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Numerical Analysis on Growth of Angiogenesis Cancer with delay differential equations

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Abstract:A mathematical model presented with the help of delay differential equations and a systematic study of the growth on angiogenesis cancer. This model is investigated using stability theory as well as equilibria. Using the theory of delay differential equations and the basic reproduction R_0 is a measure of the potential for disease spread in a population. We observe that the growth of cancer infection free equilibrium is unstable because the basic reproduction number $R_0 < 1$.

Keywords: Differential Equations, Angiogenesis cancer

Introduction:A tumor is an abnormal growth of unwanted body cells. Tumors caused by uncontrolled cleavage and development in cells can be recognized by the immune system.Cancer refers to a quite number of different diseases characterized by DNA damage that causes abnormal cell growth. The malignant cancer cells have two important roles: first, they can no longer be divisible or differentiated normally; second, they can invade surrounding tissues and go to distant places in the body. The healthy body is well equipped to defend itself against cancer. Cancer can occur when the immune system and other defence mechanisms fail [Ucar, E et al. 2019].Orme, M. E., & Chaplain, M. A. J. (cancer cells are different from normal cells in terms of cell size, shape, number, differentiation, function, and ability to move to distant tissues1997), the most common types of cancer are carcinomas (cancers of epithelia), which are solid tumours of the internal and external surfaces of tissues and organs. So, the disease cannot be cured by treating the primary tumour alone. Widespread metastases can be difficult to treat, and they often prove fatal. **Peirce et. al. (2008)** overviewed different types of mathematical and computational modelling approaches that have been employed in the study of angiogenesis and summarized an array of published

models aimed at answering different questions relevant to angiogenesis-related processes. They also discussed some of the challenges associated with constructing and utilizing mathematical and computational angiogenesis models. **Dixit et al. (2012)**developed a modeling framework for studying avascular tumor growth with the effect of dose of the Adriamycin. The numerical simulation mainly involved the study of the effects on tumor cell survival of the dimensionless parameter which encapsulates the extent of penetration of the drug. They had introduced a tumor cell energy model and used tumor cell density with the effect of Adriamycin to describe the movement of tumor cells. Vaghi, C. et al. 2020Mathematical models for tumor growth kinetics have been widely used since severaldecades but mostly fitted to individual or average growth curves. Here we compared threeclassical models (exponential, logistic and Gompertz) using a population approach, whichaccounts for inter-animal variability. The exponential and the logistic models failed to fitthe experimental data while the Gompertz model showed excellent descriptive power.**Bodnaret. al. (2016)** proposed a family of angiogenesis models that is a generalisation of the Hahnfeldt et al. model. Considered family of models consists of two differential equations with distributed time delays. The global existence and the uniqueness of the solutions are proved. **Gabriella Bretti et al. 2021,** Recruitment of immune cells to a tumor is a key parameter in cancer prognosis and response to therapy and the complex relationship between cellular, noncellular components and secreted chemotactic factors plays an essential role in directing the migration of both activating and suppressive immune cell types. Moreover, in order to better analyze the short-range dynamics and interactions between tumor and immune cells, we restricted our study on a subarea of the left chamber of length and height equal to 200μm. The main reason for considering only a portion of the chip is motivated by:

- the reduction of the computational cost in view of the optimization procedure for the parameter estimation;
- the focus on short-range interactions.

As mentioned above, we assume the presence of forces between cells, which are established due to the chemoattractant and due to the nature of the cells itself. Such a model includes a classical reaction-diffusion partial differential equation (PDE) used to describe the evolution of the concentration of chemicals released by TCs in the tumor milieu, coupled with ordinary differential equations (ODEs) for the inter-cellular dynamics of ICs, which establishes both due to the presence of the chemoattractant and to the forces generated between the cells.**Mahardika et al. 2019**, consider the given polynomial is,$P(\lambda) = \lambda^n + a_1\lambda^{n-1} + \ldots +$

$a_{n-1}\lambda + a_n$,Where the coefficients $a_i; i = 1,2,\ldots,n$, are all real constants. Using these coefficients, construct the form Hurwitz matrices $H_j;\ j = 1,2,..,n$ for the given system of equations as:

$$H_1 = (a_1), H_2 = \begin{pmatrix} a_1 & 1 \\ a_3 & a_2 \end{pmatrix},$$

$$H_3 = \begin{pmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{pmatrix} \text{ and}$$

$$H_n = \begin{pmatrix} a_1 & 1 & 0 & & 0 \\ a_3 & a_2 & a_1 & \cdots & 0 \\ a_5 & a_4 & a_3 & & 0 \\ & \vdots & & \ddots & \vdots \\ 0 & 0 & 0 & \cdots & a_n \end{pmatrix}$$

For all $i > n,\ a_j = 0$.

All roots of the polynomial $P(\lambda)$ are negative or have negative real part iff the determinants of all Hurwitz matrices are positive as: $\det(H_j) > 0,\ j = 1,2,..,n$.For the polynomials of degree n = 2, 3, 4 and 5, the Routh-Hurwitz criterion is summarized as:

For $n = 2$: $a_1 > 0\ and\ a_2 > 0$.

For $n = 3$: $a_1 > 0, a_3 > 0\ and\ a_1a_2 > a_3$.

For $n = 4$: $a_1 > 0, a_3 > 0, a_4 > 0\ and\ a_1a_2a_3 > a_3^2 + a_1^2a_4$.

For $n = 5$: $a_i > 0; i = 1,2,3,4,5, a_1a_2a_3 > a_3^2 + a_1^2a_4$ and $(a_1a_4 - a_5)(a_1a_2a_3 - a_3^2 -$ a12a4>[a5(a1a2−a4)2+a1a52] and so on.TheRouth Hurwitz matrix of a stable polynomial satisfying, if $f(0) > 0$ is totally nonnegative.

Base Model for Cancer: De Pillis et al. 2003 has given a model on cancer model. In this model the study is on the interaction between the normal cells and the cancer cells. The governing equation of the model are given as

$$\frac{dI}{dt} = s + \frac{\rho IT}{\alpha + T} - c_1IT - d_1I$$

$$\frac{dT}{dt} = r_1T(1 - b_1T) - c_2IT - c_3TN$$

$$\frac{dN}{dt} = r_2N(1 - b_2N) - c_4TN$$

Where I(t) denote the density of immunity cells at time t, T(t) the density of cancer cells at time t, and N(t) the density of normal cells at time t. The term $\frac{\rho IT}{\alpha+T}$ express the immune system response due to the cancer cells. d_1 is the death rate of healthy cells. $r_1, r_2$are the growth rate for the cancer cells and normal cells in the body respectively. b_1, b_2 shows the

inverse of the carrying capacity for the tumour cells and normal cells and c_1, c_2, c_3, c_4 all are the competition coefficients.

Improved Model: De Pillis et al. 2003 has given a model on cancer model. In this model the study is on the interaction between the normal cells and the cancer cells. The governing equation of the model are given as

$$\frac{dI}{dt} = s + \frac{\rho I(t-\tau)T(t-\tau)}{\alpha + T(t-\tau)} - c_1 I(t-\tau)T(t-\tau) - d_1 I(t-\tau) \quad (1)$$

$$\frac{dT}{dt} = r_1 T(t-\tau)(1 - b_1 T(t-\tau)) - c_2 I(t-\tau)T(t-\tau) - c_3 T(t-\tau)N \quad (2)$$

$$\frac{dN}{dt} = r_2 N(1 - b_2 N) - c_4 T(t-\tau)N \quad (3)$$

Where $I(t-\tau)$ denote the density of immunity cells at time t with delay, $T(t-\tau)$the density of cancer cells at time t with delay, and N(t) the density of normal cells at time t. The term $\frac{\rho IT}{\alpha + T}$ express the immune system response due to the cancer cells. d_1 is the death rate of healthy cells. $r_1, r_2$are the growth rate for the cancer cells and normal cells in the body respectively. b_1, b_2 shows the inverse of the carrying capacity for the tumour cells and normal cells and c_1, c_2, c_3, c_4 all are the competition coefficients.

Where the parameters and variables are defined as:

S.No.	Parameters and Variables	Explanation of parameters and variables	Values [Ref]
1	I	Immune cells	0.1 [5]
2	T	Tumour cells	1.0 [4]
3	N	Normal cells	1
4	t	Time	1 – 7 days
5	ρ	Positive constant (0.1 – 2.0)	1
6	α	Growth of fat cells	25
7	μ	Growth of normal cells	0.1 [10]
8	r_1	Intrinsic growth of T cells	10 [10]
9	r_2	Intrinsic growth of N	20 [10]
10	τ_1	Daley bifurcation/incubation for immunity	0.1 [5]
11	τ_2	Daley bifurcation/incubation for tumour	0.15 [5]
12	d_1	Death rate	1 [5]
13	b_1	Inhabiting effect on the growth of T	0.2 [5]
14	b_2	Inhabiting effect on the growth of N	0.51
15	C_1	Capturing rate (range 0.60 – 0.93)	0.6
16	C_2	Conversion rate (low or high i.e. 0.25 or 2.5)	0.25
17	C_3	Positive constant	1
18	C_4	Positive constant	1

Numerical Analysis:

i. Disease Free Equilibrium (DEE) points: H_0

We have $\frac{dI}{dt} = \frac{dT}{dt} = \frac{dN}{dt} = 0$ (4)

When $I = 0$ that is in absence of tumor cells means infection. The DEE (H_0) is given by

$$H_0 = \left(\frac{s}{d_1}, 0,0\right)$$

ii. The Jacobian of the governing equation is given by J for stability and defined by

$J =$

$$\begin{pmatrix} \frac{\rho T(t-\tau)}{\alpha+T(t-\tau)} - c_1 T(t-\tau) - d_1 & \frac{\alpha\rho I(t-\tau)}{(\alpha+T(t-\tau))^2} - c_1 I(t-\tau) & 0 \\ -c_2 I(t-\tau) & r_1 - 2r_1 b_1 T(t-\tau) - c_2 I(t-\tau) - c_3 N & -c_3 T(t-\tau) \\ 0 & -c_4 N & r_2 - 2r_2 b_2 N - c_4 T(t-\tau) \end{pmatrix} \quad (5)$$

The characteristic equation is given by $|J - \lambda I_3| = 0$ that is

$$\lambda^3 + B_1\lambda^2 + B_2\lambda^1 + B_3 = 0 \quad (6)$$

Where B's are defined as:

$B_1 = -(A + G + D)$

$B_2 = -(BC + EF - AG - AD - DG)$

$B_3 = -(ADG - AEF - BCG)$

Also, A, B, C, D, E, F, G are defined as below:

$A = \frac{\rho T(t-\tau)}{\alpha+T(t-\tau)} - c_1 T(t-\tau) - d_1,$

$B = \frac{\alpha\rho I(t-\tau)}{(\alpha+T(t-\tau))^2} - c_1 I(t-\tau),$

$C = -c_2 I(t-\tau),$

$D = r_1 - 2r_1 b_1 T(t-\tau) - c_2 I(t-\tau) - c_3 N,$

$E = -c_3 T(t-\tau),$

$F = -c_4 N,$

$G = r_2 - 2r_2 b_2 N - c_4 T(t-\tau).$

By using Routh – Hurwitz criterion, we conclude that all the roots of characteristic equation (6) will have negative real roots. Here, the conditionsfor $n = 3$: $B_1 > 0, B_3 > 0$ *and* $B_1 B_2 > B_3$is not satisfied. Then, the given system is not asymptotically stable that is unstable.

iii. Singular Points: There are three singular points E_0, E_1 *and* E_3.

$$E_0 = (0,0,0)$$

$$E_1 = \left(0, \frac{1}{b_1}, 0\right)$$

$$E_2 = \left(0,0, \frac{1}{b_2}\right)$$

iv. Stability Analysis

At a first singular point $E_0 = (0,0,0)$ the Jacobian matrix (6) is given by

$$J_{E_0} = \begin{pmatrix} -d_1 & 0 & 0 \\ 0 & r_1 & 0 \\ 0 & 0 & r_2 \end{pmatrix}$$

The characteristic equation is given by $|J_{E_0} - \lambda I| = 0$

$$\begin{vmatrix} -d_1 - \lambda & 0 & 0 \\ 0 & r_1 - \lambda & 0 \\ 0 & 0 & r_2 - \lambda \end{vmatrix} = 0$$

After solving we get the following characteristic roots, that is $\lambda_1 = -d_1 < 0, \lambda_2 = r_1 > 0,$ and $\lambda_3 = r_2 > 0.$ (8)

At a second singular point $E_1 = (0, \frac{1}{b_1}, 0)$ the Jacobian matrix (6) is given by

$$J_{E_1} = \begin{pmatrix} \frac{\rho\left(\frac{1}{b_1}\right)}{\alpha + \left(\frac{1}{b_1}\right)} - c_1\left(\frac{1}{b_1}\right) - d_1 & 0 & 0 \\ 0 & -r_1 & -c_3\left(\frac{1}{b_1}\right) \\ 0 & 0 & r_2 - c_4\left(\frac{1}{b_1}\right) \end{pmatrix}$$

The characteristic equation is given by $|J_{E_1} - \lambda I| = 0$

$$\begin{vmatrix} \frac{\rho\left(\frac{1}{b_1}\right)}{\alpha + \left(\frac{1}{b_1}\right)} - c_1\left(\frac{1}{b_1}\right) - d_1 - \lambda & 0 & 0 \\ 0 & -r_1 - \lambda & -c_3\left(\frac{1}{b_1}\right) \\ 0 & 0 & r_2 - c_4\left(\frac{1}{b_1}\right) - \lambda \end{vmatrix} = 0$$

After solving we get the following characteristic roots, that is $\lambda_1 = \frac{\rho\left(\frac{1}{b_1}\right)}{\alpha + \left(\frac{1}{b_1}\right)} - c_1\left(\frac{1}{b_1}\right) - d_1, \lambda_2 = -r_1,$ and$\lambda_3 = r_2 - c_4\left(\frac{1}{b_1}\right).$

At a third singular point $E_2 = (0,0,\frac{1}{b_2})$ the Jacobian matrix (6) is given by

$$J_{E_2} = \begin{pmatrix} -d_1 & 0 & 0 \\ 0 & r_1 - c_3\left(\frac{1}{b_2}\right) & 0 \\ 0 & -c_4\left(\frac{1}{b_2}\right) & -r_2 \end{pmatrix}$$

The characteristic equation is given by $|J_{E_2} - \lambda I| = 0$

$$\begin{vmatrix} -d_1 - \lambda & 0 & 0 \\ 0 & r_1 - c_3\left(\frac{1}{b_2}\right) - \lambda & 0 \\ 0 & -c_4\left(\frac{1}{b_2}\right) & -r_2 - \lambda \end{vmatrix} = 0$$

After solving we get the following characteristic roots, that is $\lambda_1 = -d_1\lambda_2 = r_1 - \frac{c_3}{b_2}$, and $\lambda_3 = -r_2$.

At each singular point, some eigen values are positive and other are negative. In that situation the system will be semi-stable.

And eigen values are discussed also with delay in the following Lemma:

v. Lemma 1:

Let P be an exponential polynomial

$$\begin{aligned} P\left(\lambda, e^{\lambda\tau_1}, e^{\lambda\tau_2}, e^{\lambda\tau_3}, \dots\dots e^{\lambda\tau_s}\right) \\ &= \lambda^n + p_1^{(0)}\lambda^{n-1} + \cdots\dots\dots\dots + p_{n-1}^{(0)}\lambda + p_n^{(0)} \\ &+ \left[p_1^{(1)}\lambda^{n-1} + \cdots . + p_{n-1}^{(1)}\lambda + p_n^{(1)}\right]e^{-\lambda\tau_1} \\ &+ \left[p_1^{(2)}\lambda^{n-1} + \cdots . + p_{n-1}^{(2)}\lambda + p_n^{(2)}\right]e^{-\lambda\tau_2} + \cdots \\ &+ \left[p_1^{(s)}\lambda^{n-1} + \cdots . + p_{n-1}^{(s)}\lambda + p_n^{(s)}\right]e^{-\lambda\tau_s} = 0 \end{aligned}$$

where $\tau_i \geq 0$ $(i = 0,1,2,3,\dots . . s)$ and $p_j^{(i)}(i = 0,1,2,\dots s; j = 1,2,\dots,n)$ are constants. Here, $\tau_i \geq 0$ $(i = 0,1,2,3,\dots . . s)$ very, the sum of orders of the zeros of $P\left(\lambda, e^{\lambda\tau_1}, e^{\lambda\tau_2}, e^{\lambda\tau_3}, \dots\dots e^{\lambda\tau_s}\right)$ in the open right half plane can change only if a zero appears on or crosses the imaginary axis[9]. Therefore, the study of stability of all singular points can be performed by considering time delays as a parameter in the model.

For the investigating improved tumor model with delay parameters $\tau_i \geq 0$ $(i = 1,2)$, we have to check to investigate the stability of the singular point for time delay parameters.

The conditions are given below:

Case 1: $\tau_i = 0$ $(i = 1,2)$

The characteristics equation is reduced without delay to

$\lambda^3 + B_1\lambda^2 + B_2\lambda^1 + B_3 = 0$

If the condition $B_3 > 0$. Consequently, using the Routh-Hurwitz criterion, all the eigen roots of the equation have negative real part that is $B_1 > 0, and\ B_1B_2 > B_3$.

Hence, at $\tau_i = 0$ $(i = 1,2)$, the singular point E_0 is stable.

Case 2: $\tau_1 = 0\ and\ \tau_2 > 0$.

In this case, the tumorcells instantaneously reduce the activity of immune cells, but due to delay before the immune system starts killing the tumor cells with the condition $\tau_2 > 0$.

Case 3: $\tau_1 > 0\ and\ \tau_2 > 0$. In this case, influence of the two positive delays at a singular point E*, all the roots of the characteristic's equation have the negative real roots then the growth of tumor cells will increase.

vi. Numerical Analysis of Basic Reproduction Number

The real parts of all the eigenvalues of the equation (6) are negative for all values of the delay greater than zero. From above calculation, we have the following result:

$$\mathrm{R}_0 = \frac{CI_0}{[(\alpha + T(\mathrm{t} - \tau))/\rho]} = \frac{C\rho}{(\alpha + T(\mathrm{t} - \tau))}$$

Where $I_0 = 1\ and\ C\ is\ constant.$

If basic reproduction number ($\mathrm{R}_0 < 1$), then the equilibrium condition is asymptotically unstable for all the numerical value of the delay.

Conclusion: We improved a mathematical model with the help of delay differential equations and a systematic study of the growth of tumor. This model is investigated using stability theory as well as equilibria. Using the theory of delay differential equations and the basic reproduction R_0 is a measure of the potential for disease spread in a population. We observe that the growth of tumor infection free equilibrium is unstable because the basic reproduction number$R_0 < 1$.

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