A nonlinear mathematical model of the mammary carcinoma-immune system: An analytical approach

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   Abstract- The mathematical modeling of the mammary carcinoma–immune system by an external stimulus is discussed. This model is based on a system of six ordinary differential equations which contains a nonlinear term related to various parameters and cell populations. Approximated closed analytical expressions for cell populations have been derived for all values of parameters for steady and non-steady state conditions. As time tends to infinity, the analytical expressions corresponding to the cell populations for non-steady state conditions approach the steady state values. These analytical results are of great interest both in the applied and theoretical sciences. Furthermore, in this work the numerical simulation of the problem is also reported using Matlab program.

   Index Terms- Mathematical biology, Non-linear ODE, Tumors, Mammary carcinoma, Homotopy perturbation method

1. Introduction

   The global challenge of the mathematicians around the world is the formation of mathematical models of real life complex occurrences that are qualitatively and quantitatively consistent with experimental results. Also the aim of mathematical models is to offer outlook to biologists and physicians on the suitability of experimental data and they in turn can help to improve the mathematical models. Thus mathematical modeling provides the opportunity of improving both the understanding and prediction of biological phenomena. The most well-known approach is the ordinary differential equation-based model and this approach views the particles (human cells, molecules) in the model as homogeneousness and ignores the spatial structure of the biological system in the microscopic scale. The interactions are performed through ordinary differential equation based on parameters, populations and sub populations.

   This paper compacts with the theoretical advance of an ODE-based model as simple as possible in order to explore the competition among the immune system, the vaccine cells, and the mammary carcinogenesis. The mathematical model, which is realized upon the same theoretical scheme used for the computational model [1] takes into account both the humeral and cellular branches of the immune response and includes the following entities: vaccine cells (V), cancer cells (C), natural killer cells (NK), thymus cytotoxic cells (Tc), thymus helper cells (Th) and antibodies (AB) release by the bone (B) cells.

   Mammary carcinoma, also known as breast cancer, is the cancer of the breasts or the lymph nodes under the armpits. Though it can affect both genders, breast cancer is considered the second most common type of cancer diagnosed in women, and is also considered the second deadliest female cancer. The triplex vaccine developed by [2] for effective treatment against mammary carcinoma, adopts a common approach in oncology by combining different stimuli. Simtriplex is a multi-agent model of the immune system whose major feature is given by the possibility of reproducing different individuals simply by changing the seed of the random number generator.

   To analyze the role of the parameters in the competition dynamics and to explore the phenomena depicted by the model in order to identify an optimal vaccine protocol by considering the constant injection case. Recently researchers [3] have been found the concentration profiles of V, Tc, Th, and AB cells.

   . Finally, they depict the competition among the cells populations and emerging behavior by means of numerical simulations after setting the magnitude of the parameters properly. So for no general analytical expressions for the steady and non-steady concentrations of the cancer cells for all values of the parameters had been found. The purpose of this paper is to derive approximate analytical expression for the concentrations of cancer cells by Homotopy perturbation method.

2. THE MATHEMATICAL MODEL

   The mathematical model [3] proposed in the present paper taken into account simplified biological assumptions. This model involves six ordinary differential equations for six types of cells by using generic function interaction forms. The intent is to reproduce the qualitative behavior observed [4],[5] by constructing a model as simple as possible and with a limited number of parameters. The cell populations involved in this model are natural killer (NK) cells, vaccine (V) cells, thymus helper (Th) cells, antibodies (AB) released by bone cells, thymus cytotoxic (Tc) cells and cancer cells (C). Particularly the number of natural killer (NK) cells is assumed as a constant in time. To analyze the competition dynamics between vaccine cells and cancer cells by considering the case of vaccine that is injected continuously and with constant magnitude k > 0. The proposed mathematical model is the system of following six ordinary differential equations

$$\frac{dNK}{dt} = 0 \qquad\qquad (2.1)$$

$$\frac{dV}{dt} = -\beta_1 V - \beta_2 NKV + k \qquad (2.2)$$

$$\frac{dTh}{dt} = -\beta_3 Th + \alpha_1 V \qquad (2.3)$$

$$\frac{dAB}{dt} = -\beta_4 AB + \alpha_2 Th \qquad (2.4)$$

$$\frac{dTc}{dt} = (\alpha_4 - \beta_8)Tc \qquad (2.5)$$

$$\frac{dC}{dt} = \left(\alpha_3 - \frac{C}{C_{max}}\right)C - (\beta_5 NK + \beta_6 Tc + \beta_7 AB)C \qquad (2.6)$$

The initial conditions for the above equations are as follows:

$NK(t = 0) = NK \neq 0$ (2.7)
$V(t = 0) = Th(t = 0) = AB(t = 0) = 0$ (2.8)
$Tc(t = 0) = T_0 \neq 0$ and $C(t = 0) = C_0 \neq 0$ (2.9)

Where the parameters α_i for $i \in (1,2,3,4)$ denote proliferation rates due to natural birth and interactions. The parameters β_i for $i \in (1,2..8)$ represent destruction rates due to natural death and competition. The interactions of the cell populations and the related parameters are given in the Table-1.

3. ANALYTICAL EXPRESSION OF CELL FUNCTIONS FOR STEADY STATE CONDITIONS

The solutions of (2.2) – (2.6) for the steady state conditions (derivatives taken as zeros) are as follows:

$$V_s = \frac{k}{\beta} \text{ where } \beta = \beta_1 + \beta_2 NK. \qquad (3.1)$$

$$Th_s = \frac{\alpha_1 k}{\beta \beta_3}. \qquad (3.2)$$

$$AB_s = \frac{\alpha_1 \alpha_2 k}{\beta \beta_3 \beta_4}. \qquad (3.3)$$

$$Tc_s = 0 \quad \text{when} \quad (\alpha_4 - \beta_8) \neq 0. \qquad (3.4)$$

$$C_s = C_{max}(\alpha_3 - \beta_5 NK + \beta_6 Tc_s + \beta_7 AB_s).$$

$$= C_{max}\left[\alpha_3 - \beta_5 NK - \frac{\beta_7 \alpha_1 \alpha_2 k}{\beta \beta_3 \beta_4}\right]. \qquad (3.5)$$

4. ANALYTICAL EXPRESSION OF CELL FUNCTIONS FOR NON-STEADY STATE CONDITIONS

This section deals with the non-steady state analysis of the mathematical model. The aim of this section is to analyze the role of the parameters in the competition dynamics and to explore the phenomena depicted by the model in order to identify an optimal vaccine protocol and depict the competition among the cells populations and emerging behavior by means of

analytical solution after setting the magnitude of the parameters properly. In addition we analyze the competition dynamics between vaccine cells and cancer cells by considering the case of vaccine that is injected continuously and with constant magnitude k > 0. A qualitative analysis of the solutions of the model is achieved by furnishing an exact solution for V, Tc, Th, AB cells functions .The approximate solutions for the cancer cells function C are obtained through three cases and two of them by Homotopy perturbation method. The exact solutions of (2.2) and (2.3) are

$$V(t) = \frac{k}{\beta}(1 - e^{-\beta t}) \qquad (4.1)$$

$$Th(t) = A[\beta_3(1 - e^{-\beta t}) - \beta(1 - e^{-\beta_3 t})] \qquad (4.2)$$

$$\text{where } A = \frac{k\alpha_1}{\beta \beta_3(\beta_3 - \beta)}$$

We have obtained the following solution for (2.4)

$$AB(t) = A\alpha_2 \left[\begin{array}{c} \left(\frac{\beta_3 - \beta}{\beta_4}\right)\left(1 - e^{-\beta_4 t}\right) + \left(\frac{\beta_3}{\beta_4 - \beta}\right)\left(e^{-\beta_4 t} - e^{-\beta t}\right) \\ + \left(\frac{\beta}{\beta_4 - \beta_3}\right)\left(e^{-\beta_3 t} - e^{-\beta_4 t}\right) \end{array} \right] \qquad (4.3)$$

Carlo Bianca and Marzio Pennisi have derived a solution [3] for (2.4) which is not a correct one. The solution (4.3) is the new corrected solution against the solution obtained by Carlo Bianca and Marzio Pennisi [3]. The general solution of (2.5) is

$Tc(t) = T_0 e^{\alpha t}$ where $\alpha = \alpha_4 - \beta_8$ (4.4) The cell function C(t) can be obtained by solving the nonlinear ordinary differential (2.6) for the following three limiting cases .

Case I: We consider the interaction between cancer cells C and NK cells only. In this case $\beta_6 = 0$ and $\beta_7 = 0$ now (2.6) becomes

$$\frac{dC}{dt} = (\alpha_3 - \beta_5 NK)C - \frac{C^2}{C_{max}} \qquad (4.5)$$

The solution of (4.5) is [3] as follows

$$C(t) = \left[e^{-\gamma t}\left(\frac{1}{C_0} - \frac{C_1}{\gamma}\right) + \frac{C_1}{\gamma}\right]^{-1} \qquad (4.6)$$

where $C_1 = 1/C_{max}$ and $\gamma = (\alpha_3 - \beta_5 NK)$.

When the proliferation rate α_3 of the cancer cells is greater than of the destruction rate β_5 due to the interactions between cancer cells and natural killer cells, the number of cancer cells increase towards its plateau; vice versa cancer cells are totally depleted by natural killer cells. In this case from the (4.6), the maximum number of cancer cells C(t) is γC_{max} and minimum number is C_0.

Case II: We consider the action of Tc cells and NK cells only. In this case $\beta_6 \neq 0$ and $\beta_7 = 0$, now (2.6) becomes

$$\frac{dC}{dt} = \left(\alpha_3 - \frac{C}{C_{max}}\right)C - (\beta_5 NK + \beta_6 Tc)C \qquad (4.7)$$

By taking $C(t) = 1/Y(t)$ and using (4.4) and (4.7) becomes

$$\frac{dY}{dt} + (\gamma Y - C_1) + (\beta_6 T_0 e^{\alpha t})Y = 0 \qquad (4.8)$$

The equation (4.8) is a non-linear differential equation. Recently; many authors have applied the HPM to various problems and demonstrated the efficiency of the HPM for

handling non-linear structures and solving various physics and engineering problems [6],[7],[8],[9]. This method is a combination in topology and classic perturbation techniques. Ji Huan He used the HPM to solve the Lighthill [10] equation, the Duffing equation [11] and the Blasius equation [12]. The idea has been used to solve non-linear boundary value problems, integral equations and many other problems [13],[14]. The HPM is unique in its applicability, accuracy and efficiency. The HPM uses the imbedding parameter p as a small parameter and only a few iterations are needed to search for an asymptotic solution. The basic concept of HPM is given in Appendix- A. Using this method (Refer Appendix-B), we can obtain the following solution to the Eq. (4.7).

$$C(t) = \left\{ \begin{array}{l} \dfrac{C_1}{\gamma} + \left(\dfrac{1}{C_0} - \dfrac{C_1}{\gamma}\right)e^{-\gamma t} - \dfrac{\beta_6 T_0 C_1}{\gamma}\left[\dfrac{e^{\alpha t}}{\alpha + \gamma} + \left(\dfrac{1}{C_0} - \dfrac{C_1}{\gamma}\right)\dfrac{e^{(\alpha - \gamma)t}}{\alpha}\right] \\ + \dfrac{\beta_6 T_0 C_1}{\gamma}\left[\dfrac{1}{\alpha + \gamma} + \left(\dfrac{1}{C_0} - \dfrac{C_1}{\gamma}\right)\dfrac{1}{\alpha}\right]e^{-\gamma t} \end{array} \right\}^{-1}$$

(4.9)

This equation (4.9) is the new analytical expression of cancer cell C(t) when $\beta_6 \neq 0$ and $\beta_7 = 0$. In this case the action of NK cells prevail the action of Th cells when the death rate of Th cells is greater than the birth rate of Th. Also the proliferation rate of C cells is less than the interaction destruction rate between NK cells and C cells. When the birth rate of Th cells is greater than the death rate of Th cells the action of NK can be neglected. Also competition occurs among the immune system cells and cancer cells, but there is a partial depletion of C cells and then need the injection of the vaccine. From (4.9) we can obtain the maximum number of cancer cells C(t) is γC_{max} and minimum number is C_0 .

Case III: We consider the action of the NK cells, Tc cells, and AB cells. That is $\beta_6 \neq 0$ and $\beta_7 \neq 0$

Now the (2.6) becomes

$$\dfrac{dC}{dt} = \left(\alpha_3 - \dfrac{C}{C_{max}}\right)C - (\beta_5 NK + \beta_6 Tc + \beta_7 AB)C$$ (4.10)

By taking $C(t) = 1/Z(t)$ and replace the values of Tc and AB, the above (4.10) becomes

$$\left[\dfrac{dZ}{dt} + (\gamma - E)Z - C_1\right] + \left[-\beta_6 T_0 e^{\alpha t} - Fe^{-\beta_3 t} - He^{-\beta_4 t} - Ge^{-\beta t}\right]Z = 0$$

(4.11)

where $F = \dfrac{A\alpha_2 \beta_3 \beta_7}{\beta_4 - \beta}$, $G = \dfrac{A\alpha_2 \beta \beta_7}{\beta_4 - \beta_3}$ and H = - (E-F+G).

Homotopy perturbation method (Refer Appendix-A) gives the approximate solution of (4.10) as

$$C(t) = \left[P + Qe^{-(\gamma - E)t} + P\left[\begin{array}{c} \dfrac{\beta_6 T_0 e^{\alpha t}}{(\alpha + \gamma - E)} + \dfrac{Fe^{-\beta t}}{(-\beta + \gamma - E)} \\ + \dfrac{He^{-\beta_4 t}}{(-\beta_4 + \gamma - E)} + \dfrac{Ge^{-\beta_3 t}}{(-\beta_3 + \gamma - E)} \end{array}\right] \right.$$
$$+ Q\left[\dfrac{\beta_6 T_0 e^{(\alpha - \gamma - E)t}}{\alpha} - \dfrac{Fe^{(-\beta - \gamma - E)t}}{\beta} - \dfrac{He^{(-\beta_4 - \gamma - E)t}}{\beta_4} - \dfrac{Ge^{(-\beta_3 - \gamma - E)t}}{\beta_3}\right]$$
$$\left. - \left[PR + QSe^{-(\gamma - E)t}\right]\right]^{-1}$$

(4.12)

Where the constants P, Q, R and S are defined as follows

$$P = \dfrac{C_1}{\gamma - E} \; ; Q = \dfrac{1}{C_0} - \dfrac{C_1}{\gamma - E}$$

$$R = \dfrac{\beta_6 T_0}{(\alpha + \gamma - E)} + \dfrac{F}{(-\beta + \gamma - E)} + \dfrac{H}{(-\beta_4 + \gamma - E)} + \dfrac{G}{(-\beta_3 + \gamma - E)} \text{ and}$$

$$S = \dfrac{\beta_6 T_0}{\alpha} - \dfrac{F}{\beta} - \dfrac{H}{\beta_4} - \dfrac{G}{\beta_3}$$

This equation (4.12) is the new analytical expression of cancer cell C(t) when $\beta_6 \neq 0$ and $\beta_7 \neq 0$. In this case the action of AB cells modifies the competition dynamics and increases the complexity of the biological scenario of the emerging phenomena. Specifically the relation among β_3 (the natural death rate of Th cells), β_4 (the natural death rate of AB cells), and β (the natural death rate of V cells) influences the lower bound for the number of cancer cells at infinity and their partial or total depletion. In this case the maximum number of cancer cells C(t) is

$$C_{max}\left[\alpha_3 - \beta_5 NK - \dfrac{\beta_7 \alpha_1 \alpha_2 k}{\beta \beta_3 \beta_4}\right] \text{ and minimum number is } C_0 .$$

5. NUMERICAL SIMULATIONS

Simulations are to show the typical phenomena of the mammary carcinoma–immune system competition and can be technically addressed to analyze how different values of the parameters may be inserted into the model to describe phenomena of interest in biological and medical sciences. The time length of the simulations is fixed from 0 to 400 days according to Simtriplex simulations.

In order to investigate the accuracy of the Homotopy perturbation method with a finite number of terms, the system of differential equation was also solved numerically. To show the efficiency of the present method, our problem is also compared with the numerical solution (MATLAB program). We have used the function pdex1 in MATLAB software to solve numerically the initial-boundary value problems for the nonlinear differential equation. The MATLAB programs are also given in Appendix C.

The default parameters employed in [3] and in this work are given in Table-2. The numerical solution is compared with our analytical results in Figures 5(a)-5(d). Comparison reveals that the relative difference between the analytical result and numerical is very small for all values of the parameters considered in the simulations.

6. Discussion

When $t \to \infty$, the non-steady solutions (4.1) – (4.4) become steady solutions (3.1) – (3.4). The vaccine cells function V(t) , thymus helper cells function Th(t), antibodies function AB(t), thymus cytotoxic cells function Tc(t) versus time (days) with various values of k are plotted in Figs. 1-4. From these figures, we can infer that the values of the V(t), Th(t), AB(t) decrease

when the value of the parameter k increase. Also Tc(t) increases when k increases. The functions $(\beta/k)V(t)$, $(\beta\beta_3/k\alpha_1)Th(t)$, and $(\beta\beta_3\beta_4/k\alpha_1\alpha_2)AB(t)$ has attained the maximum value one on 30, 50, 60 days respectively. Thymus cytotoxic cells function Tc(t) value decreases when time increases and reaches the steady value (=0) when t = 100 days for all values of k. In Figs 5(a)-5(c) Comparison of exact and approximate solutions with simulation are made. Fig 5(d) exhibits comparison of growth rate of cancer cells against time for all the three cases .From these figures it is inferred that, when $0 \le t(days) \le 200$, the growth rate of cancer cell is less against $200 \le t(days) \le 300$,in that period the cancer cells growth rate rise rapidly and attain the peak value (steady state) above 300 days for all cases. Therefore the growth rate of the cancer cells is under control for a period of 200 days.

7. CONCLUSION

This paper reports a mathematical treatment for analyzing mammary carcinoma–immune system. A theoretical expression of cell functioning in triplex vaccine has been evaluated. The novelty of this article is the application of Homotopy perturbation method to the first-order nonlinear ordinary differential equations. Moreover, analytical expressions corresponding to the non-steady states current response are also presented. The approximate analytical expressions of all cell functions for all values of parameters will be useful to the cancer immunologist for upcoming research and medical treatment. Hence this work contributes significantly to the proper understanding of carcinoma-immune interaction in an appropriate mathematical language and to the development of immunological medicine.

7.1. Appendix-A. Basic concepts of the Homotopy perturbation method.

The HPM method has overcome the limitations of traditional perturbation methods. It can take full advantage of the traditional perturbation techniques, so a considerable deal of research has been conducted to apply the homotopy technique [7],[8] to solve various strong non-linear equations. To explain this method, let us consider the following function:

$$D_0(u) - f(r) = 0, r \in \Omega \tag{A1}$$

with the boundary conditions of $B_0(u, \frac{\partial u}{\partial n}) = 0, r \in \Omega$ (A2)

where D_0 is a general differential operator, B_0 is a boundary operator , f(r) is a known analytical function and Γ is the boundary of the domain Ω. Generally speaking, D_0 the operator can be divided into a linear part L and a non-linear part N, (A1) can therefore be written as

$$L(u) + N(u) - f(r) = 0 \tag{A3}$$

Construct a homotopy $v(r,p) : \Omega \times [0,1] \to R$ that satisfies

$$H(v,p) = (1-p)[L(u) - L(u_0)] + p[D_0(v) - f(r)] = 0 \tag{A4}$$

$$H(v,p) = L(v) - L(u_0) + pL(u_0) + p[N(v) - f(r)] = 0 \tag{A5}$$

where $p \in [0,1]$ is an embedding parameter and u_0 is an initial approximation of Eq. (A1) that satisfies the boundary conditions. From Eq. (A4) and (A5), we have

$$H(v,0) = L(u) - L(u_0) = 0 \tag{A6}$$

$$H(v,p) = D_0(v) - f(r) = 0 \tag{A7}$$

When p = 0, (A4) and (A5) become linear equations. When p = 1, they become non-linear equations. The process of changing p from zero to unity is that of $L(u) - L(u_0) = 0$ to $D_0(v) - f(r) = 0$ We first use the embedding parameter p as a "small parameter" and assume that the solutions of (A4) and (A5) can be written as a power series in p

$$v = v_0 + pv_1 + p^2 v_2 + \dots \tag{A8}$$

Setting p = 1 result in the approximate solution of (A1)

$$u = \lim_{p \to 0} v = u_0 + u_1 + u_2 + \dots \tag{A9}$$

This is the basic technique in Homotopy perturbation method.

7.2. Appendix-B. Approximate analytical solutions of the Case II and Case III

$$(1-p)\left(\frac{dY}{dt} + (\gamma Y - C_1)\right) + p\left(\frac{dY}{dt} + (\gamma Y - C_1) + \beta_6 T_0 e^{\alpha t} Y\right) = 0 \tag{B1}$$

$$(1-p)\left(\frac{dZ}{dt} + (\gamma - E)Z - C_1\right) +$$
$$p\left[\left(\frac{dZ}{dt} + (\gamma - E)Z - C_1\right) + \left(-\beta_6 T_0 e^{\alpha t} - Fe^{-\beta t} - He^{-\beta_4 t} - Ge^{-\beta_3 t}\right)Z\right] = 0 \tag{B2}$$

Assume the approximate solution of (B1) is

$$Y = y_0 + py_1 + p^2 y_2 + \dots \tag{B3}$$

Assume the approximate solution of (B2) is

$$Z = z_0 + pz_1 + p^2 z_2 + \dots \tag{B4}$$

Substituting (B3) into (B1) and arranging the coefficients of p- powers, we have $p^0 : \frac{dy_0}{dt} + (\gamma y_0 - C_1) = 0$ (B5)

$$p^1 : \frac{dy_1}{dt} + (\gamma y_1 - C_1) + (\beta_6 T_0 e^{\alpha t}) y_0 = 0 \tag{B6}$$

Substituting (B4) into (B2) and arranging the coefficients of p powers, we have

$$p^0 : \frac{dz_0}{dt} + (\gamma - E)z_0 - C_1 = 0 \tag{B7}$$

$$p^1 : \frac{dz_1}{dt} + (\gamma - E)z_1 - C_1 + \left\{-\beta_6 T_0 e^{\alpha t} - Fe^{-\beta t} - He^{-\beta_4 t} - Ge^{-\beta_3 t}\right\}z_0 = 0 \tag{B8}$$

With the initial approximations $y_0(0) = C_0, y_i(0) = 0$ and $z_0(0) = C_0, z_i(0) = 0$ for all i=1,2……
Solving (B5) we get

$$y_0 = \frac{C_1}{\gamma} + \left(\frac{1}{C_0} - \frac{C_1}{\gamma}\right)e^{-\gamma t} \tag{B9}$$

Solving (B6) we get

$$y_1 = -\frac{\beta_6 T_0 C_1}{\gamma}\left[\frac{e^{\alpha t}}{\alpha + \gamma} + \left(\frac{1}{C_0} - \frac{C_1}{\gamma}\right)\frac{e^{(\alpha - \gamma)t}}{\alpha}\right]$$
$$+ \frac{\beta_6 T_0 C_1}{\gamma}\left[\frac{1}{\alpha + \gamma} + \left(\frac{1}{C_0} - \frac{C_1}{\gamma}\right)\frac{1}{\alpha}\right]e^{-\gamma t}$$

(B10)

Adding (B9) and (B10) and $C(t) = \dfrac{1}{Y(t)}$,we get C(t) for the

case II.

$$C(t) = \left[\begin{array}{l} \dfrac{C_1}{\gamma} + \left(\dfrac{1}{C_0} - \dfrac{C_1}{\gamma}\right)e^{-\gamma t} - \dfrac{\beta_6 T_0 C_1}{\gamma}\left[\dfrac{e^{\alpha t}}{\alpha + \gamma} + \left(\dfrac{1}{C_0} - \dfrac{C_1}{\gamma}\right)\dfrac{e^{(\alpha - \gamma)t}}{\alpha}\right] \\ \qquad + \dfrac{\beta_6 T_0 C_1}{\gamma}\left[\dfrac{1}{\alpha + \gamma} + \left(\dfrac{1}{C_0} - \dfrac{C_1}{\gamma}\right)\dfrac{1}{\alpha}\right]e^{-\gamma t} \end{array} \right]^{-1}$$

(B11)

Solving (B7) we get

$$z_0 = \dfrac{C_1}{\gamma - E} + \left(\dfrac{1}{C_0} - \dfrac{C_1}{\gamma - E}\right)e^{-(\gamma - E)t}$$ (B12)

Solving (B$_8$) we get

$$z_1 = \dfrac{C_1}{\gamma - E}\left[\begin{array}{l}\dfrac{\beta_6 T_0 e^{\alpha t}}{(\alpha + \gamma - E)} + \dfrac{Fe^{-\beta t}}{(-\beta + \gamma - E)} \\ + \dfrac{He^{-\beta_4 t}}{(-\beta_4 + \gamma - E)} + \dfrac{Ge^{-\beta_3 t}}{(-\beta_3 + \gamma - E)}\end{array}\right]$$

$$+ \left(\dfrac{1}{C_0} - \dfrac{C_1}{\gamma - E}\right)\left[\begin{array}{l}\dfrac{\beta_6 T_0 e^{(\alpha - \gamma - E)t}}{\alpha} - \dfrac{Fe^{(-\beta - \gamma - E)t}}{\beta} \\ - \dfrac{He^{(-\beta_4 - \gamma - E)t}}{\beta_4} - \dfrac{Ge^{(-\beta_3 - \gamma - E)t}}{\beta_3}\end{array}\right] -$$

$$\left\{\dfrac{C_1}{\gamma - E}\left[\begin{array}{l}\dfrac{\beta_6 T_0}{(\alpha + \gamma - E)} + \dfrac{F}{(-\beta + \gamma - E)} + \\ \dfrac{H}{(-\beta_4 + \gamma - E)} + \dfrac{G}{(-\beta_3 + \gamma - E)}\end{array}\right]\right.$$

$$\left. + \left(\dfrac{1}{C_0} - \dfrac{C_1}{\gamma}\right)\left[\dfrac{\beta_6 T_0}{\alpha} - \dfrac{F}{\beta} - \dfrac{H}{\beta_4} - \dfrac{G}{\beta_3}\right]\right\}e^{-(\gamma - E)t}$$ (B13)

Adding (B$_{12}$) and (B$_{13}$) and $C(t) = \dfrac{1}{Z(t)}$ we get C(t) for the case

III.

7.3. Appendix-C. MATLAB programs for numerical simulation of (4.5), (4.7) and (4.10)

For Case-I
```
function xamfile1
options= odeset('RelTol',1e-6,'Stats','on');
Xo = 1000;
tspan = [0,400];
tic
[t,X] = ode45(@TestFunction,tspan,Xo,options);
toc
figure
hold on
plot(t, X(:,1))
return
function [dx_dt]= TestFunction(t,x)
a3=0.06695;
cmax=(149365*10^6);
b5=5*10^-7;
NK=1176;
b6=5*10^-6;
a=-0.04142857143;
T0=400;
dx_dt(1) =(a3-b5*NK)*x(1)-x(1)*x(1)/cmax;
dx_dt = dx_dt';
```

For Case-II
```
function xamfile2
options= odeset('RelTol',1e-6,'Stats','on');
Xo = 1000;
tspan = [0,400];
tic
[t,X] = ode45(@TestFunction,tspan,Xo,options);
toc
figure
hold on
plot(t, X(:,1))
return
function [dx_dt]= TestFunction(t,x)
a3=0.06695;
cmax=(149365*10^6);
b5=5*10^-7;
NK=1176;
b6=5*10^-6;
a=-0.4142857143e-1;
T0=400;
dx_dt(1) =(a3-x(1)/cmax)*x(1)
-(b5*NK+b6*T0*exp(a*t))*x(1);
dx_dt = dx_dt';
```

For Case-III
```
function xamfile6
options= odeset('RelTol',1e-6,'Stats','on');
Xo = 1000;
tspan = [0,400];
tic
[t,X] = ode45(@TestFunction,tspan,Xo,options);
toc
figure
hold on
plot(t, X(:,1))
return
function [dx_dt]= TestFunction(t,x)
a3=0.06695;
cmax=(149365*10^6);
b5=5*10^-7;
NK=1176;
b6=5*10^-6;
a=-0.04142857143;
T0=400;
E=0.006295557853;
F=0.0070613111736;
G=0.03930566480;
H=-0.3853991092e-1;
b3=1.5/15;
b4=1.5/21;
b=0.1667842667;
dx_dt(1)=(a3-x(1)/cmax)*x(1)-(b5*NK+b6*T0*exp(a*t)
+E+F*exp(-b*t)+H*exp(-b4*t)+G*exp(-b3*t))*x(1);
dx_dt = dx_dt';
```

Table-1: The interactions of the cell populations and the related parameters

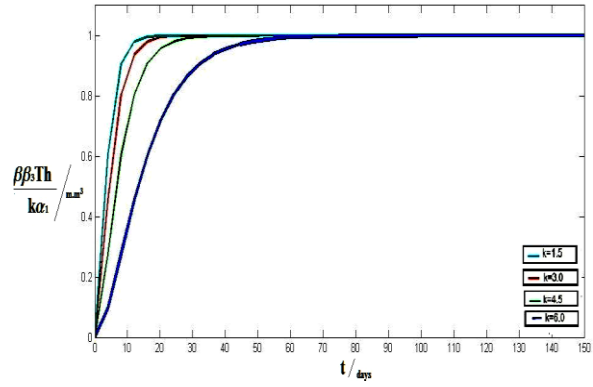| interactions		V	C	AB	Th	Tc	NK
V	External injection	k					
	Natural death	β_1					
	Destructive					β_2	
Th	Proliferative	α_1					
	Natural death				β_3		
AB	Proliferative				α_2		
	Natural death			β_4			
Tc	Natural birth					α_4	
	Natural death						β_8
C	Natural birth		α_3				
	Destructive		C_{max}^{-1}	β_7		β_6	β_5

Figure 2 : *Sensitivity analysis of the thymus helper cells function* $(\beta\beta_3/k\alpha_1)\mathrm{Th(t)}$ *on the parameter k, using(4.2)*

Table-2: *Numerical values of all parameters used in this work.*

β_1	β_2	β_3	β_4	β_5	β_6	β_7	β_8
k/9	$1*10^{-7}$	k/15	k/21	$5*10^{-7}$	$5*10^{-6}$	$5*10^{-5}$	k/21

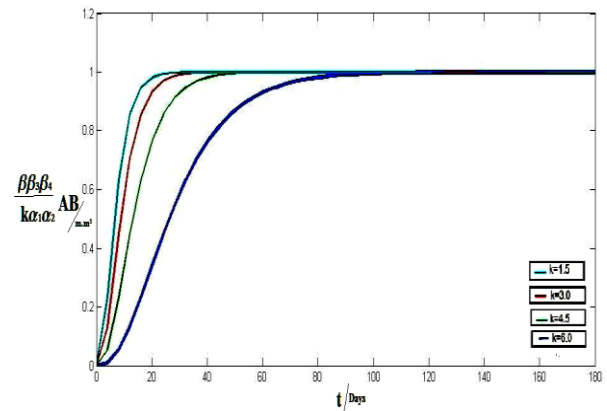| α_1	α_2	α_3	α_4	C_{max}	k	NK	T_0	C_0
0.05	2	0.06695	0.03	$49,365*10^6$	1.5	1176	400	1000

Figure 3: *Sensitivity analysis of the Antibodies function*

$(\beta\beta_3\beta_4/k\alpha_1\alpha_2)\mathrm{AB(t)}$ *on the parameter k, using (4.3).*

Figure 1: *Sensitivity analysis of the vaccine cells function* $(\mathrm{k}/\beta)\mathrm{V(t)}$ *on the parameter k using (4.1).*
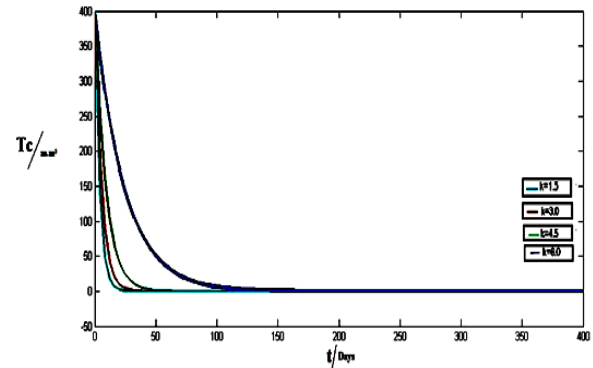

Figure 4: *Sensitivity analysis of the Thymus cytotoxic cells Tc(t)   on the parameter k, using (4.4).*
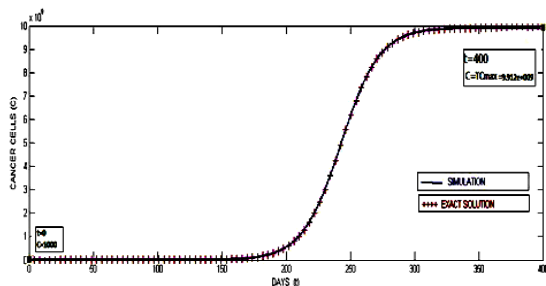
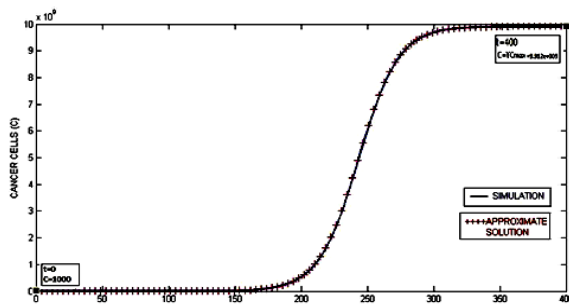*Figure 5(a): Graphical comparison of exact solution with simulation for case I using (4.6).*

Figure 5(b) : Graphical comparison of approximate solution with simulation for case II using (4.9).
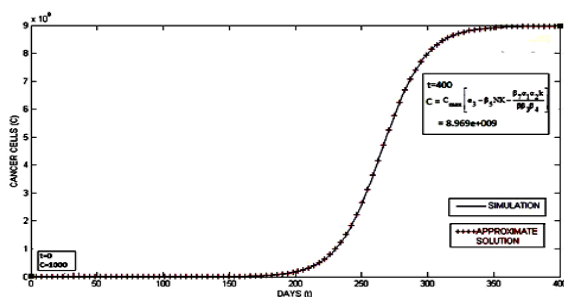

Figure 5(c) : Graphical comparison of approximate solution with simulation for case III using (4.12).
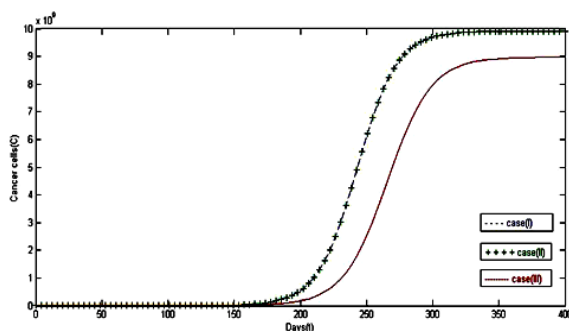

Figure 5(d): Graphical comparisons of growth rate of cancer cells against ime for all the three cases using (4.6, 4.9, 4.12)

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