_2^2}{2}) - c_2\tau\frac{s}{2}(-d_1 + \tau(\frac{\rho}{\alpha} - c_1) - \alpha_1\mu_2 - \frac{\alpha_1\mu_2^2}{2} - \frac{\rho\tau^2}{\alpha^2} + \frac{\rho\tau^3}{\alpha^3})]\frac{t^3}{3} - \frac{c_2^2s^2\tau}{2}\frac{t^4}{4}$$

(20)

$$C(t) = \mu_2 - \mu_2 d_2 t + \mu_2\frac{d_2^2t^2}{2} \quad (21)$$

5. EVALUATION OF a AND b SATISFYING THE CONDITION $0 < a < \frac{b}{3}$

As mentioned before that we need to use real data of patients in order to get the value of a and b in model (3). This medical data provide the period of therapy in addition to the size of the tumor. The period of therapy will be measured by months and the number of tumor cells will be used instead of the size of the mass (tumor). Table (1) contains a data of a patient suffering from lung cancer during the treatment with chemotherapy.

Table (1)

Period of therapy (by months)	Number of tumor cells
0	3181775
4	922715
10.5	4104489

The above data will be used in Equation (17) to find a relation between the time of therapy t and the number of tumor cells T. the estimated values and the description of the parameters s, $\rho, \alpha, c_1, d_1, d_2, c_2, \alpha_1, \alpha_2$ are given in Table (2).

Table (2)

Parameter	Description	Estimated value	Source
s	Normal rate of flow of immune cells into the tumor site	1.300×10^{4}	Kuznetsov et al. 1994 [10]
$\boldsymbol{\rho}$	Maximum immune cells recruitment rate	1.245×10^{-1}	Kuznetsov et al. 1994 [10]
$\boldsymbol{\alpha}$	Steepness coefficient of immune cell recruitment	2.020×10^{7}	Kuznetsov et al. 1994 [10]
$\mathbf{c_1}$	Immune cells death rate due to interaction with tumor cells	3.420×10^{-10}	Kuznetsov et al. 1994 [10]
$\mathbf{c_2}$	Fractional tumor cells kill by immune cells	1.100×10^{-7}	Kuznetsov et al. 1994 [10]
$\mathbf{d_1}$	Nature death rate of immune cells	4.120×10^{-2}	Kuznetsov et al. 1994 [10]
$\mathbf{d_2}$	Rate of chemotherapy drug decay	3.466×10^{-1}	Estimated [13]
$\boldsymbol{\alpha_1}$	Fractional immune cells kill by chemotherapy	3.400×10^{-2}	De Pillis et al. 2006 [7]
$\boldsymbol{\alpha_2}$	Fractional tumor cells kill by chemotherapy	9.000×10^{-1}	De Pillis et al. 2006 [7]

The number of tumor cells at time t=0 is denoted by $T_0 = \tau$ = 3181775 cells.

The number of CTL cells at time t=0 is denoted by $E_0 = \mu_1$= 566666 cells [13].

The increment of the blood drug concentration due to delivering chemotherapy drug at time t=0 is denoted by $C_0 = \mu_2 = 1.400$ mg/L [13].

The values in Table (1), Table (2) and above information will be substituted into equation (17) as follows:

$$T(t) = 3181775+(3416304759\times 10^{16} - 161056553 \times 10^{11}(a + b) + 1012369215 \times 10^{4}ab)\, t + (1467248715 \times 10^{36} - 6922311374 \times 10^{32}(a +b) + 6521947842 \times 10^{23}\, ab + 2445730441 \times 10^{23}(a + b)^2 - 2562228568 \times 10^{17}ab\,(a + b) + 6442262118 \times 10^{10}a^2b^2)\,\frac{t^2}{2} - (1465594741 \times 10^{14} - 5757771769 \times 10^{7}(a + b) + 28953759540\, ab)\,\frac{t^3}{3} + 1.2780625\, t^2 \quad \ldots (22)$$

When t=4 and T= 922715 in (22) we get

$$922715 = 1173798972 \times 10^{37} - 5537849099 \times 10^{33}(a+b) + 5217558274 \times 10^{24}\, ab$$
$$+1956584353 \times 10^{24}(a+b)^2 - 2049782854 \times 10^{18}ab(a+b) + 5153809694 \times 10^{11}a^2b^2$$

… (23)

When t=10.5 and T= 4104489 in (22) we get

$$4104489 = 8088208541 \times 10^{37} - 3815924145 \times 10^{34}(a+b) + 3595223748 \times 10^{25}ab + 1348208906 \times 10^{25}(a+b)^2 - 1412428498 \times 10^{19}ab(a+b) + 3551296993 \times 10^{12}a^2b^2$$

… (24)

Now, starting with nonlinear least square fitting method to find the minimum values of a and b from equation (23) and (24), we obtain the following two equations:

$$[(1173798972 \times 10^{37} - 5537849099 \times 10^{33}(a+b) + 5217558274 \times 10^{24}\, ab + 1956584353 \times 10^{24}(a+b)^2 - 2049782854 \times 10^{18}ab(a+b) + 5153809694 \times 10^{11}a^2b^2) - 922715]^2 = 0$$ … (25)

$$[(8088208541 \times 10^{37} - 3815924145 \times 10^{34}(a+b) + 3595223748 \times 10^{25}ab + 1348208906 \times 10^{25}(a+b)^2 - 1412428498 \times 10^{19}ab(a+b) + 3551296993 \times 10^{12}a^2b^2) - 4104489\ ]^2 = 0$$

… (26)

Equation (25) and (26) will be used in a Matlab program code with unconstrained optimization by fminunc to find the values of a and b with objective function:

$$f = \frac{1}{2}\,[(1173798972 \times 10^{37} - 5537849099 \times 10^{33}(a+b) + 5217558274 \times 10^{24}\, ab + 1956584353 \times 10^{24}(a+b)^2 - 2049782854 \times 10^{18}ab(a+b) + 5153809694 \times 10^{11}a^2b^2) - 922715]^2 + \frac{1}{2}[(8088208541 \times 10^{37} - 3815924145 \times 10^{34}(a+b) + 595223748 \times 10^{25}ab + 1348208906 \times 10^{25}(a+b)^2 - 1412428498 \times 10^{19}ab(a+b) + 3551296993 \times 10^{12}a^2b^2) - 4104489\ ]^2$$

The following table shows of the values of the parameters a and b obtained by the program with initial guess for each parameter.

Table (3)

Initial Guess		**Final Values** **a < b/3**	
a	**b**	**a**	**b**
10^{-77}	2×10^{3}	59.797595039309	2059.797697153575
59.797595039309	2059.797697153575	59.797595039309	2059.797697153575

After obtaining the values of a and b, a relation between t and T will be found by substituting these values into equation (22) as follows:

$$T(t)= 3181775 + 3412891137\times 10^{16}t + 1712258499\times 10^{28}t^{2} - 4881247874 \times 10^{13}t^{3} + 0.813301462\, t^{4} \quad \ldots(27)$$

Figure (3) shows the curve of (27), and we notice that the tumor will continue in growing with time in spite of the treatment.

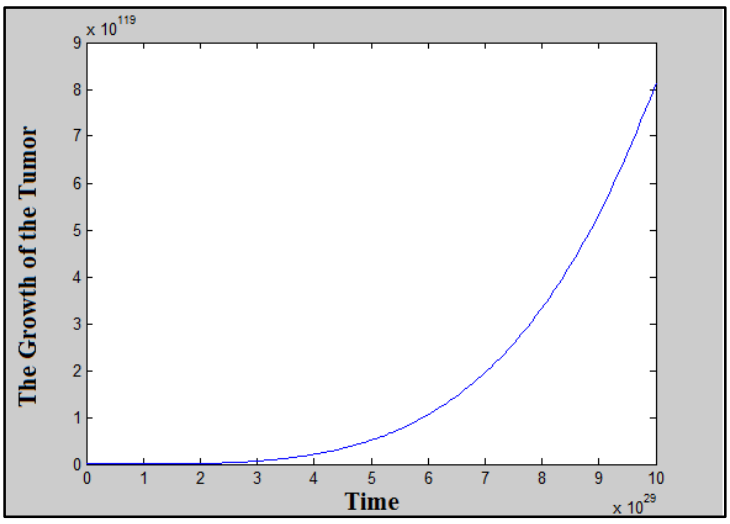


Figure (3)

6. STABILITY OF THE MODIFIED KUZNETSOV MODEL

In this section, we study the stability of model (3) using set of parameters in Table (2) and the values of a and b from Table (3).

$\frac{dE}{dt} = s + \frac{\rho ET}{\alpha+T} - c_1ET - d_1E - \alpha_1(e^C - 1)E$

$\frac{dT}{dt} = (\frac{T^4}{3} - \frac{(a+b)T^3}{2} + abT^2) - c_2ET - \alpha_2(e^C - 1)T$

$\frac{dC}{dt} = -d_2C$

First, setting ($\frac{dE}{dt} = 0, \frac{dT}{dt} = 0, \frac{dC}{dt} = 0$), we get the following three equations

$s + \frac{\rho ET}{\alpha+T} - c_1ET - d_1E - \alpha_1(e^C - 1)E = 0$

$\frac{T^4}{3} - \frac{(a+b)T^3}{2} + abT^2 - c_2ET - \alpha_2(e^C - 1)T = 0$

$-d_2C = 0$

From the last equation we get C = 0

The second equation gives: T= 0 or $E = \frac{1}{c_2}(\frac{T^3}{3} - \frac{(a+b)T^2}{2} + abT)$

When T= 0 in the first equation, we get the first equilibrium point

(E, T, C) = (315533.9806, 0, 0)

When $E = \frac{1}{c_2}(\frac{T^3}{3} - \frac{(a+b)T^2}{2} + abT)$ in the first equation, we get

$-\frac{c_1}{3}T^5 + (\frac{\rho}{3} - \frac{c_1\alpha}{3} + \frac{c_1(a+b)}{2} - \frac{d_1}{3})T^4 - (\frac{\rho(a+b)}{2} - \frac{c_1\alpha(a+b)}{2} + c_1ab + \frac{\alpha d_1}{3})T^3 +$

$(\rho ab - c_1\alpha ab + \frac{\alpha d_1(a+b)}{2} - d_1ab)T^2 + (sc_2 - \alpha d_1ab)T + sc_2\alpha = 0$ (28)

Substituting the values of the parameters in Table (2) and Table (3) into (28) we obtain

$T^5 - 223370433.8\,T^4 + 2434543479 \times 10^7T^3 - 7736977212 \times 10^9T^2 +$

$899191143 \times 10^{10}T - 2533859649 \times 10^5 = 0$ (29)

The roots of the above equation are the values of T:

316.6343615810154, 1.166452821273335, $2.818000498601014 \times 10^{-5}$,

111685057.999579 + 108957843.326762i, 111685057.999579 - 108957843.326762i

The complex roots will be neglected, also the root 316.6343615810154 will be neglected too since it gives $E = -5151879867 \times 10^5$.

The remaining roots give the following two equilibrium points

$(1293015054 \times 10^3, 1.166452821273335, 0)$

$(31554155.49, 2.81800049860101410^{-5}, 0)$

The Jacobian matrix of system (3) is:

$$J = \begin{bmatrix} \frac{\rho T}{\alpha+T} - c_1 T - d_1 - \alpha_1(e^C - 1) & \frac{\alpha\rho E}{(\alpha+T)^2} - c_1 E & -\alpha_1 e^C E \\ -c_2 T & \frac{4T^3}{3} - \frac{3(a+b)T^2}{2} + 2abT - c_2 E - \alpha_2(e^C - 1) & -\alpha_2 e^C T \\ 0 & 0 & -d_2 \end{bmatrix}$$

Now, we will find the eigenvalues of J at each equilibrium point

$$1)\ J_{(315533.9806,0,0)} = \begin{bmatrix} -0.0412 & 1.836838893 \times 10^{-3} & -10728.15534 \\ 0 & -0.034708737 & 0 \\ 0 & 0 & -0.3466 \end{bmatrix}$$

$$\lambda_1 = -0.034708737, \quad \lambda_2 = -0.0412, \quad \lambda_3 = -0.3466$$

This case is in the absence of tumor cells, we see that all the eigenvalues are negative which means that this is an asymptotically stable equilibrium point.

$$2)\ J_{(1293015054\times10^3,1.166452821273335,0)} =$$

$$\begin{bmatrix} -0.041199993 & 7527.113388 & -43962511840 \\ -1.283098103 \times 10^{-7} & 282880.1647 & -1.049807539 \\ 0 & 0 & -0.3466 \end{bmatrix}$$

$$P(\lambda) = \det(J - \lambda I) = 0$$

$$\begin{vmatrix} -0.041199993 - \lambda & 7527.113388 & -43962511840 \\ -1.283098103 \times 10^{-7} & 282880.1647 - \lambda & -1.049807539 \\ 0 & 0 & -0.3466 - \lambda \end{vmatrix} = 0$$

$$(-0.3466 - \lambda)(\lambda^2 - 282880.1235\lambda - 11654.65984) = 0$$

$$\lambda_1 = 282880.1647, \quad \lambda_2 = -0.041199989, \quad \lambda_3 = -0.3466$$

$$3)\ J_{(31554155.49,2.81800049860101410^{-5},0)} =$$

$$\begin{bmatrix} -0.040935905 & 0.183688298 & -1072841.287 \\ -3.099800548 \times 10^{-12} & 3.470956263 & -2.536200449 \times 10^{-5} \\ 0 & 0 & -0.3466 \end{bmatrix}$$

$$P(\lambda) = \det(J - \lambda I) = 0$$

$$\begin{vmatrix} -0.040935905 - \lambda & 0.183688298 & -1072841.287 \\ -3.099800548 \times 10^{-12} & 3.470956263 - \lambda & -2.536200449 \times 10^{-5} \\ 0 & 0 & -0.3466 - \lambda \end{vmatrix} = 0$$

$$(-0.3466 - \lambda)(\lambda^2 - 3.430020358\lambda - 0.142086735) = 0$$

$$\lambda_1 = 3.470956263, \quad \lambda_2 = -0.040935904, \quad \lambda_3 = -0.3466$$

The last two cases when the tumor is exist, we notice that they have positive eigenvalues which means that the points:

$(1293015054 \times 10^3, 1.166452821273335, 0)$
$(31554155.49, 2.81800049860101410^{-5}, 0)$

are unstable equilibrium points .

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