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Homotopy Perturbation Method for Solving Cell Cycle of Tumoural Cells

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Abstract

In this work we present a mathematical model for tumour growth based on the biology of the cell cycle. Our model reproduces the dynamics of three different tumour cell populations: Quiescent cells, cells during the inter phase and mitotic cells. Here, we investigate the stability analysis of the cancer-free equilibrium. We have implemented Homotopy perturbation method to give approximated analytical solutions of non-linear ordinary differential equations of system such as model for Tumoural growth. A modification of the homotopy perturbation method based on the use of Pade approximations is done. Some plots are presented to show the reliability and simplicity of the methods.

Keywords: Tumour, Cell cycle, Stability, Homotopy perturbation method, Pade approximation.
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1 Introduction

Cancer is nowadays one of the most common severe diseases in the world. A better understanding of the dynamics of cancer and tumour growth is therefore crucial.

In the last two decades many mathematical models for the description of tumour growth have been developed. When investigating tumour growth, one cannot neglect the process of cell ageing and cell division. In particular cell ageing and cell-cycle have been considered in many and different [1, 2, 3, 4] approaches. Cells enter the cell cycle through two quite distinct processes. One is the unique process of fertilization, and the other is cell proliferation activated by growth factors. A classical cell cycle model, the G_0 -model, has been developed by Mackey [5]. Examples of the more recent work done with mathematical models of [6] and [7] cycle specific chemotherapy are by Webb. They develop linear and non linear age-structured models of cycle-specific chemotherapy. Another[8] work interest by Birkhead, in which a four compartment linear system is developed to model the cycling, resistant and resting cells. Their results are limited to a few numerical calculations on four specific types of treatments. Swan [9] examines cycle-specific chemotherapy in his review article. In general [10, 11] the cells undergo the cell cycle, a sort of "life cycle" which consists of four phases: The G_1 phase is necessary for the cell to grow up, before the DNA is replicated in the S phase, A second growth phase G_2 follows and the mitotic phase (M) concludes the cycle, with division of nucleus and cytoplasm. The result of a completed cell cycle are two daughter cells which enter the cycle in G_1. The first three phases of the cycle are often summed up together and referred to as 'interphase'. Here the primary focus will be on the cell cycle events that occur when G_0 cells are stimulated to proliferate by growth factors. There is a complex cell cycle network of signalling pathways that interact with each other to control whether or not cells will grow and divide. There is an extensive cell cycle tool kit that contains both the signalling molecules and the large number of targets that are engaged as the cell passes through the cell cycle. Growth factors act early in G_1 through a growth factor signalling/cell cycle interface to engage the cell cycle signalling system that then takes over and presides over the orderly sequence of events that culminates in cell division to give two daughter cells. The most typical normal cell will have a cell cycle duration of approximately 24 hours, with various exceptions(e.g.liver cells can take up to a year to complete their cycle). However a study made by Tubiana [12] on 30 solid human tumours reveal that the median duration of these phases can be even higher with a cell cycle duration lasting a median time of 2 days and distributed as 1 day for G_1, 18 hours for S, 6 hours for G_2, leaving just approximately 1 hour for mitosis M. These values are median values and one must be cautioned to the fact that different cell lines have different cell cycle times(normal and cancerous cells), they give evidence that the cell cycle time is approximately twice as large in man than in animals. In

this article, we consider the following model (1) for cell cycle of tumoural cells. In this model, the inducement of this article is to expand the application of the analytic Homotopy perturbation method to solve for tumoural cell cycle. Ji-Huan He is a Chinese Mathematician, He was the first person to propose the Homotopy perturbation method. The first connection between series solution methods such as an Adomain decomposition method and Pade approximates was established. In section 2, we investigate the stability analysis for cell cycle of tumoural cells model with positiveness and boundedness of solutions. In section 3 and 4 we discuss the pade approximation method and homotopy perturbation method for investigating the approximate solutions of the above said model (1). In section 5, we derived the approximate solutions of the model (1) using section 3 & 4 and also plotted the approximate solutions. Finally this article end with the conclusions in section 6.

2 Model

The general model [13] described for the cell cycle for the tumoural cells as follows:

$$\begin{aligned} Q'(t) &= \mu_Q V(t) - (b_Q + \mu_{G_0})Q(t) \\ U'(t) &= 2b_1 U(t) + b_Q Q_(t) - \mu_1 U(t) \\ V'(t) &= -(\mu_0 + \mu_Q)V(t) \end{aligned} \tag{2.1}$$

The system (1) needs to be analysed with the following initial conditions:

$$Q(0) > 0, U(0) > 0, V(0) > 0$$

we denote,

$$\Re^3_+ = \{(Q,U,V) \in \Re^3_+, Q(0) \geq 0, U(0) \geq 0, V(0) \geq 0\}$$

Table I:

Parameter	Description
$Q(t)$	Number of quiescent (G_0) cells at a time t
$U(t)$	Number of mitotic cells at a time t
$V(t)$	Number of interphase (G_1, S and G_2-phase) cells at a time t

Table II: Parameter Values and Range [[13]]

Variable	Description	Value	Dimension
μ_{G_0}	death rate G_0 cells	$0.1/10^4$	time
μ_Q	transition rate from G_1 to G_0	0.02	time
b_Q	transition rate from G_0 to G_1	0.2	time
b_1	division rate of M cells	0-1 day	time
μ_0	death rate G_1 cells	0.11	time
μ_1	death rate M cells	0.28	time

2.1 Positive Invariance

The model (1) can be written in the form,

$$X'(t) = F(X(t))$$

where

$$F = (F_1, F_2, F_3)^T := (Q,U,T)^T, F(0) = (Q(0), U(0), V(0))^T \in \Re^3_+.$$

and

$$F(X) = \begin{bmatrix} F_1(X) \\ F_2(X) \\ F_3(X) \end{bmatrix} = \begin{bmatrix} \mu_Q V(t) - (b_Q + \mu_{G_0})Q(t) \\ 2b_1 U(t) + b_Q Q_(t) - \mu_1 U(t) \\ -(\mu_0 + \mu_Q)V(t) \end{bmatrix}.$$

It is easy to check that $F_i(X)|X_i(t) \geq 0, i = 1, 2, 3.$,

Due to lemma Yang [14] any solution of the above equation with initial point $X_0 \in \Re^3_+$, say $X(t) = X(t, X_0)$ is such that $X(t) \in \Re^3_+$ for all $t > 0$.

Remark 1:
Any positive solution of system (2) with initial conditions are bounded.

2.2 Stability Analysis

For biomedical reasons, it is important to look at the long-term behaviour of tumoural cell populations. In this section, we investigate only the stability of the cancer free-steady state and determine conditions on the model parameters for tumour growth eradication.

The system (1) is a linear system with the stationary points $(Q^*, U^*, V^*) = (0, 0, 0)$. The eigenvalues associated with the matrix are given by,

$$B = \begin{bmatrix} -(b_Q + \mu_{G_0}) & 0 & 0 \\ b_Q & 2b_1 - \mu_1 & 0 \\ 0 & 0 & -(\mu_0 + \mu_Q) \end{bmatrix}.$$

From the above matrix gives the characteristic equations by

$$\lambda^3 + a_1\lambda^2 + a_2\lambda - a_3 = 0$$

where,
$a_1 = \mu_1 - 2b_1 - (b_Q + \mu_{G_0} + \mu_0 + \mu_Q)$
$a_2 = (\mu_0 + \mu_Q)(b_Q + \mu_{G_0}) + (\mu_0 + \mu_Q)(2b_1 - \mu_1) + (b_Q + \mu_{G_0})(2b_1 - \mu_1)$
$a_3 = (2b_1 - \mu_1)(b_Q + \mu_{G_0})(\mu_0 + \mu_Q)$

The roots of the above characteristic equation are ,

$$\begin{aligned} \lambda_1 &= -(b_Q + \mu_{G_0}) \\ \lambda_2 &= 2b_1 - \mu_1 \\ \lambda_3 &= -(\mu_0 + \mu_Q) \end{aligned}$$

From the the above it is trivial to see that all roots of the characteristic equations are real and that $\lambda_1 < 0$, and $\lambda_3 < 0$.

Remark 2:
The cancer free steady state is locally asymptotically stable if $b_1 < \frac{\mu_1}{2}$.

Biomedical Interpretation: Note that μ_1 represents the death rate of the mitotic cells and b_1 represents the division rate of the mitotic cells.
Assume that $b_1 > \frac{\mu_1}{2}$, then the cells can be divided and the tumour cell is going to the interphase stage that the cancer is to be growth. Hence the necessary condition for the cancer cell decay is $b_1 < \frac{\mu_1}{2}$, in this case the death rate of the mitotic cells is greater than the division rate, therefore the cancer cells will not grow.(according to this model). This fact will be confirmed by the more complex models later and also has been identified for radiation treatment in [15].

3 Pade Approximation

A rational approximation to $f(x)$ on [a,b] is the quotient of two polynomials $P_N(x)$ and $Q_M(x)$ of degrees N and M, respectively. We use the notation $R_{N,M}(x)$, $M(x)$ to denote this quotient. The $R_{N,M}(x)$ Pade approximations to a function $f(x)$ are given by [16],

$$R_{N,M}(x) = \frac{P_N(x)}{Q_M(x)}, \qquad for \quad a \leq x \leq b. \tag{3.1}$$

The method of Pade requires that $f(x)$ and its derivatives be continous at $x = 0$. The polynomial used in (2)are,

$$P_N(x) = p_0 + p_1x + p_2x^2 + \cdots + p_Nx^N, \tag{3.2}$$
$$Q_M(x) = q_0 + q_1x + q_2x^2 + \cdots + q_Mx^M. \tag{3.3}$$

The polynomial in (4)and (5) are constructed so that $f(x)$ and $R_{N,M}(x)$ agree at $x = 0$ and their derivatives upto $N + M$ agree at $x = 0$. In the case $Q_0(x) = 1$, the approximation is just the Maclaurin expansion for $f(x)$. For a fixed value of $N + M$ the error is smallest when $P_N(x)$ and $Q_M(x)$ have the same degree or when $P_N(x)$ has degree one higher than $Q_M(x)$. Notice that the constant coefficient of $Q_M(x)$ is $q_0 = 1$. This is permissible, because it is noticed to be 0 and $R_{N,M}(x)$ is not changed when both $P_N(x)$ and $Q_M(x)$ are divided by coefficients. Assume that $f(x)$ is analytic and has the Maclaurin expansion,

$$f(x) = a_0 + a_1x + a_2x^2 + \cdots + a_kx^k + \cdots, \tag{3.4}$$

and from the difference $f(x)Q_M(x)$ - $P_N(x) = Z(x)$,

$$\left[\sum a_ix^i\right]\left[\sum q_ix^i\right] - \left[\sum p_ix^i\right] = \left[\sum c_ix^i\right] \tag{3.5}$$

The lower index $i = N + M + 1$in the summation on the right side of (7) is chosen because the first $N + M$ derivatives of $f(x)$ and $R_{N,M}(x)$ are agree at $x = 0$. When the left side of (7) is multiplied out and the coefficient of the powers of x_i are set equal to zero for k $= 0, 1, 2, \cdots N + M$, the result is a system of $N + M + 1$ linear equations:

$$\begin{aligned} a_0 &= p_0, \\ q_1a_0 + a_1 &= p_1, \\ q_2a_0 + q_1a_1 + a_2 &= p_2, \\ q_3a_0 + q_2a_1 + q_1a_2 + a_3 &= p_3, \\ q_Ma_{N-M} + q_{M-1}a_{N-M+1} + a_N &= p_N, \end{aligned} \tag{3.6}$$

and

$$\begin{aligned} q_Ma_{N-M+1} + q_{M-1}a_{N-M+2} + ... + q_1a_N + a_{N+1} &= 0, \\ q_Ma_{N-M+2} + q_{M-1}a_{N-M+3} + ... + q_1a_{N+1} + a_{N+2} &= 0, \\ &\vdots \\ q_Ma_{N-M+1} + q_{M-1}a_{N+1} + ... + q_1a_{N+M+1} + a_{N+M} &= 0. \end{aligned} \tag{3.7}$$

Notice that in each equations the sum of the subscripts on the factors of each products the same,and this sum increase consecutively from 0 to $N + M$.

The M equation in (9) involve only the unknowns $q_1, q_2, q_3, \cdots q_M$ and must be solved first. Then the equations in (8) are used successively to find $p_1, p_2, p_3, ..., p_N$ [16].

4 Homotopy Perturbation Method

To illustrate the homotopy perturbation method (HPM) for solving nonlinear differential equations, He [17, 18] considered , the following nonlinear differential equation:

$$A(u) = f(r), \quad r \in \Omega \tag{4.1}$$

with the following boundary condition:

$$B\left(u, \frac{\partial u}{\partial t}\right) = 0, \quad r \in \Gamma \tag{4.2}$$

where A is general differential operator, B a boundary operator, $f(r)$ is known analytical function and Γ is the boundary of the domain and denotes differentiation along the normal vector drawn outwards from Ω. The operator A can be decomposed into two operators M and N, where M is linear, and N is nonlinear opearator. Equation (10) can be therefore, written as follows:

$$M(u) + N(u) - f(r) = 0. \tag{4.3}$$

He [17, 19] considered a homotopy $v(r, p) : \Omega \times [0, 1] \to \Re$ which satisfies,

$$H(v, p) = (1 - p)[M(v) - M(u_0)] + p[A(v) - f(r)] = 0 \tag{4.4}$$

which is equivalent to,

$$H(v, p) = M(v) - M(u_0) + pM(u_0) + p[N(v) - f(r)] = 0 \tag{4.5}$$

where $p \in [0, 1]$ is an embedding parameter, and u_0 is an initial approximation of (10). Obviously, we have,

$$H(v, 0) = M(v) - M(u_0) = 0, H(v, 1) = A(v) - f(r)] = 0 \tag{4.6}$$

The changing process of p from zero to unity is just that of $H(v, p)$ from $M(v) - M(u_0)$ to$A(v) - f(r)$. In topolgy, this is called deformation, $M(v) - M(u_0)$ and $A(v) - f(r)$ are homotopic. According to the homotopy perturbation method, the parameter p is used as a smaller parameter, and the solution of equation (13) can be expressed as a series in p is the form,

$$v = v_0 + pv_1 + p^2v_2 + p^3v_3 + +... \tag{4.7}$$

When $p \to 1$, equation (13) corresponds to the original one, equations (12) and (16) become the approximate solution of equation (12),
i.e.,

$$u = \lim_{p \to 1} v = v_0 + v_1 + v_2 + v_3 + ... \tag{4.8}$$

4.1 Convergence

From [20, 21] Let us write Eq (13) in the following form,

$$M(v) = M(u_0) + p[f(r) - N(v) - M(u_0)] = 0 \tag{4.9}$$

Applying the inverse operator, L^{-1} to both sides of Eq (17), we obtain

$$v = u_0 + p[L^{-1}f(r) - L^{-1}N(v) - u_0] \tag{4.10}$$

Suppose that

$$v = \sum_{i=0}^{\infty} p^i v_i, \tag{4.11}$$

substituting (19) into the right-hand side of Eq(18) in the following form

$$v = u_0 + p\left[L^{-1}f(r) - L^{-1}N(\sum_{i=0}^{\infty} p^i v_i) - u_0\right] \tag{4.12}$$

If $p \to 1$, the exact solution may be obtained by using,

$$\begin{aligned} u &= \lim_{p\to 1} v \\ &= L^{-1}f(r) - L^{-1}N\left[\sum_{i=0}^{\infty} v_i\right] \\ &= L^{-1}f(r) - \sum_{i=0}^{\infty}(L^{-1}N)(v_i). \end{aligned}$$

To study the convergence of the method let us state the following theorem.

Theorem:(Sufficient Condition of Convergence).

From [20, 21] Suppose that X and Y are Banach spaces and N: X $\to$ Y is contractive nonlinear mapping, that is

$$\forall w, w^* \in X; \| N(w) - N(w^*) \| \leq \gamma \| w - w^* \|, 0 < \gamma < 1$$

Then according to Banach's fixed point theorem N has a unique fixed point u, that is N(u)= u.

Assume that the sequence generated by homotopy perturbation method can be written as

$$W_n = N(W_{n-1}), N(W_{n-1}) = \sum_{i=0}^{n-1} w_i, n = 1, 2, 3..,$$

and suppose that $W_0 = W_0 \in B_r(w)$ where $B_r(w) = \{w^* \in X | \| W^* - W \| < r\}$, then we have,

i) $W_n \in B_r(w)$,

ii) $\lim_{n\to\infty} = w$.

Proof:

(i) By inductive approach , for $n = 1$, we have,

$$\| W_1 - w \| = \| N(W_0) - N(w) \| \leq \gamma \| w_0 - w \|$$

Assume that,

$$\| W_{n-1} - w \| \leq \gamma^{n-1} \| w_0 - w \|$$

as induction hypothesis,then

$$\| W_n - w \| = \| N(W_{n-1}) - N(w) \| \leq \| W_{n-1} - w \| \leq \gamma^n \| w_0 - w \| .$$

Using (i), we have

$$\| W_n - w \| \leq \gamma^n \| w_0 - w \| \leq \gamma^n \gamma < r \Rightarrow W_n \in B_r(w).$$

(ii) Because of ,

$$\| W_n - w \| \leq \gamma^n \| w_0 - w \| \; and \lim_{n\to\infty} \gamma^n = 0, \lim_{n\to\infty} \| W_n - w \| = 0$$

that is,

$$\lim_{n\to\infty} W_n = w$$

5 Application

We have applied the homotopy perturbation method to non linear ordinary differential systems (1), then we use Laplace transformation and Pade Approximation to compute analytical solution of the system (1),

5.1 Homotopy Perturbation Method to a cell cycle of the tumoral Model

We derive the correct functional according to perturbation method as follows:

$$\begin{aligned}
(1-p)(\dot{v_1} - \dot{x_0}) + p(\dot{v_1} - \mu_Q v_3 + (b_Q + \mu_{G_0})v_1) &= 0 \\
(1-p)(\dot{v_2} - \dot{y_0}) + p(\dot{v_2} - 2b_1 v_2 - b_Q v_1 + \mu_1 v_2) &= 0 \\
(1-p)(\dot{v_3} - \dot{z_0}) + p(\dot{v_3} + (\mu_0 + \mu_Q)v_3) &= 0
\end{aligned} \tag{5.1}$$

here "." the denotes differentiation with respect to t(for example,$\dot{v} = \frac{dv}{dt}$), and the initial conditions are as follows:

$$\begin{aligned}
v_{1,0}(t) &= x_0(t) = Q(0) = r_1 \\
v_{2,0}(t) &= y_0(t) = U(0) = r_2 \\
v_{3,0}(t) &= z_0(t) = V(0) = r_3
\end{aligned} \tag{5.2}$$

and

$$\begin{aligned} v_1 &= v_{1,0} + pv_{1,1} + p_2v_{1,2} + p_3v_{1,3} + \cdots, \\ v_2 &= v_{2,0} + pv_{2,1} + p_2v_{2,2} + p_3v_{2,3} + \cdots, \\ v_3 &= v_{3,0} + pv_{3,1} + p_2v_{3,2} + p_3v_{3,3} + \cdots, \end{aligned} \tag{5.3}$$

where $v_{i,j}, i, j = 1, 2, 3, \cdots$ are functions yet to be determined. Substituting equations (19) and (20) into (18) and arranging the coefficients in terms of "p" powers, we have,

$$[\dot{v}_{1,1} - \mu_Q r_3 + (b_Q + \mu_{G_0})r_1]p + [\dot{v}_{1,2} - \mu_Q v_{3,1} + (b_Q + \mu_{G_0})v_{1,1}]p_2 +$$

$$[\dot{v}_{1,3} - \mu_Q v_{3,2} + (b_Q + \mu_{G_0})v_{1,2}]p_3 + \cdots = 0$$

$$[\dot{v}_{2,1} - 2b_1r_2 - b_Q r_1 + \mu_1 r_2]p + [\dot{v}_{2,2} - 2b_1v_{2,1} - b_Q v_{1,1} + \mu_1 v_{2,1}]p_2 +$$

$$[\dot{v}_{2,3} - 2b_1v_{2,2} - b_Q v_{1,2} + \mu_1 v_{2,2}]p_3 + \cdots = 0$$

and

$$[\dot{v}_{3,1} + (\mu_0 + \mu_Q)r_3]p + [\dot{v}_{3,2} + (\mu_0 + \mu_Q)v_{3,2}]p_2 +$$

$$[\dot{v}_{3,3} + (\mu_0 + \mu_Q)v_{3,2}]p_3 + \cdots = 0 \tag{5.4}$$

To obtain the unknowns $v_{i,j}(t)$,i,j=1,2,3, we will construct and solve the following system which includes nine equations with nine unknown, considering the initial conditions, $v_{i,j}(0) = 0$,i,j=1,2,3.

$$\begin{aligned} \dot{v}_{1,1} - \mu_Q r_3 + (b_Q + \mu_{G_0})r_1 &= 0, \\ \dot{v}_{1,2} - \mu_Q v_{3,1} + (b_Q + \mu_{G_0})v_{1,1} &= 0, \\ \dot{v}_{1,3} - \mu_Q v_{3,2} + (b_Q + \mu_{G_0})v_{1,2} &= 0, \\ \dot{v}_{2,1} - 2b_1r_2 - b_Q r_1 + \mu_1 r_2 &= 0, \\ \dot{v}_{2,2} - 2b_1v_{2,1} - b_Q v_{1,1} + \mu_1 v_{2,1} &= 0, \\ \dot{v}_{2,3} - 2b_1v_{2,2} - b_Q v_{1,2} + \mu_1 v_{2,2} &= 0, \\ \dot{v}_{3,1} + (\mu_0 + \mu_Q)r_3 &= 0, \\ \dot{v}_{3,2} + (\mu_0 + \mu_Q)v_{3,2} &= 0, \\ \dot{v}_{3,3} + (\mu_0 + \mu_Q)v_{3,2} &= 0. \end{aligned} \tag{5.5}$$

From equation (17), if the three terms approximation are sufficient, then we obtained:

$$\begin{aligned} Q(t) &= \lim_{p\to 1} v_1(t) = \sum_{k=0}^{2} v_{1,k}(t) \\ U(t) &= \lim_{p\to 1} v_2(t) = \sum_{k=0}^{2} v_{2,k}(t) \\ V(t) &= \lim_{p\to 1} v_3(t) = \sum_{k=0}^{2} v_{3,k}(t) \end{aligned} \tag{5.6}$$

Now, we have

$$\begin{aligned} Q(t) &= r_1 + (\mu_Q r_3 - (b_Q + \mu_{G_0})r_1]t + (-\mu_Q(\mu_0 + \mu_Q)r_3 - (b_Q + \mu_{G_0}) \\ &\quad (\mu_Q r_3 - (b_Q + \mu_{G_0})r_1)t^2 \\ U(t) &= r_2 + (2b_1 r_2 + b_Q r_1 - \mu_1 r_2)t + (2b_1(2b_1 r_2 + b_Q r_1 - \mu_1 r_2) + \\ &\quad b_Q(\mu_Q r_3 - (b_Q + \mu_{G_0})r_1) - \mu_1(2b_1 r_2 + b_Q r_1 - \mu_1 r_2))t^2 \\ V(t) &= r_3 + (-(\mu_0 + \mu_Q)r_3)t + (\mu_0 + \mu_Q)^2 r_3 t^2 \end{aligned} \tag{5.7}$$

Here, we should take $Q(0) = 2 * 10^5, U(0) = 1 * 10^5, V(0) = 4 * 10^5$, for this model,[16] to compute $Q(t), U(t), V(t)$. A first few approximations for $Q(t), U(t), V(t)$ are computed and given below:

Three terms approximations:

$$\begin{aligned} Q(t) &= 200000 - 32002t + \frac{268036001}{100000}t^2 - \frac{4684988056001}{30000000000}t^3 \\ U(t) &= 100000 + 212000t + \frac{895599}{5}t^2 + \frac{154311064001}{1500000}t^3 \\ V(t) &= 4000 - 52000t + 3380t^2 - \frac{2197}{15}t^3 \end{aligned} \tag{5.8}$$

Four terms approximations:

$$\begin{aligned} Q(t) &= 200000 - 32002t + \frac{268036001}{100000}t^2 - \frac{4684988056001}{30000000000}t^3 \\ &\quad + \frac{849164461080760}{120000000000000}t^4 \\ U(t) &= 100000 + 212000t + \frac{895599}{5}t^2 + \frac{154311064001}{1500000}t^3 \\ &\quad + \frac{884560600670533}{200000000000}t^4 \\ V(t) &= 4000 - 52000t + 3380t^2 - \frac{2197}{15}t^3 + \frac{28561}{6000}t^4 \end{aligned} \tag{5.9}$$

Five terms approximations:

$$\begin{aligned} Q(t) &= 200000 - 32002t + \frac{268036001}{100000}t^2 - \frac{4684988056001}{30000000000}t^3 \\ &\quad + \frac{849164461080760}{120000000000000}t^4 - \frac{158416983860762}{600000000000000}t^5 \\ U(t) &= 100000 + 212000t + \frac{895599}{5}t^2 + \frac{154311064001}{1500000}t^3 \\ &\quad + \frac{884560600670533}{200000000000}t^4 + \frac{456441761590}{300000000000000}t^5 \\ V(t) &= 4000 - 52000t + 3380t^2 - \frac{2197}{15}t^3 + \frac{28561}{6000}t^4 \\ &\quad - \frac{371293}{3000000}t^5 \end{aligned} \tag{5.10}$$

Six terms approximations:

$$\begin{aligned}
Q(t) &= 200000 - 32002t + \frac{268036001}{100000}t^2 - \frac{4684988056001}{30000000000}t^3 \\
&\quad + \frac{849164461080760}{120000000000000}t^4 - \frac{158416983860762}{600000000000000}t^5 \\
&\quad + \frac{301998089419911}{360000000000000}t^6 \\
U(t) &= 100000 + 212000t + \frac{895599}{5}t^2 + \frac{154311064001}{1500000}t^3 \\
&\quad + \frac{884560600670533}{200000000000}t^4 + \frac{456441761590}{300000000000000}t^5 \\
&\quad + \frac{261692748588}{600000000000000}t^6 \\
V(t) &= 4000 - 52000t + 3380t^2 - \frac{2197}{15}t^3 + \frac{28561}{6000}t^4 \\
&\quad - \frac{371293}{3000000}t^5 + \frac{4826809}{1800000000}t^6
\end{aligned} \tag{5.11}$$

Using Laplace transformation to (31) we have,

$$\begin{aligned}
L(Q(s)) &= \frac{200000}{s} - \frac{32002}{s^2} + \frac{268036001}{50000s^3} - \frac{4684988056001}{5000000000s^4} \\
&\quad + \frac{849164461080760}{500000000000000s^5} - \frac{1584169838607628096001}{50000000000000000000s^6} \\
&\quad + \frac{3019980894199116954811 6001}{5000000000000000000000000s^7} \\
L(U(s)) &= \frac{100000}{s} + \frac{212000}{s^2} + \frac{1791198}{5s^3} + \frac{154311064001}{250000s^4} \\
&\quad + \frac{26536818020115999}{25000000000s^5} + \frac{4564417615906059904001}{2500000000000000s^6} \\
&\quad + \frac{7850782457660036958600 75999}{2500000000000000000000s^7} \\
L(V(s)) &= \frac{400000}{s} - \frac{52000}{s^2} + \frac{6760}{s^3} - \frac{4394}{5s^4} + \frac{28561}{250s^5} \\
&\quad - \frac{371293}{25000s^6} + \frac{4826809}{2500000s^7}
\end{aligned} \tag{5.12}$$

Substituting $s = \frac{1}{t}$ in (32), we have,

$$\begin{aligned}
L(Q(t)) &= 200000t - 32002t^2 + 5360.72002t^3 - 936.9976112002t^4 \\
&\quad + 169.832892216152002t^5 - 31.6833967721525619 2002t^6 \\
&\quad + 6.039961788398233909623200 2t^7 \\
L(U(t)) &= 100000t + 21200t^2 + 3.582396 * 10^5 t^3 + 6.17244256004 * 10^5 t^4 \\
&\quad + 1.06147272080463996 * 10^6 t^5 + 1.8257670463624239616004 * 10^6 t^6 \\
&\quad + 3.1403129830640147834403039 96 * 10^6 t^7 \\
L(V(t)) &= 400000t - 52000t^2 + 6760t^3 - 878.8t^4 + 114.244t^5 \\
&\quad - 14.85172t^6 + 1.9307236t^7
\end{aligned} \tag{5.13}$$

Using Pade approximant [[16]] of (33) and substituting $t = 1/s$, we get [[16]] in terms of s. By using the inverse Laplace transformations, we have,

$$
\begin{aligned}
Q(t) &= \frac{2.000000000}{10^{25}} Dirac(t)(3.019980894 * 10^{25} t^7 - 1.584169839 * 10^{26} t^6 \\
&\quad +8.491644611 * 10^{26} t^5 - 4.684988056 * 10^{27} t^4 + 2.680360010 * 10^{28} t^3 \\
&\quad -1.600100000 * 10^{29} t^2 + 1.000000000 * 10^{30} t) \\
U(t) &= \frac{4.000000000}{10^{21}} Dirac(t)(7.850782458 * 10^{26} t^7 + 4.564417616 * 10^{26} t^6 \\
&\quad +2.653681802 * 10^{26} t^5 + 1.543110640 * 10^{26} t^4 + 8.955990000 * 10^{25} t^3 \\
&\quad +5.300000000 * 10^{24} t^2 + 2.500000000 * 10^{25} t) \\
V(t) &= \frac{4.000000000}{10^{7}} Dirac(t)(4.826809 * 10^{6} t^7 - 3.7129300 * 10^{7} t^6 \\
&\quad +2.85610000 * 10^{8} t^5 - 2.197000000 * 10^{9} t^4 + 1.690000000 * 10^{10} t^3 \\
&\quad -1.300000000 * 10^{11} t^2 + 1.000000000 * 10^{12} t)
\end{aligned}
\tag{5.14}
$$

Using the equations (29) and (31), we plot for the fourth (Fig 1) and sixth (Fig 2) approximations of quiescent cells($Q(t)$), mitotic cells ($U(t)$), interphase cells($V(t)$) , are presented below respectively:

Fig 1: Fourth Approximation

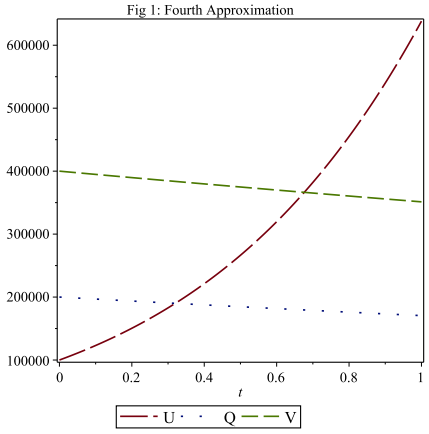
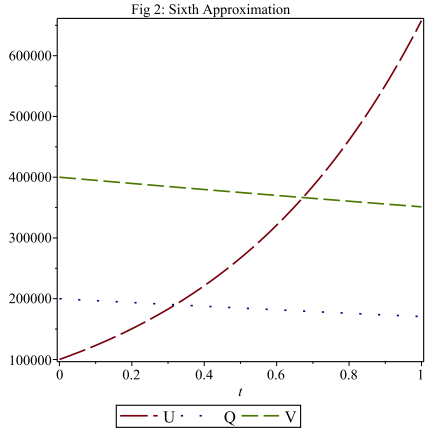


Fig 2: Sixth Approximation



From the above fig 1 and fig 2, it is easily seen that, whenever the time (t) is increasing then the quiescent cells and interphase cells have to be decreased, simultaneously mitotic cells are increasing the given time (t) in both approximations.
Suppose we take this system with immunotherapy for constant treatment,the time between one mitosis and next is large enough and the division rate is small, then the tumour vanishes independently of the delivered dose. However cancer is due to the uncontrolled growth of cells, so a large division is plausible. Further, we assume that the interphase time is very short we see at the effects of constant immunotherapy. Finally, the tumour vanishes when the immune system is highly stimulated by the increasing dosage.

6 Discussion

The main advantage of the method is the fact that it provides its user with an analytical approximation, in many cases an exact solution, in a rapidly convergent sequence with elegantly computed term. Thus, we have studied this model with the help of the Homotopy Perturbation Method. Moreover, we have obtained a solution for this model, when the exact solution could not be found. The comparison of our solution with the corresponding numerical solution showed the high degree of accuracy for the approximate solution. It also has several disadvantages inherent in any approximate method. Unfortunately, this method is very sensitive to the choice of homotopy, which often determines the possibility of the rapid convergence of approximate solution to the exact one. Moreover, it is not clear yet how to fine-tune the free parameter. Note also that solution process itself can be improved [22, 15, 20, 21]. We hope to consider all these problems in our further works. In the present paper, we just wanted to draw the attention of researchers to the possible application of the HPM in this model. We did not aim to investigate the accuracy of the HPM and to estimate the errors of approximation. We simply showed that this method can be used with good results where it is impossible to solve this type of equations in explicit analytical form. In our view, the results of the present work reveal that the HPM is very effective and simple for obtaining approximate solutions of this model in tumoural cell cycles.

7 Conclusion

In this paper we study the effect of a cell-cycle during the M phase, the G_0 phase and the interphase (G_1, S, G_2). In the absence of any treatments, we see that the cancer growth mainly depends on the death rate of cells in the mitotic phase and the division rate at which cells in the mitotic phase go into the G_1 phase (see lemma).Cancer will begin to grow if the division rate is greater than the death rate of cells in mitotic phase.Cell cycle duration is an important factor which can give rise to oscillation of solutions.We have used the Homotopy perturbation method for finding the solutions of non-linear ordinary differential systems such as a model for cell cycle of tumoural cells. The accuracy and efficiency of these methods are demonstrated here by solving some ordinary differential equation system. We have also used Laplace Transform and Pade approximate to obtain some analytic solution and to improve the accuracy of the homotopy perturbation method. He's homotopy perturbation methods is used to calculate certain difficult integrals. The graphs and computations presented here is done with the help of Maple. This gives a solution to a mathematical model of tumour growth, which will be very useful to study about the tumour growth model.

Competing Interests

The authors declare that no competing interests exist.

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