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Stability Analysis For Tumour Growth Model Through The Lambertz W Function

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Abstract

In this paper we investigate the stability of the tumor growth system. An approach of the matrix Lambert W function for the analytical solution to system of delay differential equations is applied to this problem and compared with the result obtained by a bifurcation analysis.

Keywords: Delay differential equations; Tumor-growth; Stability; Bifurcation.

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1 INTRODUCTION

Delay differential equations were initially introduced in the 18th century by Laplace and Condorcet [1]. However, the rapid development of the theory and applications of those equations did not come until after the Second World War, and continues today. Delay differential equations are often solved using numerical methods, asymptotic solutions, and graphical tools [2].

A recent related study on analytic solution of linear DDEs can be found in [3]. A Fourier-like analysis of the existence of the solution and its properties for the non linear DDEs is studied by Wright [4]. Similar approaches to linear and non linear DDEs are also reported by Bellman [5]. The uniqueness of the solution and its properties for the linear DDEs with varying coefficients is studied by Wright [4]. Solution properties for the linear DDEs with asymptotically constant coefficients are also studied by Wright in [6].

The Lambert W function, known to be useful for solving scalar first-order DDEs, has recently been extended to a matrix Lambert W function approach to solve systems of DDEs. The essential advantages of the matrix Lambert W approach are not only the similarity to the concept of the state transition matrix in linear ordinary differential equations, enabling its use for general classes of linear delay differential equations, but also the observation that we need only the principal branch among an infinite number of roots to determine the stability of a system of DDEs.

We specify the dynamics of tumour growth model [7,8] introduced the delay between the different rates at which cell cycle or reproduction. The cell cycle process can be obtained from [7, 8]. The cell cycle is the process between two cell divisions (or mitosis) [9, 10], and it can be divided into 4 phases: the G_1 phase is a resting phase(or gap period) called pre-synthetic phase. G_1 could last as long as 48 hours and is the longest phase of the cycle. The next phase is the S phase or synthetic period, where the replication of DNA occurs. This phase may last between 8 and 20 hours. The cells complete the DNA replication and enter another gap period G_2 called the post-synthetic phase. G_2 is a preparation phase for mitosis. The last phase is mitosis M in which the cells segregate the duplicated sets of chromosomes between daughter cells. Mitosis is shortest phase of all, lasting up to one hour.

In this work we exclude the quiescent phase. This assumption is a simplification of the model whose effect will be worth exploring in more detail in future work since it is known that the cells in this phase are resistant to most cytotoxic agents and that approximately only 20% of the cells are cycling [11]. We assume that the drug is cytotoxic to both immune system (which interacts with tumour cells a any stage of their cycle) and the tumour cells. The drug acts on the different stages of cycle have modelled and the inclusion of the immune system in mathematical model and also the importance of DDE have studied by [12-14]. This assumption comes from the fact that cycles specific drugs are more cytotoxic to rapidly proliferating cells including those in the bone marrow, among others. We will assume that the drugs arrest tumour cells in mitosis, and that the concentration of drug decays exponentially with time. Since mitosis is short comparison with the rest of the cycle we will assume that mitosis is an instantaneous process. And the stability of this model can be obtained from the characteristic equations of the linear DDEs [7].

In this paper we presented a new approach to solve the transcendental characteristic equation of a system of DDEs, based upon a class of function called Lambert W function. Also we analyses the stability of the system via the matrix Lambert W function and compared with the bifurcation techniques.

2 DDE TUMOUR GROWTH MODEL

In the absence of immune response, the general model [7] described for tumour growth as follows:

$$T_I' = 2a_4 T_M - (d_2 + a_1) T_I,$$

$$T_M' = a_1 T_1 - d T_M \qquad (1)$$

This is linear system with the only fixed point being ($T_I(t)$, $T_M(t)$) = (0,0) and $d = d_3 + a_4$. where $T_I(t)$ denote the population of tumour cells during inter-phase at time t, and inter-phase is the pre-mitotic phase and let $T_M(t)$ be the tumour population during mitosis at time t, the terms $d_2 T_I$,d in the model equation represent proportions of natural cell death or apoptosis, a_1 and a_4 represent the different rates at which cells cycle or reproduce.

The terms T_M and T_I are standard competitions terms that in our model will represent losses due to encounters among the different cell types. For high concentrations of drug we know that the drug arrest tumour cells in mitosis where they die naturally when they fail to continue in the cycle. One way to view this is by assuming that once the drug encounters the tumour cell, the tumour cell is taken out of the cycle and can no longer proliferate.

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Table I: Parameter Values and Range

Parameter	Estimated value	Source and Comments
τ	22 hr.(0.9167 days)	[17] Mitosis is considered instantaneous so $\tau = T_c$
a_1	0.8470 day $^{-1}$	[17] Regress on equations with no drugs, and no immune.
a_4	0.9159 day $^{-1}$	[17] Regress on equations with no drugs, and no immune.
d_2	0.1145 day $^{-1}$	[17],[15] Consider the discrepancy between T_d and T
d_3	0.6641 day $^{-1}$	[17],[15] Consider the discrepancy between T_d and T

3 DRUG-FREE SYSTEM

We first determine the type of dynamics that can arise in the system without the presence of drug. The rationale behind this is to use the information about the drug-free system when designing chemotherapeutic protocols: when we stop treatment, we would like the patient to be "cured", or to be inside the basin of attraction of the tumour free fixed point. We therefore begin by eliminating all drug terms in the model, computing the fixed points of this new drug-free system, and analysing their stability. It is also of interest to study how the delay τ affects the behaviour of our system and how each element contributed to the overall stability. Here we commence a drug-free model in a delay case in the absence of immune response.

3.1 Model Description

In this model, we consider the drug-free model when $\tau > 0$ in the absence of immune response then we've,

$$T_I' = 2a_4 T_M - d_2 T_I + a_1 T_I(t-\tau)$$

$$T_M' = a_1 T_I(t-\tau) - dT_M \qquad (2)$$

As before the only fixed point of this system is the point (0,0). The determination of stability in this case of a DDE is analogous to the ODE case: we linearise the system around the fixed point and consider exponential solutions which are characterized by the eigen values or exponents of these solutions. These eigen values are the roots of the characteristic equation of the system, which in general has infinitely many solutions (for more details on DDE refer to [5] or Hale and lunel [22]). The characteristic equation of (2) as follows,

$$[(\lambda + d)(\lambda + d_2 + a_1 e^{-\lambda\tau})] - 2a_1 a_4 e^{-\lambda\tau} = 0. \qquad (3)$$

It is equivalent to the following transcendental equation,

$$\lambda^2 + (d + d_2)\lambda + dd_2 + e^{-\lambda\tau}(a_1\lambda + (a_1 d - 2a_1 a_4)) = 0 \qquad (4)$$

Rewriting the above equation focusing only on the quadratic term as,

$$H(\lambda, \tau) = P(\lambda) + Q(\lambda)e^{-\lambda\tau}, \qquad (5)$$

Where,

$$P(\lambda) = \lambda^2 + (d + d_2)\lambda + dd_2$$
$$Q(\lambda) = a_1\lambda + (a_1 d - 2a_1 a_4)$$

The characteristic equation for the system (2) with no delay is

$$H_1(\lambda) = P(\lambda) + Q(\lambda) = 0. \qquad (6)$$

Since the model we consider a retarded not neutral type, P (λ) is higher order than Q(λ). This ensures that $\tau \to 0$, [16] n of the roots of equation (5) tend towards the roots of equation (6) while the remaining have real parts tending to large negative values. Hence as $\tau \to 0$, the stability properties of equilibrium points in the non-delay model equation (1) are recovered.

4 SOLVING DDES USING THE LAMBERT W FUNCTION

The linearised tumour growth equation can be expressed in state space as,

$$\dot{x}(t) + Bx(t-\tau) + Cx(t) = 0. \tag{7}$$

where,

$$B = \begin{bmatrix} -a_1 & 0 \\ a_1 & 0 \end{bmatrix} C = \begin{bmatrix} -d_2 & 2a_4 \\ 0 & -d \end{bmatrix}.$$

Defining $x=\{T_I,T_M\}^T$, where T indicates transpose. B and C are the linearised coefficient matrix of the tumour growth model and are functions of in vitro model parameters. Also in this case the rank of B is one.

The analytical method to solve scalar DDEs and system of DDEs as in equation (7) using the matrix Lambert W function was introduced by Asl and Ulsoy [18] but is exact only in the case where the matrices B and C are commute.

We assume the solution for equation (7) is of the form as,

$$x(t) = e^{\alpha t} x_0, \tag{8}$$

Where α is an n×n matrix. The characteristic equation for equation(7) is obtained from the equation (2) looking for non-trivial solution of the form βe^{at} where a is a scalar variable and β is a constant [21]. However, such an approach can neither lead to any interesting result nor help in deriving a solution to a systems of DDEs in (7). Alternatively, one could assume the form of equation(8) to derive the solution to system of DDEs in equation (7) using the matrix Lambert W function.

Substituting equation (8) into equation (7) yields,

$$\alpha e^{\alpha t} x_0 + B e^{\alpha t} e^{-\alpha \tau} x_0 + C e^{\alpha t} x_0 = 0. \tag{9}$$

It can be rewritten as

$$(\alpha + B e^{-\alpha \tau} + C) e^{\alpha t} x_0 = 0. \tag{10}$$

Because the matrix α is a inherent characteristic of a system and independent of initial condition, we can conclude that for equation (9) to be satisfied for any arbitrary initial condition x_0, and for every time t, we must have,

$$\alpha + C = -B e^{-\alpha \tau}. \tag{11}$$

In the special case that B = 0, the delay term in equation (8) disappears, then the DDEs changes into ODEs and equation (10) becomes,

$$\alpha = - C.$$

Substituting the value of α into equation (8), we get,

$$x(t) = e^{-Ct} x_0. \tag{12}$$

It is known as typical solution of ODEs in terms of the matrix exponential. Multiply $\tau e^{\alpha \tau} e^{C\tau}$ on both sides of equation (11) and rearrange then we have,

$$\tau(\alpha + C) e^{\alpha \tau} e^{C\tau} = -B\tau e^{C\tau}. \tag{13}$$

In the general case, when the matrices B and C don't commute, neither do α and C [23]. Thus

$$\tau(\alpha + C) e^{\alpha \tau} e^{C\tau} \neq \tau(\alpha + C) e^{(\alpha + C)\tau}. \tag{14}$$

The definition of the matrix Lambert W function is

$$W(S) e^{W(S)} = S \tag{15}$$

We introduce an unknown matrix M so that satisfies,

$$\tau(\alpha + C)e^{(\alpha+C)\tau} = -B\tau M \quad (16)$$

Comparing equation (14) and equation (15), we have,

$$\tau(\alpha + C) = W(-B\tau M) \quad (17)$$

Then from equation (16) we obtain,

$$\alpha = \frac{1}{\tau}W(-B\tau M) - C \quad (18)$$

Substituting equation (17) into equation (13), yields the following condition which can be used to solve for the unknown matrix M,

$$W(-B\tau M)e^{W(-B\tau M)} = -B\tau e^{C\tau} \quad (19)$$

In the many examples we have studied, (23) always has a unique solution M_k for each branch, k. The solution is obtained numerically, for a variety of initial conditions, using the `fsolve' function in Matlab. The matrix Lambert W function defined in (15) contains an infinite number of branches [24] corresponding to each branch, k (=−∞, ∞) of this function for S_k = -BτM_k. We compute the characteristic values λ_{ki}, i = 1,2 of S_k and the corresponding characteristic vector matrix V_k. Hence, the matrix Lambert W function is

$$W_k(S_k) = V_k \begin{pmatrix} W_{k(\lambda_{k1})} & 0 \\ 0 & W_k(\lambda_{k2}) \end{pmatrix} V_k^{-1} \quad (20)$$

Finally,α_k is computed corresponding to W_k from equation(18) and summed to be the solution to the system of DDEs (7) as ,

$$x(t) = \sum_{k=-\infty}^{\infty} \beta_{ke}{}^{\alpha_k \tau} \quad (21)$$

Where β_k is the 2×1 coefficient matrix computed from a given preshape function x(t) = g(t), which is initial state of DDEs (7), for $t \in [-\tau, 0]$ [25]. Each branch of the Lambert W function can be computed analytically as shown in [24]

5 STABILITY BY THE LAMBERT W FUNCTION

Now we apply the matrix Lambert W function to the equation (2). Assume, the unknown matrix M in equation(19) as,

$$M = (m_{ij})_{2\times 2} \quad (22)$$

The argument of the Lambert W function, " - BτM" from the matrix B with equation(22) is,

$$-B\tau M = \begin{pmatrix} \gamma m_{11} & \gamma m_{12} \\ -\gamma m_{11} & -\gamma m_{12} \end{pmatrix} \quad (23)$$

The characteristic value of equation (23) is, $\lambda_1 = \gamma m_{11} - \gamma m_{12}$; $\lambda_2 = 0$;

Hence the corresponding characteristic vector matrix V and the respective diagonal matrix d are,

$$V = \begin{pmatrix} 1 & -1 \\ \frac{m_{22}}{m_{21}} & 1 \end{pmatrix}$$

$$d = \begin{pmatrix} \gamma m_{11} - \gamma m_{12} & 0 \\ 0 & 0 \end{pmatrix}$$

Then we have one characteristic values are zero. This point makes the system of equation unusual, because of the following property of the Lambert W function [24].

$$W_k(0) = \begin{cases} 0, & when\ k = 0 \\ -\infty, & when\ k \neq 0 \end{cases} \quad (24)$$

Because of the property in contrast to the typical case [25] where identical branches (k1 = k2) are used in equation (20), here it is necessary to use hybrid branches ($k_1 \neq k_2$) of the matrix Lambert W function defined as

$$W_{k1,k2}(-B\tau M) = V \begin{pmatrix} W_k(\gamma m_{11} - \gamma m_{12}) & 0 \\ 0 & W_{k2}(0) \end{pmatrix} V^{-1} \quad (25)$$

By setting $k_2 = 0$ and varying only k_1 from $-\infty$ to ∞, we can solve (19) to get $M_{k1,0}$; then using equation(18), we determine the transition matrices of the system equation(7).

Using the various commercial software packages, such as Maple, Matlab, Mathematica, we can plot the characteristic values which is obtained by the principal branch that are closest to the imaginary axes and determine the stability of the

system.

Therefore,

Re { characteristic values for $k_1 = k_2 = 0$ } $\geq$ Re { all other characteristic values }.

For the scalar DDE case, it has been proven that the root obtained using the principal branch always determines stability [26], and such a proof can readily be extended to systems of DDEs where B and C commute. That is, the eigen values of $\alpha_{0,0}$, obtained using the principal branch for each of k_1, and k_2 are closest to the imaginary axis, and their real parts are negative.

Furthermore, using additional branches to calculate the characteristic values always yields characteristic values whose real parts are further to the left in the plane. Thus, we conclude that the system is stable.

6 BIFURCATION ANALYSIS

The bifurcation analysis prescribed here provides a useful algorithm for determining the stability of the DDEs. Substitute $\lambda = iv, v \in R$ in equation (3) looking for the purely imaginary roots.

The characteristic equation (5) becomes,

$$P(iv) + Q(iv)e^{-iv\tau} = 0 \tag{26}$$

After a little algebraic computation, we obtain,

$$\left(R_1(v) + iC_1(v)\right) + \left(R_2(v) + iC_2(v)\right)(\cos v\tau - i \sin v\tau) = 0 \tag{27}$$

i.e.,

$$R_1(v) + R_2(v)\cos(v\tau) + C_2(v)\sin(v\tau) = 0$$

$$C_1(v) - R_2(v)\sin(v\tau) + C_2(v)\cos(v\tau) = 0$$

where,

$$R_1(v) = -v^2 + dd_2\,;\; R_2(v) = a_1 d - 2a_1 a_4$$

$$C_1(v) = vd + vd_2\,, C_2(v) = a_1 v$$

Squaring and adding the above equations, we get,

$$\left(R_1(v)\right)^2 + \left(C_1(v)\right)^2 = \left(R_2(v)\right)^2 + \left(C_2(v)\right)^2 \tag{28}$$

Here the delay α term has been eliminated. By defining new variable $\mu = v^2$, equation(27) can be written in terms of μ as

$$\varphi(\mu) = \mu^2 + \left(d^2 + {d_2}^2 - {a_1}^2\right)\mu + (dd_2)^2 + (a_1 d - 2a_1 a_4)^2 \tag{29}$$

If all the roots of equation (29) are negative, there can be no simultaneous solution v^* of equation (27). Conversely, if there is positive real parts of equation (29), then there is a delay τ^* corresponding to $v^* = \pm\sqrt{\mu^*}$ which solves both equations in equation (27). This provides an analytic method to determine the exact values of delay τ^* that cause bifurcation. The characteristic equation (5) has negative roots in left-half plane at initial condition and in the region under the borderline no bifurcation occurs. Therefore, the region under the borderline is a stable one. At the bifurcation point the root crosses the imaginary axis of the complex plane if and only if

$$R_1(v^*)R_1'(v^*) + C_1(v^*)C_1'(v^*) \neq R_2(v^*)R_2'(v^*) + C_2(v^*)C_2'(v^*) \tag{30}$$

The point satisfies this condition therefore, the right side is a stable region, and the left side is an unstable region.

7 CONCLUSION

In this paper, two new approaches for the stability analysis of tumour growth dynamical problems, which can be expressed as systems of linear delay differential equations, have been presented using the matrix Lambert function and a bifurcation analysis. The main advantage of the analytical approach based on the matrix Lambert function lies in the fact that one can obtain the solution to systems of linear DDEs in the time domain, and the solution has a form analogous to the state transition matrix in systems of linear ordinary differential equations. It can be applied to systems of linear DDEs of arbitrary order, and thus can be used in tumour growth models that include multiple structural vibration models. Though the solution is in the form of an infinite series of modes computed with different branches, we observe that the principal branch always determines the stability of a system. Therefore, it appears that one has only to check the solution using the principal branch to determine the stability of the system. This method is very useful to study the stability of the tumour growth dynamical problem.

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