

Research article

Mathematical modeling and analysis of solid cancer growth with angiogenesis

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Abstract

A mathematical model of solid cancer growth with angiogenesis in the absence of cancer controlling mechanism has been discussed. The initial conditions supplied to the dynamical system consists of a perturbation in the form of pulse. The aim of this method is to derive the approximated analytical solution of non-linear differential equations in the dynamics of cancer growth using the Homotopy perturbation method. Our analytical results are compared with the numerical simulation and a satisfactory agreement is observed. This method can be easily extended to solve the strongly nonlinear initial and boundary value problems arising in all applied sciences and technology problems.

Keywords: Mathematical modeling; Cancer growth; System of nonlinear differential equation; Homotopy perturbation method; Numerical simulation.

1. Introduction

Mathematical models of cancer growth have been the subject of research activity for many years. Cancer arises when within a single cell multiple malfunctions of control systems occur, which are broad, the system that promote cell growth and the system that protect against erratic growth [1]. In Gompertzian model [2-3], logistic and power function have been extensively used to describe tumor growth dynamics [4-5]. These simple formalisms have been also used to investigate different therapeutic strategies such as antiangiogenic or radiation treatments [6].

Angiogenesis, the formation of blood vessels from a pre-existing vasculature, is a crucial component of many mammalian growth processes [7]. The first event of tumor-induced angiogenesis involves the cancerous cells of a solid tumor secreting a number of chemicals, collectively known as tumor angiogenic factors, or TAF [8], into the surrounding tissue.

Angiogenesis is a complex method, whereby existing micro vessels give produce to new capillaries (via sprouting) that are capable of delivering additional oxygen and nutrients to a growing, injured, or inflamed tissue. This method happens throughout normal growth and development and in pathological adaptations, like embryogenesis, tumor genesis, peripheral blood vessel disease, diabetic retinopathy, and wound healing. Angiogenesis is complex in that it depends on the precise coordination of various cell types, variety of various cellular behaviors (i.e. Proliferation and migration), and biomechanical and biochemical signals that operate regionally (i.e. at cell-cell contact interfaces) and across distances spanning many microns within the tissue .The outcome may be a remodeled micro vascular network that contains a replacement cohort of capillary-sized vessels. At the tissue-level, the new vessels are ready to augment blood flow and oxygenation to the extent needed by the metabolic demand of the tissue or induced by the pathology (e.g. tumor). Since the middle 1900's, a number of experimental models have been developed to review each physiological and pathological angiogenesis [11,16] Models aimed at describing the growth of tumors in the vascular phase including also the development of the vasculature are rather few. A simple mathematical model that emphasizes the concept that the tumour growth is a process strictly controlled by the development of the vasculature has been proposed by Hahnfeldt et al. [10]. Recently Yang [1] developed the mathematical model to describe the solid cancer growth dynamics inducing angiogenesis in the absence of cancer controlling mechanism. To the best of our knowledge the analytical expression of the normal cells C , epithelial cells E , cancer cells T , pre-angiogenesis cells P and angiogenesis cells A have not been derived. The purpose of this communication is devise that simple form an analytical expression of the normal cells C , epithelial cells E , cancer cells T , pre-angiogenesis cells P and angiogenesis cells A are derived using the HPM method.

2. Mathematical formulation of the problem and analysis

Our aim is the development of analytical technique to describe the cancer growth dynamics inducing angiogenesis. The model does not embrace method physiological processes just like the diffusion of oxygen into a solid wherever it's consumed by metabolic processes, the outward diffusion of carboxylic acid from a solid that produces it by metabolic processes and also the diffusion of oxygen away from a blood vessel into a region with associate physiological state. The dynamics of cancer growth described by the following system of the nonlinear equations:

$$\left. \begin{aligned} \frac{dC}{dt} &= \alpha_1 C \left[1 - \frac{C}{k_1(E)} - \frac{\beta_1' T}{k_1(E)} \right] - \mu_1 C - C_m \delta_{D(t)} \\ \frac{dE}{dt} &= \alpha_2 E \left[1 - \frac{E}{k_2(C)} \right] - \gamma ET - \mu_2 E \\ \frac{dT}{dt} &= C_m \delta_{D(t)} + \alpha_3 A T \left[1 - \frac{T}{k_3} \right] + \alpha_3' T \left[1 - \frac{T}{k_1(E)} - \frac{\beta_2' C}{k_1(E)} \right] - \mu_3 T \\ \frac{dP}{dt} &= \gamma ET - \delta P - \mu_4 P \\ \frac{dA}{dt} &= \delta P + \varepsilon T A \left[1 - \frac{A}{k_4} \right] - \mu_5 A \end{aligned} \right\} \quad (1)$$

In this model we can assume that $\delta_{D(t)} = 0$, since the normal cells are mutual to cancer cell. Also we assume that k_1 and k_2 are constants. Also the interaction parameters β_1 and β_2 are defined as follows:

$$\beta_1 = \frac{\beta_1' \alpha_1}{k_1} \quad \text{and} \quad \beta_2 = \frac{\beta_2' \alpha_3}{k_1} \quad (2)$$

Another simplification assumes that the rate at which cancer cell increase due to new vascularization is much higher than due to existing one.

$$\frac{dC}{dt} = \alpha_1 C \left(1 - \frac{C}{k_1} \right) - \beta_1 CT - \mu_1 C \quad (3)$$

$$\frac{dE}{dt} = \alpha_2 E \left(1 - \frac{E}{k_2} \right) - \gamma ET - \mu_2 E \quad (4)$$

$$\frac{dT}{dt} = \alpha_3 AT \left(1 - \frac{T}{k_3} \right) - \beta_2 CT - \mu_3 T \quad (5)$$

$$\frac{dP}{dt} = \gamma ET - \delta P - \mu_4 P \quad (6)$$

$$\frac{dA}{dt} = \delta P + \varepsilon T A \left(1 - \frac{A}{k_4} \right) - \mu_5 A \quad (7)$$

The following initial conditions to the system of the above equations become:

$$C(0) = C_a - C_m, \quad E(0) = E_b, \quad T(0) = C_m, \quad P(0) = 0, \quad A(0) = 0 \quad (8)$$

where C_a and E_b are the cancer free state value and C_m is the instantaneous mutation of normal cells to initiate cancer growth.

3. Solution of the nonlinear differential equations using the Homotopy perturbation method

Linear and non-linear phenomena are of fundamental importance in various fields of science and engineering. Most models of real – life problems are still very difficult to solve. Therefore, approximate analytical solutions such as Homotopy perturbation method (HPM) [7-18] were introduced. This method is the most effective and convenient ones for both linear and non-linear equations. Perturbation method is based on assuming a small parameter. The majority of non-linear problems, especially those having strong non-linearity, have no small parameters at all and the approximate solutions obtained by the perturbation methods, in most cases, are valid only for small values of the small parameter.

Recently, many authors have applied the Homotopy perturbation method (HPM) to solve the non-linear boundary value problem in physics and engineering sciences [16-19]. Recently this method is also used to solve some of the non-linear problem in physical sciences [11-18]. This method is a combination of Homotopy in topology and classic perturbation techniques. 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. Using this method (See Appendix B), we can obtain the approximate analytical solutions to the eqns. (4)-(9) are as follows:

$$C(t) = (C_a - C_m) e^{(\alpha_1 - \mu_1)t} - \left(\frac{\alpha_1 (C_a - C_m)^2}{k_1 (\alpha_1 - \mu_1)} \right) e^{2(\alpha_1 - \mu_1)t} + \left(\frac{\beta_1 C_m (C_a - C_m)}{\mu_3} \right) e^{(\alpha_1 - \mu_1 - \mu_3)t} + \left[\left(\frac{\alpha_1 (C_a - C_m)^2}{k_1 (\alpha_1 - \mu_1)} \right) - \left(\frac{\beta_1 C_m (C_a - C_m)}{\mu_3} \right) \right] e^{(\alpha_1 - \mu_1)t} \quad (9)$$

$$E(t) = E_b e^{(\alpha_2 - \mu_2)t} - \left(\frac{\alpha_2 E_b^2}{k_2 (\alpha_2 - \mu_2)} \right) e^{2(\alpha_2 - \mu_2)t} + \left[\left(\frac{\alpha_2 E_b^2}{k_2 (\alpha_2 - \mu_2)} \right) - \left(\frac{\gamma E_b C_m}{\mu_3} \right) \right] e^{(\alpha_2 - \mu_2)t} + \left(\frac{\gamma E_b C_m}{\mu_3} \right) e^{(\alpha_2 - \mu_2 - \mu_3)t} \quad (10)$$

$$T(t) = C_m e^{-\mu_3 t} - \left(\frac{\beta_2 C_m (C_a - C_m)}{(\alpha_1 - \mu_1)} \right) e^{(\alpha_1 - \mu_1 - \mu_3)t} + \left(\frac{\beta_2 C_m (C_a - C_m)}{(\alpha_1 - \mu_1)} \right) e^{-\mu_3 t} \quad (11)$$

$$P(t) = \left(\frac{\gamma E_b C_m}{(\delta + \alpha_2 - \mu_2 - \mu_3 + \mu_4)} \right) \left(e^{(\alpha_2 - \mu_2 - \mu_3)t} - e^{-(\delta + \mu_4)t} \right) \quad (12)$$

$$A(t) = \left(\frac{\delta \gamma E_b C_m}{(\delta + \alpha_2 - \mu_2 - \mu_3 + \mu_4)} \right) \left[\frac{e^{(\alpha_2 - \mu_2 - \mu_3)t}}{(\alpha_2 - \mu_2 - \mu_3 + \mu_5)} + \frac{e^{-(\delta + \mu_4)t}}{(\delta + \mu_4 - \mu_5)} \right] - \left(\frac{\delta \gamma E_0 C_m}{(\delta + \alpha_2 - \mu_2 - \mu_3 + \mu_4)} \right) \left[\frac{1}{(\alpha_2 - \mu_2 - \mu_3 + \mu_5)} + \frac{1}{(\delta + \mu_4 - \mu_5)} \right] e^{-\mu_5 t} \quad (13)$$

4. Numerical Simulation

The non-linear differential equations (3)-(8) are also solved numerically. We have used the function main in Matlab/Scilab software to solve the initial-boundary value problems for the nonlinear differential equations numerically. This numerical solution is compared with our analytical results in Figures 1 - 10. Upon comparison, it gives a satisfactory agreement for all values of the dimensionless time t . The Matlab/Scilab program is also given in Appendix C.

5. Results and Discussions

Figure 1-10 shows the dimensionless concentration of the normal cells C , epithelial cells E , cancer cells T , pre-angiogenesis cells P and angiogenesis cells A versus the dimensionless time t . From Figs. 1 and 2, it is clear that concentration cells T (cancer cells), P (pre – angiogenesis cells) and A (angiogenesis cells) does not change and the concentration cells C (normal cells) and E (epithelial cells) increases in some fixed values of the dimensionless parameters $\alpha_1, \alpha_2, \alpha_3, \mu_1, \mu_2, \mu_3, \mu_4, \mu_5, k_1, k_2, k_3, k_4, \beta_1, \beta_2, \varepsilon, \delta, C_a, E_b$ and γ in the ranges of $t = 0 - 1$ and $0 - 5$. From Fig. 3-5, it is observed that the concentration cell T decreases, concentration cells P and A does not changes and the concentration cells increases in some fixed values of the all dimensionless parameters in the ranges of $t = 0 - 10, 0 - 20$ and $0 - 25$.

From Fig. 6, it is evident that the concentration cells T decreases, the concentration cells P and A does not changes and the concentration cells C and E increases small, in some other fixed values of the all other dimensionless parameters in the ranges of $t = 0 - 1$. From Fig. 7-10, it is noted that the concentration cells T decreases, the concentration cells P and A does not changes and the concentration cells C and E increases, in some other fixed values of the dimensionless parameters for various values of the time.

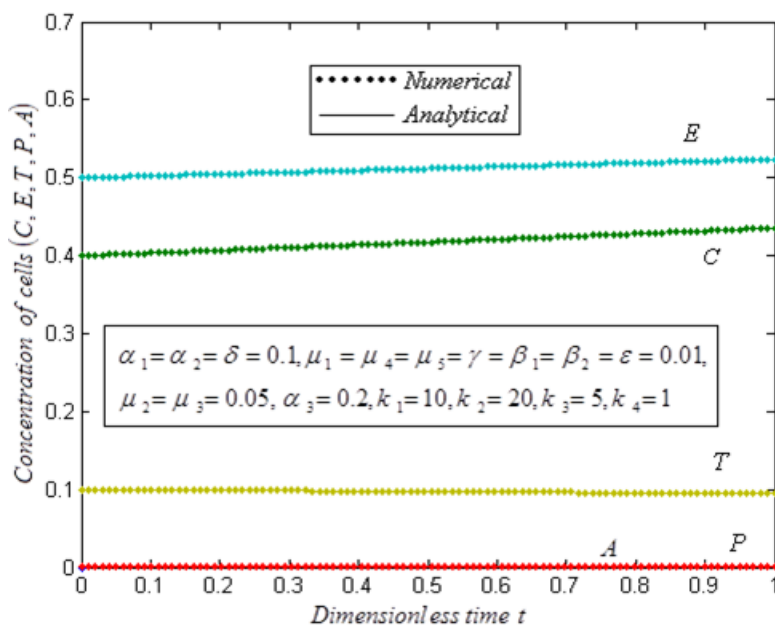


Fig. 1: Dimensionless concentrations of the cells $C(t), E(t), T(t), P(t)$ and $A(t)$ versus the dimensionless time t . The curve is plotted using the eqns. (9)-(13) in some fixed values of the dimensionless parameters $E_b = 0.5, T_c = 0.1$.

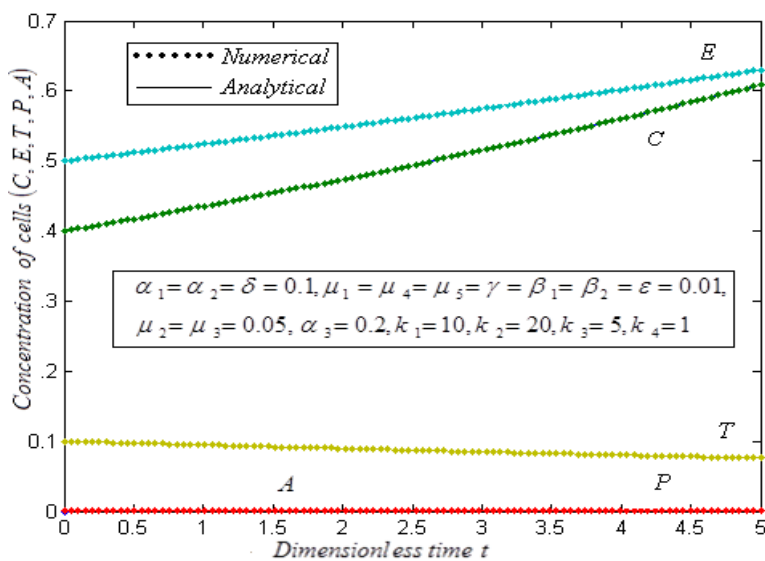


Fig. 2: Dimensionless concentrations of the cells $C(t), E(t), T(t), P(t)$ and $A(t)$ versus the dimensionless time t . The curve is plotted using the eqns. (9)-(13) in some fixed values of the dimensionless parameters $E_b = 0.5, T_c = 0.1$.

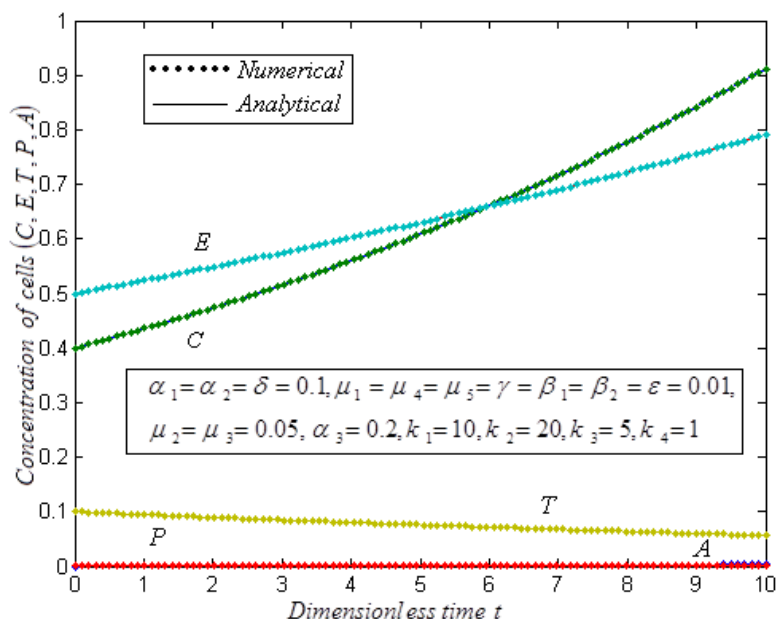


Fig. 3: Dimensionless concentrations of the cells $C(t), E(t), T(t), P(t)$ and $A(t)$ versus the dimensionless time t . The curve is plotted using the eqns. (9)-(13) in some fixed values of the dimensionless parameters $E_b = 0.5, T_c = 0.1$.

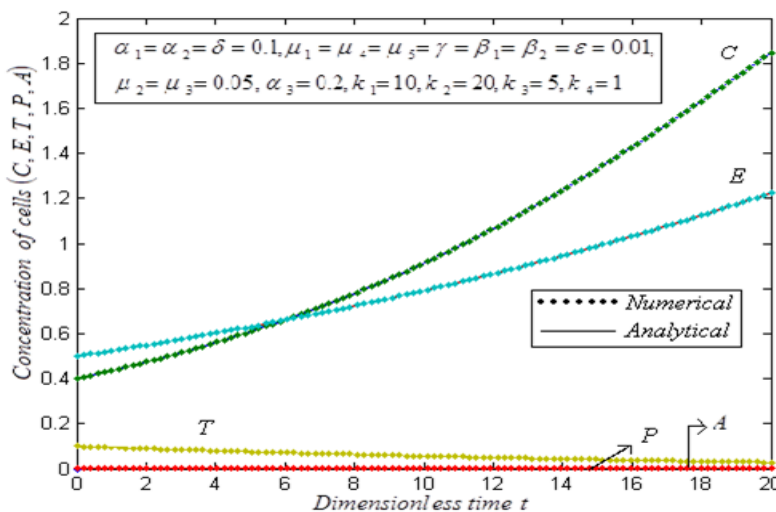


Fig. 4: Dimensionless concentrations of the cells $C(t), E(t), T(t), P(t)$ and $A(t)$ versus the dimensionless time t . The curve is plotted using the eqns. (9)-(13) in some fixed values of the dimensionless parameters $E_b = 0.5, T_c = 0.1$.

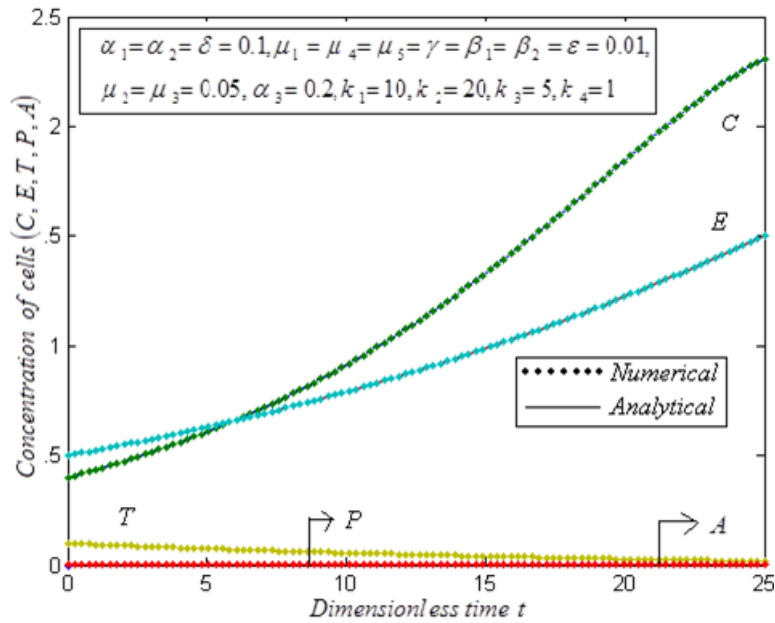


Fig. 5: Dimensionless concentrations of the cells $C(t), E(t), T(t), P(t)$ and $A(t)$ versus the dimensionless time t . The curve is plotted using the eqns. (9)-(13) in some fixed values of the dimensionless parameters $E_b = 0.5, T_c = 0.1$.

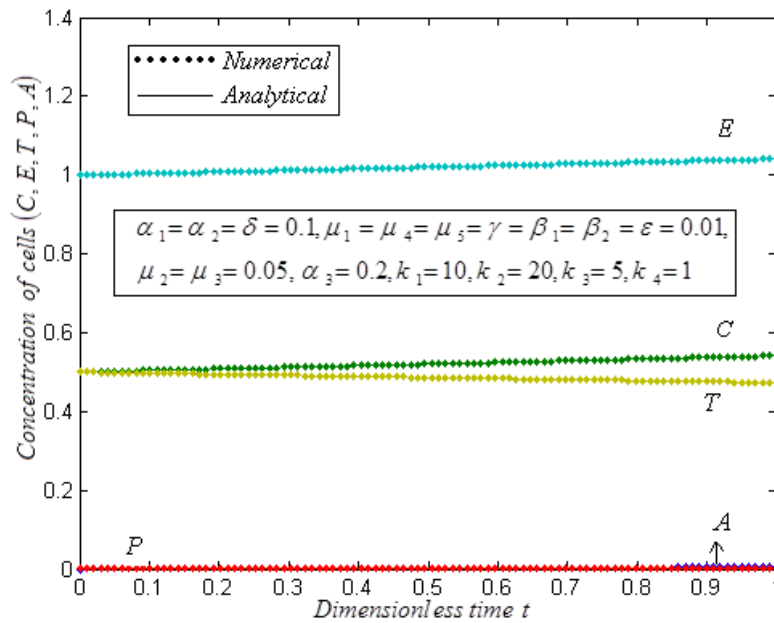


Fig. 6: Dimensionless concentrations of the cells $C(t), E(t), T(t), P(t)$ and $A(t)$ versus the dimensionless time t . The curve is plotted using the eqns. (9)-(13) in some fixed values of the dimensionless parameters $E_b = 1, T_c = 0.5$.

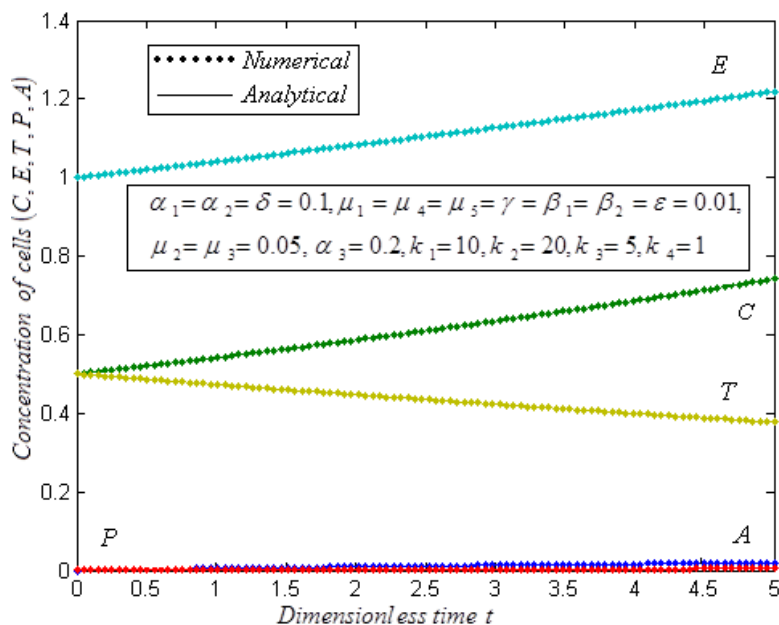


Fig. 7: Dimensionless concentrations of the cells $C(t), E(t), T(t), P(t)$ and $A(t)$ versus the dimensionless time t . The curve is plotted using the eqns. (9)-(13) in some fixed values of the dimensionless parameters $E_b = 1, T_c = 0.5$.

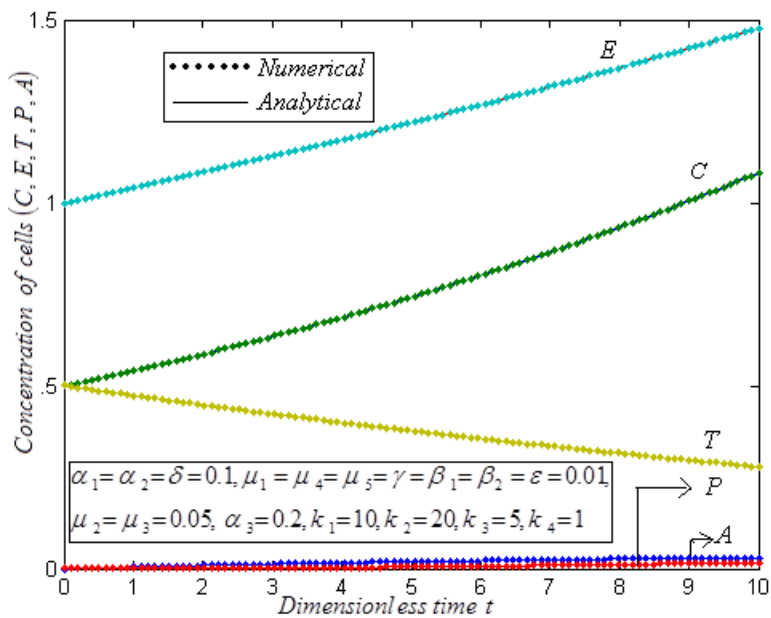


Fig. 8: Dimensionless concentrations of the cells $C(t), E(t), T(t), P(t)$ and $A(t)$ versus the dimensionless time t . The curve is plotted using the eqns. (9)-(13) in some fixed values of the dimensionless parameters $E_b = 1, T_c = 0.5$.

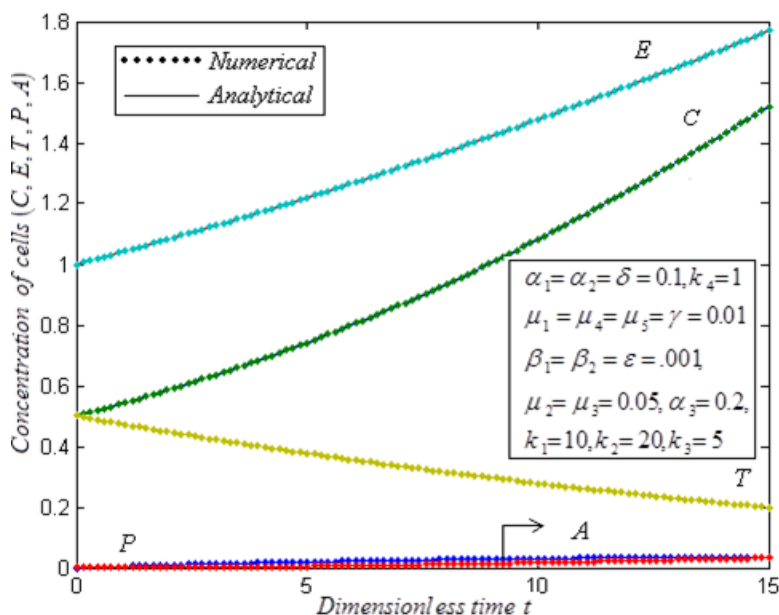


Fig. 9: Dimensionless concentrations of the cells $C(t), E(t), T(t), P(t)$ and $A(t)$ versus the dimensionless time t . The curve is plotted using the eqns. (9)-(13) in some fixed values of the dimensionless parameters $E_b = 1, T_c = 0.5$.

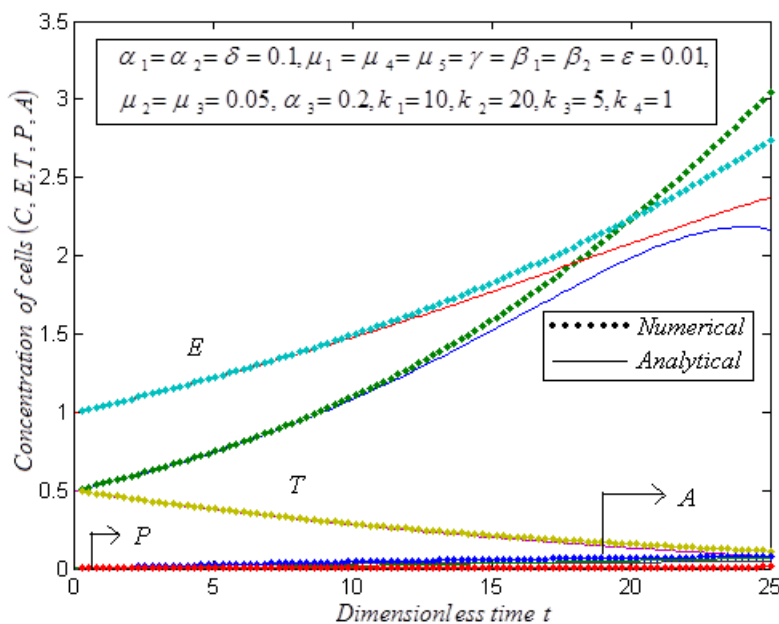


Fig. 10: Dimensionless concentrations of the cells $C(t), E(t), T(t), P(t)$ and $A(t)$ versus the dimensionless time t . The curve is plotted using the eqns. (9)-(13) in some fixed values of the dimensionless parameters $E_b = 1, T_c = 0.5$.

6. Conclusion

The time dependent non-linear differential equations of solid cancer growth with angiogenesis in the absence of cancer controlling mechanism can be solved analytically and numerically. The approximate analytical expressions of the concentration of the normal cells, epithelial cells, cancer cells, pre-angiogenesis cells and the angiogenesis cells has been derived using the Homotopy perturbation method. These analytical results can be used to analyze the a model in which the sizes of the normal and cancer cells are allowed to depend on the overall network of blood vessels: normal and cancer cells compete for nutrients provided by the pre-existing blood vessels, while cancer cells have additional source originated from angiogenesis. Our results are compared with the numerical simulation and it gives satisfactory agreement .This analytical result helps us for the better understanding of the model.

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Appendix: A

Basic concepts of the Homotopy perturbation method

To explain this method, let us consider the following function:

$$D_o(u) - f(r) = 0, \quad r \in \Omega \quad (\text{A.1})$$

with the boundary conditions of

$$B_o(u, \frac{\partial u}{\partial n}) = 0, \quad r \in \Gamma \quad (\text{A.2})$$

where D_o is a general differential operator, B_o is a boundary operator, $f(r)$ is a known analytical function and Γ is the boundary of the domain Ω . In general, the operator D_o can be divided into a linear part L and a non-linear part N . The eqn. (A.1) can therefore be written as

$$L(u) + N(u) - f(r) = 0 \quad (\text{A.3})$$

By the Homotopy technique, we construct a Homotopy $v(r, p) : \Omega \times [0,1] \rightarrow \Re$ that satisfies

$$H(v, p) = (1 - p)[L(v) - L(u_0)] + p[D_o(v) - f(r)] = 0. \quad (\text{A.4})$$

$$H(v, p) = L(v) - L(u_0) + pL(u_0) + p[N(v) - f(r)] = 0. \quad (\text{A.5})$$

where $p \in [0, 1]$ is an embedding parameter, and u_0 is an initial approximation of the eqn. (A.1) that satisfies the boundary conditions. From the eqns. (A.4) and (A.5) we have

$$H(v, 0) = L(v) - L(u_0) = 0 \quad (\text{A.6})$$

$$H(v, 1) = D_o(v) - f(r) = 0 \quad (\text{A.7})$$

When $p=0$, the eqns. (A.4) and (A.5) become linear equations. When $p=1$, they become non-linear equations. The process of changing p from zero to unity is that of $L(v) - L(u_0) = 0$ to $D_o(v) - f(r) = 0$. We first use the embedding parameter p as a small parameter and assume that the solutions of the eqns. (A.4) and (A.5) can be written as a power series in p :

$$v = v_0 + pv_1 + p^2v_2 + \dots \quad (\text{A.8})$$

Setting $p = 1$ results in the approximate solution of the eqn. (A.1):

$$u = \lim_{p \rightarrow 1} v = v_0 + v_1 + v_2 + \dots \quad (\text{A.9})$$

This is the basic idea of the HPM.

Appendix: B

Approximate analytical solution of the concentration species using Homotopy perturbation method

In this appendix, how the eqns. (9)-(13) are derived in this paper. We first construct a Homotopy as follows:

$$(1-p)\left(\frac{dC}{dt} - (\alpha_1 - \mu_1)C\right) + p\left(\frac{dC}{dt} - (\alpha_1 - \mu_1)C + \frac{\alpha_1}{k_1}C^2 + \beta_1 CT\right) = 0 \quad (\text{B.1})$$

$$(1-p)\left(\frac{dE}{dt} - (\alpha_2 - \mu_2)E\right) + p\left(\frac{dE}{dt} - (\alpha_2 - \mu_2)E + \frac{\alpha_2}{k_2}E^2 + \gamma ET\right) = 0 \quad (\text{B.2})$$

$$(1-p)\left(\frac{dT}{dt} + \mu_3 T\right) + p\left(\frac{dT}{dt} + \mu_3 T - \alpha_3 AT + \frac{\alpha_3}{k_3}AT^2 + \beta_2 CT\right) = 0 \quad (\text{B.3})$$

$$(1-p)\left(\frac{dP}{dt} + (\delta + \mu_4)P\right) + p\left(\frac{dP}{dt} + (\delta + \mu_4)P - \gamma ET\right) = 0 \quad (\text{B.4})$$

$$(1-p)\left(\frac{dA}{dt} + \mu_5 A\right) + p\left(\frac{dA}{dt} + \mu_5 A - \delta P - \varepsilon T A + \frac{\varepsilon}{k_4}T A^2\right) = 0 \quad (\text{B.5})$$

The approximate analytical solutions of the eqns. (B.1)-(B.5) are

$$C = C_0 + pC_1 + p^2C_2 + p^3C_3 \dots \quad (\text{B.6})$$

$$E = E_0 + pE_1 + p^2E_2 + p^3E_3 \dots \quad (\text{B.7})$$

$$T = T_0 + pT_1 + p^2T_2 + p^3T_3 \dots \quad (\text{B.8})$$

$$P = P_0 + pP_1 + p^2P_2 + p^3P_3 \dots \quad (\text{B.9})$$

$$A = A_0 + pA_1 + p^2A_2 + p^3A_3 \dots \quad (\text{B.10})$$

Substituting the eqns. (B.6) - (B.10) into the eqns. (B.1) - (B.5) respectively we get

$$(1-p)\left(\frac{d(C_0 + pC_1 + p^2C_2 + \dots)}{dt} - (\alpha_1 - \mu_1)(C_0 + pC_1 + p^2C_2 + \dots)\right) + p\left(\frac{d(C_0 + pC_1 + p^2C_2 + \dots)}{dt} - (\alpha_1 - \mu_1)(C_0 + pC_1 + p^2C_2 + \dots) + \frac{\alpha_1}{k_1}(C_0 + pC_1 + p^2C_2 + \dots)^2 + \beta_1(C_0 + pC_1 + p^2C_2 + p^3C_3 \dots)(T_0 + pT_1 + p^2T_2 + \dots)\right) = 0 \quad (\text{B.11})$$

$$(1-p)\left(\frac{d(E_0 + pE_1 + p^2E_2 + \dots)}{dt} - (\alpha_2 - \mu_2)(E_0 + pE_1 + p^2E_2 + \dots)\right) + p\left(\frac{d(E_0 + pE_1 + p^2E_2 + \dots)}{dt} + \gamma(E_0 + pE_1 + p^2E_2 + \dots)(T_0 + pT_1 + p^2T_2 + \dots) - (\alpha_2 - \mu_2)(E_0 + pE_1 + p^2E_2 + \dots) + \frac{\alpha_2}{k_2}(E_0 + pE_1 + p^2E_2 + \dots)^2\right) = 0 \quad (\text{B.12})$$

$$(1-p) \left(\frac{d(T_0 + pT_1 + p^2T_2 + \dots)}{dt} + \mu_3 (T_0 + pT_1 + p^2T_2 + \dots) \right) + p \left(\begin{aligned} &\frac{d(T_0 + pT_1 + p^2T_2 + \dots)}{dt} + \mu_3 (T_0 + pT_1 + p^2T_2 + \dots) \\ & - \alpha_3 (A_0 + pA_1 + p^2A_2 + \dots) (T_0 + pT_1 + p^2T_2 + \dots) \\ & + \frac{\alpha_3}{k_3} (A_0 + pA_1 + p^2A_2 + \dots) (T_0 + pT_1 + p^2T_2 + \dots)^2 \\ & + \beta_2 (C_0 + pC_1 + p^2C_2 + \dots) (T_0 + pT_1 + p^2T_2 + \dots) \end{aligned} \right) = 0 \quad (\text{B.13})$$

$$(1-p) \left(\frac{d(P_0 + pP_1 + p^2P_2 + \dots)}{dt} + (\delta + \mu_4)(P_0 + pP_1 + p^2P_2 + \dots) \right) + p \left(\begin{aligned} &\frac{d(P_0 + pP_1 + p^2P_2 + \dots)}{dt} + (\delta + \mu_4)(P_0 + pP_1 + p^2P_2 + \dots) \\ & - \gamma (E_0 + pE_1 + p^2E_2 + \dots) (T_0 + pT_1 + p^2T_2 + \dots) \end{aligned} \right) = 0 \quad (\text{B.14})$$

$$(1-p) \left(\frac{d(A_0 + pA_1 + p^2A_2 + \dots)}{dt} + \mu_5 (A_0 + pA_1 + p^2A_2 + \dots) \right) + p \left(\begin{aligned} &\frac{d(A_0 + pA_1 + p^2A_2 + \dots)}{dt} + \mu_5 (A_0 + pA_1 + p^2A_2 + \dots) \\ & - \delta (P_0 + pP_1 + p^2P_2 + \dots) - \varepsilon (T_0 + pT_1 + p^2T_2 + \dots) (A_0 + pA_1 + p^2A_2 + \dots) \\ & + \frac{\varepsilon}{k_4} (T_0 + pT_1 + p^2T_2 + \dots) (A_0 + pA_1 + p^2A_2 + \dots)^2 \end{aligned} \right) = 0 \quad (\text{B.15})$$

Comparing the coefficients of like powers of p from the eqns. (B.11)-(B.15) respectively, we can obtain the following differential equations

$$p^0 : \frac{dC_0}{dt} - (\alpha_1 - \mu_1) C_0 = 0 \quad (\text{B.16})$$

$$p^0 : \frac{dE_0}{dt} - (\alpha_2 - \mu_2) E_0 = 0 \quad (\text{B.17})$$

$$p^0 : \frac{dT_0}{dt} + \mu_3 T_0 = 0 \quad (\text{B.18})$$

$$p^0 : \frac{dP_0}{dt} + (\delta + \mu_4) P_0 = 0 \quad (\text{B.19})$$

$$p^0 : \frac{dA_0}{dt} + \mu_5 A_0 = 0 \quad (\text{B.20})$$

$$p^1 : \frac{dC_1}{dt} - (\alpha_1 - \mu_1) C_1 + \frac{\alpha_1}{k_1} C_0^2 + \beta_1 C_0 T_0 = 0 \quad (\text{B.21})$$

$$p^1 : \frac{dE_1}{dt} - (\alpha_2 - \mu_2) E_1 + \frac{\alpha_2}{k_2} E_0^2 + \gamma E_0 T_0 = 0 \quad (\text{B.22})$$

$$p^1 : \frac{dT_1}{dt} + \mu_3 T_1 - \alpha_3 A_0 T_0 + \frac{\alpha_3}{k_3} A_0 T_0^2 + \beta_2 C_0 T_0 = 0 \quad (\text{B.23})$$

$$p^1 : \frac{dP_1}{dt} + (\delta + \mu_4) P_1 - \gamma E_0 T_0 = 0 \quad (\text{B.24})$$

$$p^1 : \frac{dA_1}{dt} + \mu_5 A_1 - \delta P_0 - \varepsilon T_0 A_0 + \frac{\varepsilon}{k_4} T_0 A_0^2 = 0 \quad (\text{B.25})$$

$$p^2 : \frac{dA_2}{dt} + \mu_5 A_2 - \delta P_1 - \varepsilon (T_0 A_1 + T_1 A_0) + \frac{\varepsilon}{k_4} (T_1 A_0^2 + 2 A_0 A_1 T_0) = 0 \quad (\text{B.26})$$

The initial approximations are as follows:

$$C_0(0) = C_a - C_m; \quad E_0(0) = E_b, \quad T_0(0) = C_m, \quad P_0(0) = 0, \quad A_0(0) = 0 \quad (\text{B.27})$$

$$C_i(0) = 0; \quad E_i(0) = 0, \quad T_i(0) = 0, \quad P_i(0) = 0, \quad A_i(0) = 0, \quad \text{for } i = 1, 2, 3, \dots \quad (\text{B.28})$$

Solving the eqns. (B.16)- (B.26) and using the initial approximations eqns. (B.28)-(B.29), we get

$$C_0(t) = (C_a - C_m) e^{(\alpha_1 - \mu_1) t} \quad (\text{B.29})$$

$$E_0(t) = E_b e^{(\alpha_2 - \mu_2) t} \quad (\text{B.30})$$

$$T_0(t) = C_m e^{-\mu_3 t} \quad (\text{B.31})$$

$$P_0(t) = 0 \quad (\text{B.32})$$

$$A_0(t) = 0 \quad (\text{B.33})$$

$$C_1(t) = \left[\frac{\alpha_1 (C_a - C_m)^2}{k_1 (\alpha_1 - \mu_1)} \right] e^{2(\alpha_1 - \mu_1) t} + \left[\frac{\beta_1 C_m (C_a - C_m)}{\mu_3} \right] e^{(\alpha_1 - \mu_1 - \mu_3) t} \\ + \left[\frac{\alpha_1 (C_a - C_m)^2}{k_1 (\alpha_1 - \mu_1)} - \frac{\beta_1 C_m (C_a - C_m)}{\mu_3} \right] e^{(\alpha_1 - \mu_1) t} \quad (\text{B.34})$$

$$E_1(t) = \left[\frac{\alpha_2 E_b^2}{k_2 (\alpha_2 - \mu_2)} \right] e^{2(\alpha_2 - \mu_2) t} + \left[\frac{\gamma E_b C_m}{\mu_3} \right] e^{(\alpha_2 - \mu_2 - \mu_3) t} \\ + \left[\frac{\alpha_2 E_b^2}{k_2 (\alpha_2 - \mu_2)} - \frac{\gamma E_b C_m}{\mu_3} \right] e^{(\alpha_2 - \mu_2) t} \quad (\text{B.35})$$

$$T_1(t) = \left[\frac{\beta_2 C_m (C_a - C_m)}{(\alpha_1 - \mu_1)} \right] e^{(\alpha_1 - \mu_1 - \mu_3) t} + \left[\frac{\beta_2 C_m (C_a - C_m)}{(\alpha_1 - \mu_1)} \right] e^{-\mu_3 t} \quad (\text{B.36})$$

$$P_1(t) = \left[\frac{\gamma E_b C_m}{(\delta + \alpha_2 - \mu_2 - \mu_3 + \mu_4)} \right] \left[e^{(\alpha_2 - \mu_2 - \mu_3) t} - e^{-(\delta + \mu_4) t} \right] \quad (\text{B.37})$$

$$A_1(t) = 0 \quad (\text{B.38})$$

$$A_2(t) = \left[\frac{\delta \gamma E_b C_m}{(\delta + \alpha_2 - \mu_2 - \mu_3 + \mu_4)} \right] \left[\frac{e^{(\alpha_2 - \mu_2 - \mu_3)t}}{(\alpha_2 - \mu_2 - \mu_3 + \mu_5)} + \frac{e^{-(\delta + \mu_4)t}}{(\delta + \mu_4 - \mu_5)} \right] - \left[\frac{\delta \gamma E_b C_m}{(\delta + \alpha_2 - \mu_2 - \mu_3 + \mu_4)} \right] \left[\frac{1}{(\alpha_2 - \mu_2 - \mu_3 + \mu_5)} + \frac{1}{(\delta + \mu_4 - \mu_5)} \right] e^{-\mu_5 t} \quad (\text{B.39})$$

According to the HPM, we can conclude that

$$C = \lim_{p \rightarrow 1} C(t) = C_0 + C_1 \quad (\text{B.40})$$

$$E = \lim_{p \rightarrow 1} E(t) = E_0 + E_1 \quad (\text{B.41})$$

$$T = \lim_{p \rightarrow 1} T(t) = T_0 + T_1 \quad (\text{B.42})$$

$$P = \lim_{p \rightarrow 1} P(t) = P_0 + P_1 \quad (\text{B.43})$$

$$A = \lim_{p \rightarrow 1} A(t) = A_0 + A_1 + A_2 \quad (\text{B.44})$$

Substituting the eqns. (B.29) and (B.34) into an eqn. (B.40) and substituting the eqns. (B.30) and (B.35) into an eqn. (B.41) and substituting the eqns. (B.31) and (B.36) into an eqn. (B.42), and substituting the eqns. (B.32) and (B.33) into an eqn. (B.43) and finally substituting the eqns. (B.33), (B.38) and (B.39) into an eqn. (B.44), we can obtain the solutions in the text.

Appendix: C

Matlab/Scilab program to solve the nonlinear eqns. (3)-(8)

function

```
options= odeset ('RelTol', 1e-6,'Stats','on');
```

```
%initial conditions
```

```
x0 = [.4; .5; .1; 0; 0];
```

```
tspan = [0, 6];
```

```
tic
```

```
[t, x] = ode45(@TestFunction,tspan,x0,options);
```

```
toc
```

```
figure
```

```
hold on
```

```
plot(t, x(:,1))
```

```
plot(t, x(:,2))
```

```
plot(t, x(:,3))
```

```
plot(t, x(:,4))
```

```
plot(t, x(:,5))
```

```

legend('x1','x2','x3','x4','x5')
ylabel('x')
xlabel('t')
return
function [dx_dt]= TestFunction(t,x)
a1=0.1; a2=0.1; a3=0.2; f=0.01; c1=0.01; c2=0.05; c3=0.05; c4=0.01; c5=0.01;
k1=10; k2=20, k3=5; k4=1; e=0.01; d=0.01; b1=0.01; b2=0.01;
dx_dt(1)=a1*x(1)*(1-(x(1)/k1))-b1*x(1)*x(3)-c1*x(1);
dx_dt(2)=a2*x(2)*(1-(x(2)/k2))-d*x(2)*x(3)-c2*x(2);
dx_dt(3)=a3*x(5)*x(3)*(1-(x(3)/k3))-b2*x(1)*x(3)-c3*x(3);
dx_dt(4)=d*x(2)*x(3)-e*x(4)-c4*x(4);
dx_dt(5)=e*x(4)+(f*x(3)*x(5))*(1-(x(5)/k4))-c5*x(5);
dx_dt = dx_dt';
return
    
```

Appendix: D

Nomenclature

Symbol	Meaning	Fixed values	Units
C	Concentration of normal cells at time t		
E	Concentration of epithelial cells at time t		
T	Concentration of cancer cells at time t		
P	Concentration of pre-angiogenesis cells at time t		
A	Concentration of angiogenesis cells at time t		
α_1	Intrinsic growth rate of normal cells	0.1	$days^{-1}$
α_2	Intrinsic growth rate of epithelial cells	0.1	$days^{-1}$
α_3	Intrinsic growth rate of cancer cells	0.2	$[A]^{-1} \times days^{-1}$
ε	Intrinsic growth rate of angiogenesis cells	0.01	$[T]^{-1} \times days^{-1}$
μ_1	Mortality rate of normal cells	0.01	$days^{-1}$
μ_2	Mortality rate of epithelial cells	0.05	$days^{-1}$
μ_3	Mortality rate of cancer cells	0.05	$days^{-1}$
μ_4	Mortality rate of pre-angiogenesis cells	0.01	$days^{-1}$

μ_5	Mortality rate of angiogenesis cells	0.01	$days^{-1}$
k_1	Carrying capacity of normal cells	10	[C]
k_2	Carrying capacity of epithelial cells	20	[E]
k_3	Carrying capacity of cancer cells	5	[T]
k_4	Carrying capacity of angiogenesis cells	1	[A]
δ	Transfer rate from pre-angiogenesis to angiogenesis cells	0.1	$days^{-1}$
γ	Epithelial sprouting rate	0.01	$[T]^{-1} \times days^{-1}$
β_1	Rate of inhibition of normal cells by cancer cells	0.01	$[T]^{-1} \times days^{-1}$
β_2	Rate of inhibition of cancer cells by normal cells	0.01	$[C]^{-1} \times days^{-1}$