

Qualitative Analysis for Tumour Delay Model

N. S. Ravindran¹, M. Mohamed Sheriff^{2*}

¹Research Scholar, Research and Development Centre, Bharathiar University, Coimbatore.

²Research Supervisor, Research and Development Centre, Bharathiar University, Coimbatore.

* Corresponding author, E.mail: mmdsheriff@rediffmail.com

Abstract: In this paper we present a delay differential equation model for the dynamics between proliferating cells and quiescent cells. This model includes the positivity and boundedness of the solution. Stability has been investigated for trivial and nontrivial steady states. We analyze the sensitivity on performed parameters for the dynamical system. Using He's variational iteration method to obtain approximate solutions for the given dynamical model.

Key words: DDE's on Tumour model, Stability analysis, Sensitivity analysis, Variational iteration Method.

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I. Introduction

Recently many mathematical models for the description of tumour growth have been developed [1]. When investigating tumour growth, one cannot neglect the process of cell ageing and cell division. Cell growth, or cell proliferation, is a central topic in cell biology, immunology and tumour growth. Historically, ODEs have been used to model cell growth - this is mainly due to their mathematical simplicity and the long-standing availability of software for solving them. However, it is obvious that cell division, as well as cell differentiation and cell maturation, are not instantaneous processes but take a finite time to occur. The total number of cells in human tissue in vivo or cell culture in vitro is controlled by the processes of quiescence and cell death and the regulation of cell cycle phase duration. In non cancerous adult human tissues the total number of cells should be kept constant over time (homeostasis) and this an equilibrium may be achieved differently in different tissues [2,3]. For instance, in the hematopoietic system, the proportion of proliferating cells is very low in more differentiated stages, and eventually cell death (by apoptosis) guarantees continual renewal of the whole population. Thus, to maintain system homeostasis, high proliferative activity is expected to be balanced by a correspondingly high death rate (possibly by apoptosis), of fully differentiated quiescent cells. On the other hand, in tissues where apoptosis is a rare event, homeostasis is expected to be maintained by keeping all cells quiescent. Our model consists of two structured system of equations for the proliferating and quiescent cell compartments.

The organization of the paper is as follows: In section 2, we describe a 2-dimensional model for Tumour growth with Quiescence. In section 3, we investigate the stability analysis of the model with positiveness and boundedness of solutions. We determine the sensitivity analysis in section 4. We review the procedure and application of VIM in section 5. Finally ends with brief discussion.

II. Model Description

The mathematical model proposed by [3,11] describes the tumour growth system interaction and is given by a system of two differential equations with single delay :

$$\begin{aligned}\frac{dP}{dt} &= bP(t-\tau) - r_p(N(t))P(t) + r_Q(N(t))Q(t) \\ \frac{dQ}{dt} &= r_p(N(t))P(t) - (\mu_Q + r_Q(N(t)))Q(t)\end{aligned}\quad (1)$$

Here, we modified the above model (1) as follows,

$$\begin{aligned}\frac{dP}{dt} &= be^{-\gamma\tau} P(t-\tau) - r_p(N(t))P(t) + r_Q(N(t))Q(t) \\ \frac{dQ}{dt} &= r_p(N(t))P(t) - (\mu_Q + r_Q(N(t)))Q(t)\end{aligned}\quad (2)$$

In biological terms, $P(t)$ is the number of proliferating cells at time t and $Q(t)$ is the number of quiescent cells at time t . $N(t) = P(t) + Q(t)$ is the total number of cells in the tumour (or the size of the

tumour) at time t ; $b = \beta - \mu_p > 0$ is the intrinsic rate of the proliferating cells (where $\beta > 0$ is the division rate of the proliferating cells and $\mu_p \geq 0$ is the death rate of cells of the proliferating cells), the term $e^{-\gamma\tau}$ describes the survival rate of proliferating cells. $\mu_Q \geq 0$ is the mortality rate of the quiescent cells. $r_p(N)$ is the (nonlinear) transition rate from the proliferating class to the quiescent class and $r_Q(N)$ is the (nonlinear) transition rate from the quiescent class to the proliferating class. For this tumour population, one suppose that $r_p(N)$ is nondecreasing and $r_Q(N)$ is nonincreasing, $r_p(N)$ and $r_Q(N)$ are Lipschitz continuous on bounded sets of N in \mathfrak{R} [3] and the constant τ is the time delay which the proliferating cells needs to divide.

2.1 Positivity and boundedness

Proposition 2.1.

For all nonnegative initial condition, the unique solution $(P(t), Q(t))$ of (1) is nonnegative.

Proof:

First assume that there exists $\xi > 0$, such that $P(\xi) = 0$ and $P(t) > 0$ for $t < \xi$. Then from the above equation (1),

$$\frac{dP(\xi)}{dt} = be^{-\gamma\tau} P(t - \tau) + r_Q(N(t))Q(t) > 0,$$

Consequently, $P(t) > 0$ for $t > 0$. Next we assume that there exists $\xi > 0$ such that $Q(\xi) = 0$, and for $t < \xi$, then the same reasoning, the equation leads to

$$\frac{dQ(\xi)}{dt} = r_p(N(t))Q(t) > 0,$$

and we deduce that $Q(t) \geq 0$ for $t > 0$. As for the boundedness of (1), we have

$$N(t) = P(t) + Q(t)$$

Calculating the derivative of N along the solutions of the system (1), we find

$$\frac{dN}{dt} = be^{-\gamma\tau} P(t - \tau) - \mu_Q Q(t) \tag{3}$$

using Gronwall’s lemma [4], solve the above equation (3) we get

$$N(t) \leq N(0)e^{-\mu_Q t} + \int_0^t \mu_p(s) + bP(s - \tau)e^{-\mu_Q(t-s)} ds = M, \tag{4}$$

there exists $M > 0$ such that solutions of $N(t)$ is uniformly bounded.

Remark : . Since, the tumour cell is controlled by a proliferating cells, therefore maximum bound of tumour cells depend only on proliferating cells. Thus, we have $N(t)$ is bounded.

III. Stability Analysis

In this section we study the local stability analysis of model (1). The model (1) has two steady states: the first, called the trivial steady state E_0 and the second one is called the non-trivial steady state E_1 . The steady state points are as follows:

$$E_0 = (0,0)$$

$$E_1 = (P^*, Q^*) = \left(\frac{be^{-\gamma\tau} \mu_Q}{\mu_Q^2 + r_Q \mu_Q b - r_Q b^2 + r_p \mu_Q b}, \frac{b}{\mu_Q} P^* \right).$$

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 trivial steady state and non-trivial steady of the system (2).The linearized system of (2) at the trivial steady state (0,0) is

$$\begin{aligned} \frac{dP}{dt} &= be^{-\gamma\tau} P(t - \tau) - r_p(0)P(t) + r_Q(0)Q(t), \\ \frac{dQ}{dt} &= r_p(0)P(t) - (\mu_Q + r_Q(0))Q(t) \end{aligned} \tag{5}$$

The Jacobian matrix of the system (5) is as follows,

$$\begin{bmatrix} be^{-\gamma\tau} e^{-\lambda\tau} - r_p(0) & r_Q(0) \\ r_p(0) & -(\mu_Q + r_Q(0))Q(t) \end{bmatrix}$$

From the above matrix gives the characteristic equations by

$$\lambda^2 + a_1\lambda + a_4 + (a_4\lambda + a_3)e^{-\lambda\tau} = 0, \tag{6}$$

where,

$$a_1 = \mu_Q + r_Q(0) - r_p(0),$$

$$a_2 = be^{-\gamma\tau},$$

$$a_3 = be^{-\gamma\tau}(\mu_Q + r_Q(0)),$$

$$a_4 = r_p(0)(\mu_Q + r_Q(0)) - r_p(0)r_Q(0).$$

For $\tau = 0$, the system (6) is asymptotically stable around the trivial equilibrium point. Here the eigenvalues (λ) represent the roots of the characteristic equation (6). The system is stable around the steady state if and only if the eigenvalues have negative real parts. The conditions for this steady state to be stable (that is to obtain negative real parts of the eigenvalues) are $a_1 + a_2 > 0$ and $a_3 + a_4 > 0$ (by Routh Hurwitz's criteria). If $\tau \neq 0$, this equation has infinitely many roots. Next, we shall discuss the sum of zeros of equation (7) in the open right half plane.

Let $\lambda = i\omega(\omega > 0)$ be a root in (6), and separating the real and imaginary parts, we have

$$\omega^2 - a_4 = a_3 \cos(\omega\tau) + a_2\omega \sin(\omega\tau), \tag{7}$$

$$-a_1 = -a_3 \sin(\omega\tau) + a_2\omega \cos(\omega\tau). \tag{8}$$

Squaring and adding both equations of (7) and (8), we can obtain the following fourth degree equation for ω :

$$\omega^4 + \omega^2(a_1^2 - 2a_4 - a_2^2) + a_4^2 - a_3^2 = 0. \tag{9}$$

Putting $\omega^2 = u$ into (9), we can get the following quadratic equation

$$F(u) = u^2 + u(a_1^2 - 2a_4 - a_2^2) + a_4^2 - a_3^2 = 0. \tag{10}$$

If we assume that $a_1^2 - 2a_4 - a_2^2 > 0$ and $a_4^2 - a_3^2 > 0$, then (10) has no positive real root. In fact it is observed that,

$$F'(u) = 2u + a_1^2 - 2a_4 - a_2^2.$$

Has no positive real root by Descartes rule of sign. Thus, if $a_1^2 - 2a_4 - a_2^2 > 0$ and $a_4^2 - a_3^2 > 0$ then there is no ω such that $i\omega$ is an eigenvalue of the characteristic equation (6). i.e., λ will never be a purely imaginary root of equation (6). Thus the real parts of all eigenvalues of (6) are negative for all $\tau \geq 0$. Therefore the trivial steady state of model (2) is locally asymptotically stable when $\tau \geq 0$. For the linearized system of (2), at

$E_1 = (P^*, Q^*)$ is

$$\frac{du_1}{dt} = be^{-\gamma\tau} u_1(t - \tau) - 2r_{u_1} P^* u_1(t) - r_{u_1} Q^* u_1(t) - r_{u_1} P^* u_2(t) + r_{u_2} P^* u_2(t) + r_{u_2} Q^* u_1(t) + 2r_{u_2} Q^* u_2(t)$$

$$\frac{du_2}{dt} = 2r_{u_1} P^* u_1(t) + r_{u_1} Q^* u_1(t) + r_{u_1} P^* u_2(t) - \mu_{u_2} u_2(t) - (r_{u_2} P^* u_2(t) + r_{u_2} Q^* u_1(t) + 2r_{u_2} Q^* u_2(t)) \tag{11}$$

Then the Jacobian of the system (11) as follows,

$$\begin{bmatrix} be^{-\gamma\tau} e^{-\lambda\tau} - r_{u_1} Q^* - 2r_{u_1} P^* + r_{u_2} Q^* & -r_{u_1} P^* + 2r_{u_2} Q^* + r_{u_2} P^* \\ r_{u_1} Q^* + 2r_{u_1} P^* - r_{u_2} Q^* & -\mu_{u_2} + r_{u_1} P^* - r_{u_2} P^* - 2r_{u_2} Q^* \end{bmatrix}$$

From the above matrix gives the characteristic equations by

$$\lambda^2 + b_1\lambda + b_2 + (c_1\lambda + c_2)e^{-\lambda\tau} = 0, \tag{12}$$

where,

$$\begin{aligned} b_1 &= r_{u_1}(N^*) + r_{u_2}(N^*) + \mu_{u_2}, \\ b_2 &= 2P^* \mu_{u_2} r_{u_1} + Q^* \mu_{u_1} r_{u_1} - Q^* \mu_{u_1} r_{u_2}, \\ c_1 &= -be^{-\gamma\tau}, \\ c_2 &= e^{-\gamma\tau} (bP^* r_{u_1} - bP^* r_{u_2} - bQ^* r_{u_2} - b\mu_{u_2}). \end{aligned}$$

Let $\lambda = i\omega(\omega > 0)$ be a root in (12), and separating the real and imaginary parts, we have

$$\omega^{*2} - b_2 = -c_1 \omega^* \sin(\omega^* \tau) - c_2 \cos(\omega^* \tau), \tag{13}$$

$$-b_1 \omega^* = -c_1 \omega^* \cos(\omega^* \tau) + c_2 \sin(\omega^* \tau). \tag{14}$$

Squaring and adding both equations of (13) and (14), we can obtain the following fourth degree equation for ω^* :

$$\omega^{*4} + \omega^{*2} (b_1^2 - 2b_2 - c_1^2) + b_2^2 - c_2^2 = 0, \tag{15}$$

Putting $\omega^{*2} = u^*$ into (15), we can get the following quadratic equation

$$F(u^*) = u^{*2} + u^* (b_1^2 - 2b_2 - c_1^2) + b_2^2 - c_2^2 = 0. \tag{16}$$

Taking derivative with respect to u^* of equation (16), we get

$$F'(u^*) = 2u^* + b_1^2 - 2b_2 - c_1^2. \tag{17}$$

It is easy to verify that the coefficient in the above equation (16) are all positive. By Descartes rule of signs, equation (16) has positive root u^* and thus equation (15) has a pair of purely imaginary roots $i\omega^*$. From equation (13) and (14), we obtain

$$\tau_0^* = \frac{1}{\omega^*} \arccos\left(\frac{\omega^{*2}((c_1 b_1 - c_2) + b_2 c_2)}{c_2^2 - c_1^2 \omega^{*2}}\right) + \frac{2j\pi}{\omega^*}, \text{ where } j=0,1,\dots,$$

We can conclude that all the characteristic roots have negative real parts for any $\tau_0 \in [0, \tau_0^*)$. By using the following mathematical calculation we can say that the infected steady state of model (2) remains stable for $\tau_0 < \tau_0^*$ and Hopf bifurcation occurs when $\tau_0 = \tau_0^*$.

IV. Sensitivity Analysis

Sensitivity analysis can be used to determine the relationship between proliferating and quiescent cells for the dynamical system. Here, we show the sensitivity analysis with respect to the parameter is considered. We would like to consider how a small shift in the parameters would change the stability of the trivial equilibrium for this model. It is quite usual for a model to display high sensitivity to small variations in some parameters, while displaying robustness to variations in other parameters. Sensitivity analysis involves taking partial derivatives of the equation with respect to the parameters we want to test. Therefore, we want to find the sensitivity of the equation (11) with respect to the parameter ‘b’ and μ_p respectively. Since none of the equations of (11) depend on μ_p therefore the corresponding sensitivity system (11) with respect to the parameter μ_p is zero. The sensitivity functions with respect to an arbitrary parameter q, for the model (11) are denoted by,

$$\begin{aligned} u_{1,q} &= \frac{\partial u_1(t)}{\partial q}, \\ u_{2,q} &= \frac{\partial u_2(t)}{\partial q}. \end{aligned} \tag{18}$$

The corresponding sensitivity system (11) with respect to the parameter ‘b’ at E_2 as follows,

$$\begin{aligned}
 u_{1,q} &= e^{-\gamma\tau} u_1(t-\tau) - 2r_{u_1} P^* u_{1,b}(t,b) - r_{u_1} Q^* u_{1,b}(t,b) - r_{u_1} P^* u_{2,b}(t,b) + r_{u_2} P^* u_{2,b}(t,b) + r_{u_2} Q^* u_{1,b}(t,b) \\
 &+ 2r_{u_2} Q^* u_{2,b}(t,b) \\
 u_{2,q} &= 2r_{u_1} P^* u_{1,b}(t,b) + r_{u_1} Q^* u_{1,b}(t,b) + r_{u_1} P^* u_{2,b}(t,b) - \mu_{u_2} u_{2,b}(t,b) - (r_{u_2} P^* u_{2,b}(t,b) + r_{u_2} Q^* u_{1,b}(t,b) \\
 &+ 2r_{u_2} Q^* u_{2,b}(t,b))
 \end{aligned}$$

The semi-relative sensitivity solutions are calculated by simply multiplying the unmodified sensitivity solutions by a chosen parameter which provides information concerning the amount the state will change when that parameter is doubled (i.e., a perturbation on the order of ‘b’). It is best to calculate this type of sensitivity solution to obtain a more thorough understanding of the dynamics.

V. Variation Iteration Method

The VIM method has been employed to solve a large variety of linear and nonlinear problems with approximations converging rapidly to accurate solutions. Some advantages of this technique are

1. The initial condition can be chosen freely with some unknown parameters.
2. The unknown parameters in the initial condition can be easily identified.
3. The calculation is simple and straightforward.

This approach is successfully and effectively applied to various equations, see for example [5,6,9].

The VIM transforms the differential equation to a recurrence sequence of functions and the limit of the sequence, if exists, is considered as the solution of the differential equation. Consider the following differential equation

$$Lu(t) + Mu(t - r_i) = g(t), \tag{19}$$

Where L is a linear operator, M is a known analytic function, r_i is the delay term and $g(t)$ is an inhomogeneous term. Given an initial guess $u_0(t)$, a correctional functional as

$$u_{n+1}(t) = u_n(t) + \int_0^t \lambda(\xi)(Lu_n(\xi) + M \hat{u}_n(\xi - r_i) - g(\xi))d\xi \quad n \geq 1, \tag{20}$$

Is made, where λ is a general Lagrangian multiplier [5,6] which can be identified optimally via the variational theory and the function u_n is a restricted variation which means $\delta \hat{u}_n = 0$. After determining the Lagrange multiplier λ and selecting an appropriate initial function u_0 , the successive approximation u_n of the solution can be readily obtained [9]. Consequently, the exact solution may be obtained by using

$$u = \lim_{n \rightarrow \infty} u_n(t).$$

Now, to illustrate how to find the value of the Lagrange multiplier λ , we will consider the following case, which is dependent on the order of the operator L in (20), we will study the case operator $L = \frac{d}{dt}$ (without loss of generality).

Making the above correction functional stationary, and noticing that means $\delta \hat{u}_n = 0$, we obtain

$$\begin{aligned}
 \delta u_{n+1}(t) &= \delta u_n(t) + \delta \int_0^t \lambda(\xi)(Lu_n(\xi) + M \hat{u}_n(\xi - r_i) - g(\xi))d\xi \\
 &= \delta u_{n-1} + \lambda(\xi)\delta u_{n-1} |_{\xi=t} - \int_0^t \lambda'(\xi)(\delta u_{n-1})d\xi = 0
 \end{aligned}$$

Where $\delta \hat{u}_n$ is considered as a restricted variation i.e., $\delta \hat{u}_n = 0$, yields the following stationary conditions

$$\lambda'(\xi) = 0, \quad 1 + \lambda(\xi) |_{\xi=t} = 0, \tag{21}$$

This equation is known as Lagrange - Euler equation with natural boundary condition. The solution of this equation gives the Lagrange multiplier $\lambda(\xi) = -1$. Now, the following variational iteration formula can be obtained

$$u_{n+1}(t) = u_n(t) - \int_0^t (Lu_n(\xi) + M \hat{u}_n(\xi) - g(\xi))d\xi \tag{22}$$

We start with an initial approximation, and by using the above iteration formula (23), we can obtain directly the other components of the solution. The several approximations $u_n(t)$, $n \geq 0$, follow immediately, the exact solution may be obtained by

$$u(t) = \lim_{n \rightarrow \infty} u_n(t).$$

5.1 Application of VIM

The VIM is useful to obtain exact and approximate solutions for linear and nonlinear delay differential equations. It has been used to solve effectively, easily and accurately a large class of nonlinear problems with approximations. To show the efficiency of the VIM method, in this subsection, we apply the VIM to solve the following system of nonlinear delay differential equation (2).

According to the VIM, we can construct the correct functional as follows:

$$P_{n+1}(t) = P_n(t) + \int_0^t \lambda_1(\xi)[P_n'(\xi) - r_Q(N)\hat{Q}_n + r_P(N)P_n - be^{-\gamma\tau}P_n(t-\tau)]d\xi,$$

$$Q_{n+1}(t) = Q_n(t) + \int_0^t \lambda_2(\xi)[Q_n'(\xi) - r_P(N)\hat{P}_n + (\mu_Q + r_Q(N))Q_n]d\xi, \tag{23}$$

Where λ_1 and λ_2 are the general Lagrange multipliers, and \hat{P}_n and \hat{Q}_n denote restricted variations, i.e., $\delta \hat{P}_n = \delta \hat{Q}_n = 0$. Making the above correction functional stationary as,

$$\delta P_{n+1}(t) = \delta P_n(t) + \delta \int_0^t \lambda_1(\xi)[P_n'(\xi) + r_P(N)P_n(\xi)]d\xi, \tag{24}$$

And

$$\delta Q_{n+1}(t) = \delta Q_n(t) + \delta \int_0^t \lambda_2(\xi)[Q_n'(\xi) + (\mu_Q + r_Q(N))Q_n(\xi)]d\xi. \tag{25}$$

The equations (24) and (25) yield the following stationary conditions,

$$\lambda_1'(\xi) - r_P(N)\lambda_1(\xi) = 0, \quad 1 + \lambda_1(\xi)|_{\xi=t} = 0,$$

$$\lambda_2'(\xi) - (\mu_Q + r_Q(N))\lambda_2(\xi) = 0, \quad 1 + \lambda_2(\xi)|_{\xi=t} = 0. \tag{26}$$

The general Lagrange multipliers can be identified by solving the system of equations in (26), to obtain $\lambda_1(\xi) = -e^{r_P(N)(\xi-t)}$, $\lambda_2(\xi) = -e^{c(\xi-t)}$ (where $c = \mu_Q + r_Q(N)$). Substituting these values back into the correction functional equation (23) results into the following iteration formula:

$$P_{n+1}(t) = P_n(t) - \int_0^t e^{r_P(N)(\xi-t)} [P_n'(\xi) - r_Q(N)\hat{Q}_n + r_P(N)P_n - be^{-\gamma\tau}P_n(t-\tau)]d\xi,$$

$$Q_{n+1}(t) = Q_n(t) - \int_0^t e^{c(\xi-t)} [Q_n'(\xi) - r_P(N)\hat{P}_n + (\mu_Q + r_Q(N))Q_n]d\xi. \tag{27}$$

We start with initial approximations $P_0 = P(0), Q_0 = Q(0)$ from [7]. We obtained the value of $P_{n+1}(t)$, from the first equation of (27) and the value of $Q_{n+1}(t)$ from the second equation of (27), this increases the convergence rate. By the above iteration formula (28), we can obtain a few first terms being calculated.

Continuing this manner, the rest of components of the iteration formulas can be obtained using packages such as Maple. In our case, only three terms from the iteration formula are used to obtain the approximation for our solutions.

VI. Conclusion

In this paper we presented a model using delay differential equations to describe the dynamics of tumour growth with Quiescence cells. Here we are investigating the stability of two equilibrium for delay differential equations. From this model, we showed that the intrinsic rate of proliferating cells we can control the tumour cells. Therefore, total number of tumour cells depend only on proliferating cells. Special emphasis, was given to investigate the sensitivity of the proliferating and quiescent cells due to perturbing the parameters

appearing in the model and the initial conditions of the model using direct approach. Here the parameter 'b' plays a vital role this model. Using He's variational iteration method has been successfully applied to find the approximate solution of nonlinear delay differential equations. We can find that VIM method is extremely efficient to solve this biological model. From the solutions obtained using the suggested method we can conclude that these solutions are in excellent agreement with the exact solution and show that these approaches can solve the problem effectively.

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