Delay-induced model for tumor–immune interaction and control of malignant tumor growth

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Abstract

The paper deals with the qualitative analysis of the solutions of a system of delay differential equations describing the interaction between tumor and immune cells. The asymptotic stability of the possible steady states is showed and the occurrence of limit cycle of the system around the interior equilibrium is proved by the application of Hopf bifurcation theorem by using the delay as a bifurcation parameter. The length of the delay parameter for preserving stability of the system is also estimated, which gives the idea about the mode of action for controlling oscillations in malignant tumor cell growth. The theoretical and numerical outcomes have been supported through experimental results from literatures. This approach gives new insight of modeling tumor–immune interactions and provides significant control strategies to overcome the large oscillations in tumor cells.

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1. Introduction

The discoveries of geneticists and cell biologists have uncovered so much of basic cell mechanisms that at least the broad outlines of how cancer cells develop and act are now becoming clear (see, reviews by Lundberg and Weinberg, 1999; Hannahan and Weinberg, 2000; Hahn and Weinberg, 2002). However, evolutionary biologists and ecologists are contributing new perspectives that may significantly affect an understanding of the clinical behavior of tumors. On the biomedical front, reasonable levels of progress have been made and are being made in the fight against the disseminated cancers and precancerous disorders. In certain instances appreciable increase has been recorded in cancer remission (Majumder and Roy, 2000). Despite these advances, however, challenges remain in detection, treatment and management of this disease, that include multidisciplinary approaches in many circumstances. The approach to systems theory suggests that the problem between the interaction of the microsystems (the tumor) and the macrosystems (the organism) should be given critical attention. Indeed the systems theoretic perspective of immunology, oncology and cancer biology has been pursued by many investigators (Belair et al., 1995; Mohler et al., 1980). Several authors have also suggested different mathematical models of the disseminated cancers, which are used to capture some essential characteristics of cancer cell kinetics (Boer et al., 1985; Boer and Hogeweg, 1986; Kirschner and Panetta, 1998; Villasana and Radunskaya, 2003; Kuang

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Efforts along these lines are now being investigated through tumor–immune interactions or immunotherapy (Keilholz et al., 1994; Hara et al., 1996; Kaempfer et al., 1996). Immunotherapy refers to the use of cytokines together with Adaptive Cellular Immunotherapy (ACI) that takes several days to become protective and are designed to remove a specific antigen or infected cells or tumor cells. There are two major branches of the adaptive immune responses: humoral immunity and cell-mediated immunity. Cell-mediated immunity (CMI) involves the production of cytotoxic T-lymphocytes (CTLs), activated macrophages, activated NK cells, and release of various cytokines in response to an antigen mediated by T-lymphocytes and does not involve any antibodies. CTLs recognize and destroy infected/tumor cells. CTLs bind to epitopes from endogenous antigens bound to Major Histocompatibility Complex (MHC-I) molecules on the surface of the infected/tumor cells and lyse the cell with perforins. Cytokines activate and deactivate phagocytes and immune defense cells; increase or decrease the functions of the different immune defense cells and promote or inhibit a variety of non-specific body defenses. One of the body’s major defenses against viruses, intracellular bacteria and cancer is the destruction of infected/tumor cells by CTLs. CTLs are able to kill these cells by inducing a programmed cell death known as apoptosis. CTLs have cytoplasmic granules that contain the proteins, perforin and granzymes. When the CTLs bind to its target, the contents of the granules are discharged by exocytosis. Perforin molecules insert themselves into the plasma membrane of target cells and this enables granzymes to enter the cell. Granzymes are serine proteases that once inside the cell proceed to cleave the precursors of caspases, thus activating them to cause the cell to self-destruct by apoptosis.

The theoretical study of tumor–immunodynamics has a long history. A good summary can be found in Preziosi (2003). Kuznetsov and Taylor (1994) presented a mathematical model of the cytotoxic T lymphocyte response to the growth of an immunogenic tumor. Through mathematical modeling Kirschner and Panetta (1998) have illustrated the dynamics between tumor cells, immune effector cells and interleukin-2 (IL-2). Their efforts explain both short-term tumor oscillations in tumor sizes as well as long-term tumor relapse. They have also explored the effects of adoptive cellular immunotherapy on tumor model and have described under what circumstances the tumor can be eliminated. Kolev (2003) presented a mathematical model, showing competition between tumors and immune system, considering the role of antibodies. The model is developed with statistical methods analogous to those of the kinetic theory and is expressed in terms of a system of integrodifferential equations. Yafia (2006a, b) studied Hopf bifurcation and stability of limit cycle in a delayed model for tumor immune system with negative immune response. The basic difference between all these models and ours is that we have classified the immune system into two subclasses, namely, the hunting cells (cytotoxic T lymphocytes) and the resting cells (T Helper cells), which reveals the underlying defence mechanism of the immune system, making it biologically more realistic and hence our system has been represented by three nonlinear differential equations.

Malignant tumors have properties of great clinical significance that are difficult to deduce and explain from first principles of their cell and molecular biology alone. All cancer cells live in an ecological system that requires them to interact with immune cells. Approaches from cell biology will define the basic properties of those relationships and to predict the outcomes of these interactions. However, such considerations are important clinically. Recently, Sarkar and Banerjee (2005) have approached the problem quite differently. The model they developed for spontaneous tumor regression and progression is an interaction between the immune cells (namely, T cells) that destroy the malignant tumor cells, that is, a prey-predator like relationship (which is a very familiar phenomenon in ecological systems). They have observed two states of T-lymphocytes cells as hunting (cytotoxic T-lymphocytes (CTLs)) and resting (T-helper cells). They have studied the system under external fluctuations and proposed certain thresholds which are helpful to control the malignant tumor growth. We have already mentioned that it is always difficult to model the actual phenomenon in the tumor–immune cell interactions. Cells which react effectively with malignant cells in combination with appropriate co-stimulation are positively selected (generated by genetic re-arrangements in developing T-cell receptors which recognize the antigen) to divide rapidly and become converted. Most of the resulting cells react to eliminate the malignant tumor cells has the antigen as part of its structure, but some of the resulting cells remain as memory cells. Most CTLs also require cytokines from helper (resting) T-cells in order to be activated efficiently. Helper T-cells release interferon gamma (which activates macrophages) and IL-2 (which stimulates T-lymphocytes into CTLs/killer cells/hunting cells). A schematic representation of the above conversion is shown in Fig. 1 (a and b). It is interesting to note that this activation process and conversion of resting (or helper) T-cells into hunting cytotoxic
T-cells are not instantaneous but followed by some time lag. This occurs due to several reasons, such as, identification of malignant cells by T-cell receptors, storing information as memory cells, processing the cytolytic information to the T-helper cell for activation and simultaneous co-stimulation, etc. All the above processes require some time interval to materialize, though small but cannot be ignored (a detailed description of the above mechanisms has been given in Wodarz et al. (1998)).

Keeping in mind the above biological scenario, we therefore modify the model of Sarkar and Banerjee (2005) using the discrete time delay in conversion of resting cells to hunting cells as well as in the growth/activation of hunting cells. The study of biolog-
ical systems with time delays have been of considerable interest for a long time (Cushing, 1977; Cooke and Grossman, 1982; MacDonald, 1985; Freedman and Gopalswamy, 1988). Time delays in connection with tumor growth also appeared in different literatures (Bodnar and Foryś, 2000a, b; Byrne, 1997; Foryś and Kolev, 2002; Galach, 2003). In this paper, we study the delay-induced modified model of Sarkar and Banerjee (2005) and compare the outcomes with the real life situations. Section 2 gives the formulation of the model in details. In Section 3, we discuss the positivity and boundedness of the solution. Estimation of system parameters is given in Section 4. Section 5 deals with the stability analysis of the system without and with delay. In Section 6, we estimate the length of the delay to preserve stability of the system. Section 7 deals with the numerical results and their biological significances and Section 8 is the conclusion.

2. Model Formulation

In the present article, we offer a modification of the model proposed by Sarkar and Banerjee (2005). We consider two prominent cellular species to model the tumor–immune interaction, namely, T cells and the malignant tumor cells. T cells can be classified into hunting cells (cytotoxic T-lymphocytes (CTLs)) and resting cells (T-helper cells). CTLs attack, destroy or ingest the malignant tumor cells. CTLs while attacking tumor cells release series of cytokines, which activates the naive CTLs that coordinate the counter attack. The resting cells cannot kill tumor cells, but they also release various cytokines which activates/stimulates the naive CTLs so that they can hunt and kill more and more malignant tumor cells. This stimulation or conversion between hunting and resting cells results in a degradation of resting cells undergoing natural growth and an activation of hunting cells. We assume the growth of both tumor cells and resting T-cells as logistic growth (Foryś and Marciniak-Czochra, 2003). We consider that the tumor cells are being destroyed at a rate proportional to the densities of tumor cells and hunting CTLs according to the law of mass action. Further, there is a loss in the hunting cells due to encounters of tumor cells following the mass action law. We assume that the resting cells are converted to the hunting cells either by direct contact with them or by contact with cytokines produced by the resting cells (T helper cells). The activation process and conversion of resting (or helper) T-cells into hunting cytotoxic T-cells are not instantaneous but followed by some time lag. This inspires us to consider the time delay factor (τ units of time) in the conversion term (from resting to hunting state) and in the growth term of hunting cells. The above assumptions are well discussed in the introduction and in Fig. 1(b) we have shown schematically the model formulation based on the above assumptions. We also consider that once a cell has been converted, it will never return to the resting stage and active cells die at a constant probability per unit of time. This results in the following model:

\[
\begin{align*}
\frac{dM}{dt} &= r_1 M \left(1 - \frac{M}{k_1}\right) - \alpha_1 MN, \\
\frac{dN}{dt} &= \beta N Z(t - \tau) - d_1 N - \alpha_2 MN, \\
\frac{dZ}{dt} &= r_2 Z \left(1 - \frac{Z}{k_2}\right) - \beta N Z(t - \tau),
\end{align*}
\]

where \(M, N, Z\) are the number of tumor, hunting and resting cells, respectively, \(r_1, r_2(> 0)\) the growth rates of tumor cells and resting cells, respectively and \(k_1, k_2(> 0)\) are the maximum carrying or packing capacities for tumor cells and resting cells, respectively. The term \(-d_1 N\) is the natural death of the hunting cell (\(d_1\) is a positive constant). The terms \(-\alpha_1 MN\) represent loss of tumor cells due to encounter with the hunting cells, and \(-\alpha_2 MN\) that of hunting cells due to encounter with the tumor cells. Again, there is delay in conversion of resting stage to hunting stage of CTLs, which explains the term \(-\beta N Z(t - \tau)\) in the third equation. This delay in transformation also induce delay in the growth of hunting T-cells, and this justifies our claim for considering the term \(\beta N Z(t - \tau)\) in the second equation.

System (1) has to be analyzed with the initial conditions \(\phi = (\phi_1, \psi_1, \psi_2)\) defined in the space

\[
C_+ = \{\phi \in C([-\tau, 0], R_{0+}^3): \phi_1(\theta) = M(\theta), \psi_1(\theta) = N(\theta), \psi_2(\theta) = Z(\theta)\},
\]

where \(M(\theta) > 0, N(\theta) > 0, Z(\theta) > 0, \theta \in C[-\tau, 0]; C([-\tau, 0], R_{0+}^3)\) is the space of vector valued continuous functions and is a mapping from \([-\tau, 0]\) to \(R_{0+}^3\) \((R_{0+}^3 = \{(M, N, Z) \in \mathbb{R}_+^3 | M, N, Z \geq 0\})\). It can be shown that all solutions of the system in \(C_+\), remain in \(C_+\). Thus, \(C_+\) is positively invariant and it is sufficient to consider solutions in \(C_+\). In this region, the usual existence, uniqueness and continuation results hold for system (1) we are not proving these results but similar proofs can be found in Kuang (1993) for other systems. The positive invariance and boundedness of the system in this space have been discussed in Section 3.

In our study a pivotal role has been played by the parameters \(\beta\), the rate of conversion of resting cells to hunting cells and \(\alpha_1\), the rate of decay of malignant tumor
cells. We obtain the threshold values of these parameters which govern (or control) the growth of malignant tumor cell densities. In analogy to the population dynamics, it is very important to observe the persistence of the system as well as some consequences which restrict the growth. In this sense, study of positivity and boundedness of the solutions of the system around different steady states is very much needed. In our subsequent analysis we show that if the conversion rate $\beta$ does not exceed certain threshold, the dynamical behavior of the system represents the hunting cell-free equilibrium and it is a global attractor. But for management point of view, it is important to control the malignant tumor cell density and our aim is to keep it as low as possible. Enhancing conversion rate leads to existence of positive interior steady state consisting all three types of cells and in this case malignant tumor cell density can be controlled through different threshold values of the system parameters. Therefore, it is a more preferable situation and is an useful criteria for the disease management. In this paper, by studying the influence of time delay, we also show the occurrence of periodic solutions around this positive interior steady state.

3. Positivity and Boundedness

3.1. Positive Invariance

Let us put system (1) in a vector form by setting

$$X = \text{col}(M, N, Z) \in \mathbb{R}^3,$$  \hspace{1cm} (2)

$$F(X) = \begin{pmatrix} F_1(X) \\ F_2(X) \\ F_3(X) \end{pmatrix} = \begin{pmatrix} r_1 M \left(1 - \frac{M}{k_1}\right) - \alpha_1 MN \\ \beta N Z (t - \tau) - d_1 N - \alpha_2 MN \\ r_2 Z \left(1 - \frac{Z}{k_2}\right) - \beta N Z(t - \tau) \end{pmatrix},$$  \hspace{1cm} (3)

where $F : C_+ \to \mathbb{R}^3$ and $F \in C^\infty(\mathbb{R}^3)$. Then Eq. (1) becomes

$$\dot{X} = F(X(t)),$$  \hspace{1cm} (4)

where $\dot{X} = dX/dt$ and with $X_i(\theta) = X(t + \theta)$, $\theta \in [-\tau, 0]$ (Hale and Lunel, 1993). It is easy to check in Eq. (3) that, whenever we choose $X(\theta) \in C_+$ such that $X_i = 0$, then we obtain $F_i(X)|_{X_i(\theta)=0, X_i \in C_+} \geq 0$, $i = 1, 2, 3$. Due to lemma (Yang et al., 1996) any solution of Eq. (4) with $X_i(\theta) \in C_+$, say, $X(t) = X(t, X(0))$, is such that $X(t) \in \mathbb{R}^3_0$ for all $t > 0$.

Let us state the following lemmas.

**Lemma 1 (Kuang, 1993).** Consider the following equation

$$\dot{x} = ax(t - \tau) - bx(t),$$  \hspace{1cm} (5)

where $a, b, \tau > 0$; $x(t) > 0$ for $-\tau \leq t \leq 0$. We have:

(i) $\lim_{t \to +\infty} x(t) = 0$, if $a < b$;

(ii) $\lim_{t \to +\infty} x(t) = +\infty$, if $a > b$.

3.2. Boundedness of Solutions

**Lemma 2.** Assume that initial condition of (1) satisfies $\psi_1(\theta) + \psi_2(\theta) \geq k_2$, $\theta \in [-\tau, 0]$. Then either (i): $N(t) + Z(t) \geq k_2$, $M(t) \geq k_1$ for all $t \geq 0$ and therefore as $t \to \infty$, $(M(t), N(t), Z(t)) \to E_3 = (k_1, 0, k_2)$ or (ii): there exists a $t_1 > 0$ such that $N(t) + Z(t) < k_2$, $M(t) < k_1$, for all $t > t_1$. Finally (iii): if $\psi_1(\theta) + \psi_2(\theta) < k_2$, $\theta \in [-\tau, 0]$, then $N(t) + Z(t) < k_2$, $M(t) < k_1$ for all $t \geq 0$.

**Proof.** See, Appendix A.1. □

**Lemma 3.** There is a $B > 0$, such that, for any positive solution $(M(t), N(t), Z(t))$ of the system (1), $M(t) < B$ for all large $t$, where $B = \hat{k}/d_1, \hat{k} = (k_1/4r_1)(r_1 + d_1)^2 + (k_2/4r_2)(r_2 + d_1)^2$.

**Proof.** See, Appendix A.1. □

Let $\Omega$ be the following subset of $\mathbb{R}^3_{0+}$:

$$\Omega = \{(M, N, Z) \in \mathbb{R}^3 : N + Z \leq k_2, M \leq B\}.$$

**Theorem 1.** The set $\Omega$ is a global attractor in $\mathbb{R}^3_{0+}$ and it is positively invariant.

**Proof.** Due to Lemmas 2 and 3 for all initial condition in $C_+$ such that $(\phi_1(\theta), \psi_1(\theta), \psi_2(\theta)) \not\in \Omega$, $\theta \in [-\tau, 0]$, either there exists a positive time, say $T$, where $T = \max\{t_1, t^*\}$, such that the corresponding solution $(M(t), N(t), Z(t)) \in \text{int}\Omega$ for all $t > T$, or the corresponding solution is such that $(M(t), N(t), Z(t)) \to E_3(k_1, 0, k_2)$ as $t \to \infty$. But $E_3 \in \text{int}\Omega$. Hence the global attractivity of $\Omega$ in $\mathbb{R}^3_{0+}$ has been proved. □

Assume now that $(\phi_1(\theta), \psi_1(\theta), \psi_2(\theta)) \in \text{int}\Omega$. Then Lemma 2 implies that $N(t) + Z(t) < k_2$ for all $t > 0$ and also by Lemma 3 we know that $M(t) < B$ for all
large $t$. We observe that, if $(\phi_1(\theta), \psi_1(\theta), \psi_2(\theta)) \in \text{int} \Omega$, $\theta \in [-\pi, 0]$ since $\psi_1(\theta) + \psi_2(\theta) = k_2$ or $\phi_1(\theta) = B$ or both, then still the corresponding solutions $(M(t), N(t), Z(t))$ immediately enter $\text{int} \Omega$ or coincide with $E_3$.

Through this theorem we can prove the global attractivity of the system around $E_3$ and it shows the natural tendency of the system to move towards this steady state.

4. Estimation of System Parameters

To complete the development of the mathematical model and analysis, it is important to select appropriate parameter values, since they determine the dynamics of the system. In order to examine if system (1) is adequate, we have used the results of experiment on the dynamics of growth of highly malignant B Lymphoma/Leukemic cells (BCL1) in the spleen of chimeric mice (Siu et al., 1986). BCL1 has a number of advantages as a model tumor system. We consider this data, which represent the logistic growth of the tumor in the absence of an immune response. In our case, values of $r_1 = 0.18$ day$^{-1}$, $k_1 = 5.0 \times 10^6$ cells, give a predicted growth curve that closely approximates the data and these estimated values are used for our analysis. But, most of the other parameter values are estimated from Kuznetsov and Taylor (1994), where they have used a direct integral method (Yermakova et al., 1982) to obtain a good initial guess for the parameters followed by a nonlinear least squares fitting to the data in the above experiment. With $r_1 = 0.18$ day$^{-1}$, $k_1 = 5.0 \times 10^6$ cells, the other parameters have been estimated and is given in Table 1. In our study we have used the parameter values from the available literatures mentioned above and so small deviations may be allowed in such cases. Moreover, to satisfy our theoretical results, we have varied few parameters within certain ranges and have shown the stability as well as oscillations in the system. The detail of these parameter variations has been discussed subsequently.

5. Linear Stability Analysis

We now find all biologically feasible equilibria admitted by system (1) and study the dynamics of the system around each equilibrium. The equilibria for system (1) are as follows:

**Proposition 1.** There exists the trivial equilibrium point at the origin $E_0(0, 0, 0)$. There are two equilibria points on the boundary of the first and third octants respectively, namely, $E_1(k_1, 0, 0)$ and $E_2(0, 0, k_2)$. The $M$–$Z$ planar equilibrium and $N$–$Z$ planar equilibrium are, respectively, $E_3(k_1, 0, k_2)$ and $E_4(0, r_2(bk_2 - d_1)/\beta^2k_2, d_1/\beta)$. $E_3$ exists if $\beta > d_1/k_2$. The interior equilibrium is $E_5(M^*, N^*, Z^*)$, where $M^* = (k_1r_1k_2\beta^2 - \alpha_3r_2(bk_2 - d_1))/((\beta^2k_2r_1 - \alpha_1\alpha_2k_1r_2)$, $N^* = (r_1/\alpha_1)(1 - (M^*/k_1))$, $Z^* = (\alpha_2M^* + d_1)/\beta$, this exists if

$$x_1 < \beta, \quad \alpha_1 < x_2,$$

where

$$x_1 = \frac{\alpha_2k_1}{k_2} + \frac{d_1}{k_2}, \quad x_2 = \frac{\beta^2k_2r_1}{r_2(bk_2 - d_1)}.$$

With our set of parameter values (from Table 1), we get the ranges for the above inequalities as $x_1 = 4.2911 \times 10^{-9}, x_2 = 1.35777 \times 10^{-7}$.

**Biological implication:** For the existence of positive interior equilibrium, the parameter $\beta$ must be greater than a threshold value $4.2911 \times 10^{-9}$ and parameter $\alpha_1$ must be less than a threshold value $1.35777 \times 10^{-7}$, which is true with our choice of parameters and can be easily

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**Table 1**

Parameter values used for numerical analysis

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>$r_1$ (growth rate of malignant tumor cells)</td>
<td>$0.18$ day$^{-1}$</td>
</tr>
<tr>
<td>$k_1$ (carrying capacity of tumor cells)</td>
<td>$5.0 \times 10^6$ cells</td>
</tr>
<tr>
<td>$\alpha_1$ (decay rate of tumor cells by hunting cells)</td>
<td>$1.101 \times 10^{-7}$ cells$^{-1}$ day$^{-1}$</td>
</tr>
<tr>
<td>$\alpha_2$ (decay rate of hunting cells by tumor cells)</td>
<td>$3.422 \times 10^{-10}$ cells$^{-1}$ day$^{-1}$</td>
</tr>
<tr>
<td>$d_1$ (death rate of hunting cells)</td>
<td>$0.0412$ day$^{-1}$</td>
</tr>
<tr>
<td>$r_2$ (growth rate of resting cells)</td>
<td>$0.0245$ day$^{-1}$</td>
</tr>
<tr>
<td>$k_2$ (carrying capacity of resting cells)</td>
<td>$1.0 \times 10^7$ cells</td>
</tr>
<tr>
<td>$\beta$ (conversion rate from resting to hunting cells)</td>
<td>$6.2 \times 10^{-9}$ cells$^{-1}$ day$^{-1}$</td>
</tr>
</tbody>
</table>

* a Siu et al. (1986).
* b Kuznetsov and Taylor (1994).
* c Parameter values within a biologically meaningful range.
verified from Table 1. It is worth noting that for this condition, the steady state value of the malignant tumor cells \((M^* \text{ in } E_*)\) in the presence of hunting cells is less, than that in the absence of hunting cells \((M = k_1\) in both \(E_1\) and \(E_3\)). This result can also be verified from the parameter set considered in Table 1. We present a comparison figure to show this situation (see, Fig. 2). This justifies the need of activation of hunting cells above a certain threshold to control the malignant cell density and gives idea to avoid the hunting cell free steady state.

5.1. Stability Analysis Without Delay

We first assume that the conversion of resting cells to hunting cells is instantaneous (that is, \(\tau = 0\)).

In that case, the variational matrix of the system (1) at \(E_*(M^*, N^*, Z^*)\) is

\[
\begin{pmatrix}
  r_1 - 2r_1 \frac{M^*}{k_1} - \alpha_1 N^* & -\alpha_1 M^* & 0 \\
  -\alpha_2 N^* - \beta Z^* & \beta N^* & \beta Z^* - d_1 - \alpha_2 M^* \\
  0 & -\beta Z^* & r_2 - 2r_2 \frac{Z^*}{k_2} - \beta N^*
\end{pmatrix}
\]

We can now easily deduce the following lemmas by computing the variational matrix of system (1) around the respective biologically feasible equilibria as follows:

**Theorem 2.** The steady states \(E_0\), \(E_1\), \(E_2\) and \(E_3\) of system (1) are unstable saddle points.

**Proof.** At \(E_0(0, 0, 0)\), the eigenvalues of the variational matrix are \(\{r_1(>0), -d_1, r_2(>0)\}\). Clearly this steady state is an unstable saddle point. At \(E_1(k_1, 0, 0)\), the eigenvalues of the variational matrix are \(\{-r_1, -(d_1 + \alpha_2 k_1), r_2(>0)\}\). Clearly this steady state is an unstable saddle point. At \(E_2(0, 0, k_2)\), the eigenvalues of the variational matrix are \(\{-r_1, \beta k_2 - d_1, -r_2\}\). Now, the existence condition for the steady state \(E_4\) shows that \((\beta k_2 - d_1) > 0\), which implies that the system is unstable around the steady state \(E_3\). At \(E_3(k_1, 0, k_2)\), the eigenvalues of the variational matrix are \(\{r_1(>0), r_2(-d_1 + \alpha_2 k_1), -r_2\}\). From (6) it is clear that \(\beta k_2 - (d_1 + \alpha_2 k_1) > 0\), hence the system is unstable around this steady state because of the existence of \(E_*\).

**Note 1.** It is necessary to mention here, that, the existence of the steady state \(E_*\) can be explained in two ways: analytically and biologically. Analytically the condition (6) directly implies its existence. Biologically it means, if the conversion rate (\(\beta\)) from resting to hunting stage do not exceed certain thresholds (\(\beta = x_1\)) then the malignant cell density tends to maximum level \((k_1)\) and the steady state \(E_3\) exists. Further, the system is stable around the steady state \(E_3\) contradicting Theorem 2. Our analytical results on positivity and boundedness
Lemma 4. The existence of the positive interior equilibrium $E_*$ of system (1) implies that the steady state $E_4$ is an unstable saddle point.

Proof. At $E_4(0, r_2(\beta k_2 - d_1)/\beta^2 k_2, d_1/\beta)$, the eigenvalues of the variational matrix are $\{(-d_1 r_2 + \sqrt{d_1} \sqrt{4 \beta k_2 (r_2 d_1 - \beta k_2^2) + d_1 r_2^2})/2 \beta k_2, (-d_1 r_2 - \sqrt{d_1} \sqrt{4 \beta k_2 (r_2 d_1 - \beta k_2^2) + d_1 r_2^2})/2 \beta k_2, (r_2 \alpha_1 (\beta k_2 - d_1) - r_1 k_2 \beta^2)/\beta^2 k_2\}$. The existence condition of $E_*$ implies that the system is unstable around the steady state $E_4$. □

Note 2. The criteria for existence and stability of this steady state lead to the following thresholds:

$$x_{11} < \beta, \quad \alpha_1 < x_2,$$

where

$$x_{11} = \frac{d_1}{k_2}.$$

These thresholds play a major role as they give rise to the stable tumor-free steady state. Hence, it has a significant biological meaning in the context of tumor–immune interaction. This helps us to identify the range of the parameters $\beta$ and $\alpha_1$ for obtaining tumor cell free situation. But, from the view point of disease management, it is important to observe the system behavior and to identify the range of parameters, when malignant tumor cells are existing. Also, our main objective to observe the role of time delay when all the cells are present, that is, the dynamics of the system around $E_*$. Hence we continue our study in that direction considering the existence of $E_*$. 

Lemma 5. System (1) is locally asymptotically stable around $E_*$ if the following condition hold true

$$\alpha_1 > \frac{\beta^2 k_1 k_2 (d_1/k_1 - 2 \alpha_2)}{d_1 r_2} = x_6. \quad (8)$$

Proof. The characteristic equation at $E_*(M^*, N^*, Z^*)$ is

$$\mu^3 + a_1 \mu^2 + a_2 \mu + a_3 = 0, \quad (9)$$

where

$$a_1 = \frac{r_2 Z^*}{k_2} + \frac{M^* r_1}{k_1},$$

$$a_2 = \frac{M^* r_1 r_2 Z^*}{k_1 k_2} + \beta^2 N^* Z^* - M^* N^* \alpha_1 \alpha_2,$$

$$a_3 = M^* N^* Z^* \left\{ \frac{\beta^2 r_1}{k_1} - \frac{\alpha_1 \alpha_2 r_2}{k_2} \right\}. \quad (10)$$

Here the eigenvalues ($\mu$) represent the roots of the characteristic Eq. (9). 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 $a_1 > 0$, $a_3 > 0$ and $a_1 a_2 - a_3 > 0$. Clearly $a_1 > 0$ and $a_3$ is positive because of the existence condition of $E_*$ (from Eq. (6)). Thus, from $a_1 a_2 - a_3 > 0$, we get the condition (for details see, Appendix A.2) as

$$\alpha_1 > \frac{\beta^2 k_1 k_2 ((d_1/k_1) - 2 \alpha_2)}{d_1 r_2} = x_6.$$

Biological implication: From (8), we get a threshold in terms of $\alpha_1$, the rate at which tumor cells are destroyed by the hunting cells and the conversion rate $\beta$ along with other system parameters. With our set of parameters (from Table 1), we observe that $x_6 = 1.43866 \times 10^{-8}$. This threshold is biologically very much important as it gives the idea for the range of $\beta$ required to activate resting cells into hunting cells so as to enhance decay of malignant tumor cells (also see, Fig. 3).

We now focus our attention to the effect of time lag due to conversion of hunting cells from resting stage. In our subsequent analysis, we try to obtain some more threshold conditions on the delay factor $\tau$ for which the system enters a bifurcation. That is, there exists an $\tau_0$ such that for $\tau < \tau_0$, positive equilibrium is locally asymptotically stable; as $\tau$ increases through $\tau_0$, periodic solution can occur, and for $\tau > \tau_0$, the positive equilibrium is unstable. This result is in accordance with the fact that the models with delays are less stable than the anal-
ogous models without delays, which is accepted among both mathematicians and biologists.

5.2. Stability Analysis with Delay

The determination of stability in the case of delay differential equations (DDE) is analogous to the ordinary differential equations (ODE). We now perturb the system around the equilibrium point $E_\epsilon(M^*, N^*, Z^*)$ to obtain the following linearized system of differential equations and consider exponential solutions which are characterized by the eigenvalues or exponent of these solutions:

$$\frac{du_1}{dt} = -\frac{r_1}{k_1} M^* u_1 - \alpha_1 M^* u_2,$$

$$\frac{du_2}{dt} = -\alpha_2 N^* u_1 + \beta N^* u_3(t-\tau),$$

$$\frac{du_3}{dt} = -\beta Z^* u_2 + \left(\beta N^* - \frac{r_2 Z^*}{k_2}\right) u_3$$

$$-\beta N^* u_3(t-\tau),$$

(13)

where, $u_1(t) = M(t) - M^*$, $u_2(t) = N(t) - N^*$ and $u_3(t) = Z(t) - Z^*$.

In case of positive delay, the characteristic equation for the linearized equation around the point $(M^*, N^*, Z^*)$ is given by

$$P(\lambda) + Q(\lambda) e^{-\lambda \tau} = 0,$$

(14)

where

$$P(\lambda) = \lambda^3 + p_1 \lambda^2 + p_2 \lambda + p_3,$$

$$Q(\lambda) = q_1 \lambda^2 + q_2 \lambda + q_3,$$

$$p_1 = \frac{r_1 M^*}{k_1} - \beta N^* + \frac{r_2 Z^*}{k_2},$$

$$p_2 = \frac{1}{k_1 k_2} \left[r_1 r_2 M^* Z^* - \alpha_1 \alpha_2 k_1 k_2 M^* N^* - \beta k_2 r_1 M^* N^*\right],$$

$$p_3 = \frac{M^* N^*}{k_1 k_2} [\alpha_1 \alpha_2 k_1 (\beta k_2 N^* - r_2 Z^*)],$$

$q_1 = \beta N^* (> 0),$ $q_2 = \frac{1}{k_1 k_2} [\beta k_2 r_1 M^* N^* + \beta^2 k_1 k_2 N^* Z^*] (> 0),$ $q_3 = \frac{M^* N^*}{k_1 k_2} [\beta^2 r_1 k_2 Z^* - \alpha_1 \alpha_2 k_1 \beta N^*].$

The eigenvalues are the roots of the characteristic Eq. (14) of the system, which has infinitely many solutions. However, we are interested in finding the periodic solutions of the system as the existence of periodic solutions is relevant in cancer models. To observe the existence of periodic solutions the eigenvalues will be purely imaginary. Hence, we substitute $\lambda = i\omega$ in (14). Separating the real and imaginary parts, we obtain the system of transcendental equations as

$$p_1 \omega^2 - p_3 = (q_3 - q_1 \omega^2) \cos(\omega \tau) + q_2 \omega \sin(\omega \tau),$$

$$\omega^3 - p_2 \omega = q_2 \omega \cos(\omega \tau) - (q_3 - q_1 \omega^2) \sin(\omega \tau).$$

(15)

(16)

Squaring and adding (15) and (16) we get,

$$(q_3 - q_1 \omega^2)^2 + q_2^2 \omega^2 = (p_1 \omega^2 - p_3)^2 + (\omega^3 - p_2 \omega)^2,$$

which implies $\omega^6 + A_1 \omega^4 + A_2 \omega^2 + A_3 = 0,$

(17)

where

$$A_1 = \frac{p_1^2}{2} - 2p_2 - q_1^2,$$

$$= 2\alpha_1 \alpha_2 M^* N^* + \frac{(M^*)^2 r_1^2}{k_1^2} + \frac{r_2 Z^*}{k_2^2} \left(r_2 Z^* - 2\beta k_2 N^*\right),$$

$$A_2 = \frac{p_2^2}{2} - \frac{q_3^2}{2} + 2p_1 p_3 + 2q_1 q_3$$

$$= \alpha_1^2 \alpha_2^2 k_1^2 k_2^2 (M^*)^2 (N^*)^2$$

$$+ 2\alpha_1 \alpha_2 k_1^2 \left(M^* N^* r_2 Z^* - 2\beta k_2 N^*\right)$$

$$+ \frac{Z^* ((M^*)^2 r_1^2 r_2^2 Z^* - 2\beta k_2 r_1^2 r_2 (M^*)^2 N^*)}{k_1^2 k_2^2}$$
and \( A_3 = p_3^2 - q_3^2 = -\left(\frac{\beta^2 k_1 r_1 - \alpha_1 \alpha_2 k_1 r_2}{k_1 k_2}\right) \times \left\{ \frac{\alpha_1 \alpha_2 k_1 (r_2 Z^* - 2 \beta k_2 N^*) + \beta^2 k_2 r_1 Z^*}{k_1 k_2} \right\} \times (M^* N^*)^2 Z^*. \)

The simple assumption that (17) will have a positive root is \( A_1 > 0 \) and \( A_3 = (p_3^2 - q_3^2) < 0. \) Since, the existence condition of \( E_+ \) holds true, we have the condition for \( A_1 \) to be positive as well as \( A_3 \) to be negative as
\[
r_2 Z^* - 2 \beta k_2 N^* > 0, \tag{18}
\]
which implies, \( \alpha_1 < \frac{3 \beta (d_1 + \alpha_2 k_1) r_1 - 2 \beta^2 k_2 r_1}{\alpha_2 k_1 r_2} = x_5. \tag{19} \)

This condition for existence of positive \( \omega \) gives the range of \( \alpha_1 ( < x_5) \) for which a purely imaginary eigenvalue of (14) can be obtained and a stable periodic solution of the system can be observed in the presence of time delay. Also it helps us to identify the region in parameter space for the stability of the delayed system. If \( \alpha_1 \) is increased beyond this value the system bifurcates to unstable situation and no more stable dynamics or stable periodic orbits are available. Later, we confirm our claim through numerical simulations. It is worth noted that \( \alpha_1 \) changes with the variation in the conversion rate \( \beta. \) We present the regions of stability of the system for both delay and non-delayed cases in Fig. (3).

Thus we can say that there is a unique positive \( \omega_0 \) satisfying (17), that is, the characteristic Eq. (14) has a pair of purely imaginary roots of the form \( \pm i \omega_0. \) From (15) and (16), we get,
\[
\tan(\omega t) = \frac{(p_1 \omega^2 - p_3)(q_2 \omega) - (\omega^3 - p_2 \omega)(q_3 - q_1 \omega^2)}{(p_1 \omega^2 - p_3)(q_3 - q_1 \omega^2) + (\omega^3 - p_2 \omega)(q_2 \omega)}. \]

Then \( \tau_n^* \) corresponding to \( \omega_0 \) is given by
\[
\tau_n^* = \frac{1}{\omega_0} \arctan \left[ \frac{(p_1 \omega_0^2 - p_3)(q_2 \omega_0) - (\omega_0^3 - p_2 \omega_0)(q_3 - q_1 \omega_0^2)}{(p_1 \omega_0^2 - p_3)(q_3 - q_1 \omega_0^2) + (\omega_0^3 - p_2 \omega_0)(q_2 \omega_0)} \right] + \frac{2n\pi}{\omega_0}. \tag{20}
\]

For \( \tau = 0, E_+ \) is stable, provided condition (8) holds. Hence, by Butler’s lemma (Freedman and Rao, 1983), \( E_+ \) remains stable for \( \tau < \tau_0 \) where \( \tau_0 = \tau_0^* \) at \( n = 0. \)

\section{5.2.1. Hopf-bifurcation}

We observe that the conditions for Hopf-bifurcation (Hale and Lunel, 1993) are satisfied yielding the required periodic solution, that is,
\[
\left. \frac{d(Re\lambda)}{d\tau} \right|_{\tau=\tau_0} > 0.
\]

This signify that there exists at least one eigenvalue with positive real part for \( \tau > \tau_0. \) To see if, there is any stability switch as \( \tau \) crosses \( \tau_0, \) we take the help of some result in Theorem 1 by Cooke and van den Driessche (1986) (for the convenience of the reader, we state the theorem in Appendix B.1). The proof of the Hopf-bifurcation result is given in Appendix B.2.

\section{6. Estimation of the Length of Delay to Preserve Stability}

It must be pointed out that the above analysis cannot determine the stability of bifurcation periodic orbits, that is, the periodic solutions may exist either for \( \tau > \tau_0 \) or for \( \tau < \tau_0, \) near \( \tau_0. \) Hence, we investigate the stability of bifurcating periodic orbits and try to estimate the maximum length of delay preserving the stability of the limit cycle.

Following the lines of Freedman et al. (1986) and using Nyquist criterion (see, Appendix B.3), it can be shown that if,
\[
\tau_+ = \frac{1}{2L_1}(-L_2 + \sqrt{L_2^2 + 4L_1 L_3}), \tag{21}
\]
where
\[
L_1 = \frac{1}{2}(|q_1 \eta^* + p_1 q_2 - q_3| \eta^*),
\]
\[
L_2 = |(q_2 - p_1 q_1)| \eta^* + |p_1| |q_3|),
\]
\[
L_3 = (p_1 + q_1)(p_2 + q_2) - (p_3 + q_3), \eta^* = \frac{1}{2(|p_1| - q_1)} \times \left( q_2 + \sqrt{q_2^2 + 4(|p_1| - q_1)(|p_3| + q_3)} \right).
\]
then for \( 0 \leq \tau < \tau_+, \) the Nyquist criterion holds true and \( \tau_+ \) estimates the maximum length of delay preserving the stability of the limit cycle. The detail proof of this analytical result is given in Appendix B.4.

\section{7. Numerical Results and Biological Significance}

To some extent we have gained analytical understanding of possible dynamics of this nonlinear delay
differential equation model. However, realistic parameter values often give meaningful biological scenario of the system. Therefore, we perform some simulation work (using FORTRAN 90 programs and MATLAB) with realistic parameter values (Siu et al., 1986; Kuznetsov and Taylor, 1994) given in Table 1 and initial values \( M(0) = 2.7 \times 10^6, N(0) = 2.04 \times 10^5, Z(0) = 7.18 \times 10^6 \) (which falls in the limit cycle region) for better understanding of our analytical treatment. In fact we consider different values of the delay factor (\( \tau \)) to observe biologically plausible different dynamical scenarios of the model, enough to merit the mathematical study.

We observe that without delay there exist a unique interior equilibrium point \( E_\ast(1.01314 \times 10^6, 1.30361 \times 10^6, 6.70108 \times 10^6) \) with help of the parameter values from Table 1. Positive steady state is locally asymptotically stable, since the eigenvalues associated with the variational matrix of the system (1) at \( E_\ast \), given by \((-0.0374048, -0.00774294 + 0.0156728i, -0.00774294 - 0.0156728i)\), have negative real parts. Simulation of the model in this situation with \( \tau = 0 \), produce stable dynamics and is presented in Fig. 4 A.

With the same set of parameters, we find that \( A_1 > 0 \) and \( A_3 < 0 \), which indicates the existence of a positive root. Solving (17) numerically, we see that there exist one simple positive root of (17), namely, \( 0.0177345 (= \omega_0) \) and the condition \( x_6 < \alpha_1 < x_5 \) (which is obtained from Eqs. (8) and (9) holds true in this case for our choice of parameter set \((1.4386 \times 10^{-8} < \alpha_1 < 1.2587 \times 10^{-7})\). Hence, by Theorem 1 in Cooke and van den Driessche (1986), we can say that as \( \tau \) increases, stability switch may occur. The value of \( \tau \) where stability switch occurs (in our case from stable steady state to stable oscillatory state) is \( \tau_0 = 45.6 \approx 46.0 \) days, which can be easily calculated using (20) and (21), and also establish our analytical estimation of the length of the delay to preserve stability. Hence, by Butler’s lemma, \( E_\ast \) remains stable for \( \tau < \tau_0 (= 45.6) \), which can be seen in Fig. 4 A and

![Fig. 4. Time evolution of all the cells for the system (1) for \( \tau = 0 \) (A), \( \tau = 44 \) days (B) and \( \tau = 45.6 \) days (C), respectively. Figures A and B show stable dynamics; figure C shows small amplitude stable oscillations for large time. Initial conditions are given in the text. The parameter set is taken from Table 1.](image-url)
B, and are the solutions of the system (1) for \( \tau = 0 \) and 44.0, respectively.

At \( \tau = \tau_0 = 45.6 \) days, a small amplitude periodic solution occurs (which is evident from Fig. 4C) and is the case of Hopf-bifurcation. The importance of Hopf-bifurcation in this context is that, at the bifurcation point a limit cycle is formed around the fixed point, thus resulting in stable periodic solutions. Moreover, this stable oscillation persist up to \( \tau = 54.0 \). We present the time evolution of the cells and the phase portrait of the system in Fig. 5 for \( \tau = 50.0 \) days. The existence of periodic solutions is relevant in cancer models. It implies that the tumor levels may oscillate around a fixed point even in absence of any treatment. Such a phenomenon, which is known as Jeff's Phenomenon (Thomlinson, 1982), has been observed clinically.

We observe a stability switch in the system as the delay factor \( \tau \) crosses a threshold (that is, \( \tau = 45.6 \) days). In cancer chemotherapy, stability switching is a very important issue for designing drug protocol. We must keep in mind that in many cases the drug prevent cells from continuing through their cell cycle, thus trapping them at some point during interphase, where the cells die from natural causes. This effect can be interpreted as an increase of the delay factor (\( \tau \)). Another important issue is to find out the allowable time lag for activation of the immune cell to fight against the malignant tumor cells. The estimation of delay parameter (particularly the length of delay for preserving stability) gives the idea about the mode of action for controlling oscillations in malignant cell growth.

Fig. 5. Time evolution of all the cells for the system (1) around \( E_* \) for \( \tau = 50.0 \) days. Large amplitude stable limit cycle is observed at this value of \( \tau \). The figures A, B and C show the periodic solutions of the tumor, hunting and resting cells, respectively. The oscillatory behavior of the signal is due to a Hopf-bifurcation as \( \tau \) crosses 45.6 and stable oscillation is observed up to \( \tau = 54.0 \). Figure D is the phase portrait depicting stable limit cycle for \( \tau = 50.0 \) days. Initial conditions and the parameter set are same as before.
or large amplitude periodic oscillations of the tumor cells (see, Fig. 7).

We have another interesting observation numerically. Keeping the value of $\tau$ fixed at 45.6 days, we change the value of $\beta$ to $6.23 \times 10^{-9}$ cells $^{-1}$ day $^{-1}$. This means that the rate of conversion of cells from resting to hunting increases and this in turn activates $\alpha_1$ (rate at which hunting cells destroy tumor cells). Hence, we increase the value of $\alpha_1$ to $1.20 \times 10^{-7}$ cells $^{-1}$ day $^{-1}$ and observe the consequent changes in the graph (Fig. 8 A), which shows a decline in the number of tumor cells. Changing successively the values of $\alpha_1$ to (1.25, 1.27, 1.30, 1.33, 1.35) $\times 10^{-7}$ cells $^{-1}$ day $^{-1}$, we obtain Fig. 8 B, C, D, E and F, from which it is clear that destruction of malignant tumor cells are possible. We also observe that the number of malignant tumor cells of the positive interior equilibrium point ($E_*$) gradually decrease due to slight increment of $\beta$ (see, Fig. 2). For our choice of $\beta$, we observe that only a 1.63-fold increase in the value of $\beta$ leads to a 7.88-fold decrease in number of tumor cells and disease free survival is possible for further increments, keeping in mind the threshold conditions derived earlier. Increasing $\beta$ biologically means increasing the concentrations of cytokines (which is mainly responsible for converting resting cells to hunting cells) artificially. In practice, this can be done through Adoptive Cellular Immunotherapy (ACI). ACI refers to the injection of cultured immune cells that have anti-tumor reactivity into tumor bearing host. This is usually done in conjunction with large amounts of Interleukin-2 (IL-2), which is the main cytokine responsible for lymphocyte activation, growth and differentiation. In case of acute lymphoblastic leukaemia, the above situation can be obtained by injecting blood stem cells. To support our claim, we refer to the experiment done by Paediatricians at the University of Milano-Bicocca, Italy (Balduzzi et al., 2005). They identified 357 children and teenagers with acute lymphoblastic leukaemia, a cancer in which too many white cells form and tumors develop in the chest. Matching donors were found for 77 of the children, aggressive chemotherapy was used to kill off all these children’s white blood cells, including the cancer cells. The children were then injected with blood stem cells from donor’s bone marrow. The recommended time frame for doing that is 2 months after achievement of remission, which is near to our observed numerical value of $\tau = 45.6$ days (approximately 1.51 months). The other children were treated with normal, lower doses of chemotherapy, forcing the disease into remission. Five years on, 50% of the normal chemotherapy group and 56% of the blood stem cell group were still alive. But while survivors in the chemotherapy group continued to relapse in the 5 years following treatment, there were no further relapses in the stem cell transplant group after 2 years, leading to an overall 16% difference in disease free survival. This matches our numerical results which is evident from Fig. 8 E and F. The figures show the decline in malignant tumor cells within the time span of 600–2000 days (approximately, 1.64–5.48 years). Hence, both qualitatively and quantitatively our theoretical observations resemble with the experimental results.

We have also simulated the system (1) to see the dynamics with initial conditions sufficiently closed to the steady state level $E_*$ (figures not shown), and observed that the stable oscillations occur for the same value of $\tau$ as before but after a long time span (after 10,000 days). This fact also resembles with the phenomenon observed
Fig. 8. The time course of malignant tumor cells, illustrating periodic solutions. Parameter set and initial conditions remain same and value of $\tau$ is 45.6 days. Figures A, B, C, D, E and F show how periodicity decreases and number of tumor cells decline for $\alpha_1 = (1.20, 1.25, 1.27, 1.30, 1.33, 1.35) \times 10^{-7}$ cells$^{-1}$ day$^{-1}$, respectively, and $\beta = 6.23 \times 10^{-9}$ cells$^{-1}$ day$^{-1}$. We observe that small changes in $\beta$ and $\alpha_1$ show substantial changes in the dynamics of the system as well as reduction in number of tumor cells.

by Kirschner and Panetta (1998) in a different modelling approach. This is also important to notice that the entire idea of controlling tumor cells through the parameters (say, conversion rate of hunting cells or time lag) depend on the time when the system is in oscillatory state due to different initial conditions that is the current state for different patients. Further, we observe that a small amplitude periodic solution occurs as the delay factor $\tau$ increases through $\tau = \tau_0 = 45.6$, resulting in the formation of a stable limit cycle around the fixed point. We have noticed that the period of the cycles for tumor cells is nearly 211.5 days (7 months approximately), which is short with small amplitudes (from analytical as well as numerical calculations, also see, Fig. 8A), implying that the tumor has medium to high antigenicity. The activation rate $\beta$ of the immune cells plays an important role in the periodicity of these cycles ($\beta$ and hence $\alpha_1$, may be increased to reduce the periodicity of the cycles for tumor cells). As tumor antigenicity increases, the magnitude and the period of the oscillations for tumor cells shorten, as well as the length of time the tumor cells remain at its peak size (Kirschner and Panetta, 1998). This progresses until the oscillations decrease down to a monthly basis and the number of tumor cell is very small with a quick recovery time (for low time lag, i.e. $\tau$ near to 45.6 days, in our case). Experimental evidences also confirm the fact of these short-term oscillations in cases like Chronic Myeloid Leukemia as well as Others (Gatti et al., 1973; Kennedy, 1970; Krikorian et al., 1980). Also short-term oscillations have been observed by Gause et al. (1996) in the lymphocyte counts with a monthly period. Finally these oscillations give way to a stable oscillations with very high amplitude (higher time lag, i.e. $\tau > 48.0$), leading to a persistent oscillatory behaviour of the tumor cells that could be described as dormant.

Moreover, conventional chemotherapy treatment often uses a maximum tolerated dose (MTD) of
chemotherapeutic drugs, typically administered on a schedule that varies from once a week to every 21 days, allowing a period of rest so that healthy tissue has a chance to recover (http://www.lef.org/protocols/prtcl-days, allowing a period of rest so that healthy tissue has schedule that varies from once a week to every 21 schedule that varies from once a week to every 21 days, allowing a period of rest so that healthy tissue has schedule that varies from once a week to every 21

024d.shtml). Unfortunately, while the MTD schedule is convenient for oncologists, allowing them to squeeze more patients each month into their chemotherapy unit, the rest period enables cancer cells to recover and develop survival mechanisms such as new blood vessel growth into the tumor. This means that when the next high dose of chemotherapy is given 7–21 days later, the cancer cells have become more resistant. The administration of the MTD also exposes healthy tissues to more damage. From our result we found the lag time as 45.6 days which implies that beyond that point the self-immunity will not work and persistent oscillation can be observed. So the external treatment is needed within this allowable time lag (where the system is showing stable dynamics) and in this situation conversion rate \( \beta \) will help to identify suitable control strategy, which is possible if we use ACI to enhance self-immunity by activation of more hunting T-cells. The two-parameter bifurcation plot (Fig. 7) for \( \beta \) and \( \tau \) helps us to identify the region where we can reduce the oscillations in the tumor cells. In our observation, the presence of a stable limit cycle is another interesting intermediate result, which imply that the tumor and the immune system undergo oscillations. We have noticed that the periods of these cycles are nearly 211.5 days. This means that the periodic relapse will occur every after 211.5 days (7 months approximately) and the schedule for next treatment can be chalked out accordingly.

The above observations give the idea of conventional dosage and timings of different therapies (for example, Adoptive Cellular Immunotherapy) as well as the time required to cure the disease. The analytical and numerical results of our model are in good agreement to those observations. Further the thresholds obtained from our study may be helpful to identify a suitable treatment protocol. The exact match is not possible, but our analytical as well as numerical studies reveal more precise (yet approximate) treatment protocol. This result can change for different parameter set and initial conditions, which is quite natural as the entire treatment strategy depends on patient’s condition, their own defense mechanism and several other factors.

8. Conclusion

In this paper, we explore the effects and interactions of tumor cells and immune cells through a system of nonlinear delay differential equations. The model we propose is very simple and of general kind. The major difference between this work and that of the others in this direction is the use of delay differential equation and subsequent analysis, which appear naturally when one consider the cell interactions. In these dynamics, key roles are played by the activation rate \( \beta \) (from resting to hunting stage) of the immune cells, rate at which tumor cells are destroyed, that is, \( \alpha_1 \) and \( \tau \), the time delay in conversion of resting cells to hunting cells. Our study reveals that certain thresholds for the activation rate \( \beta \) and the tumor decay rate \( \alpha_1 \), which are effective to control the unlimited growth of malignant tumor cells so as to control the oscillations in the system. Further, this analysis shows that it is possible to reach the tumor-free stable steady state by activating resting cells into hunting cells (see, Biological implication after Lemma 5). Though from our analysis we observe that the hunting cell free steady state is a global attractor and the system has a natural tendency to converge into that steady state, still we can predict certain range for activation/conversion rate so as to obtain a tumor free steady state and the interior steady state. But, it is important to study the system dynamics when all the cells are existing (interior steady state, \( E_\infty \)). Therefore, we observe the stability/instability of the system around this equilibrium point for both delayed and non-delayed case.

Our model can provide an approximate estimate of timing and dosage of therapy that would best complement the patient’s own defense mechanism versus the tumor cells. The delay time estimation can be used to identify the time at which subsequent doses should be given to reduce the chance of occurrence of further relapse (oscillations), whereas, the other thresholds (for the parameters \( \alpha_1, \beta, \) etc.) can be used to identify the dosages for Adaptive Cellular Immunotherapy that would best suit the patient so as to control tumor progression. The two-parameter bifurcation plots for \( \beta \) and \( \tau \) help us to identify the region where we can reduce the oscillations in the tumor cells. Oncologists try to minimize damage to normal cells and to enhance the cell killing (cytotoxic) effect on cancer cells. Too often, unfortunately, this delicate balance is not achieved. We need to find out the ideal conditions for the parameters to be estimated for each patients and then identify successful treatment strategies for them. Our observations may be helpful to shed light on this issue.

We hope our approach will help to identify suitable preventive measures against the greatest killer disease, cancer, as recent report shows validation of such models through experimental evidences (Michor et al., 2005). Though our model is very general in kind and possibly valid in a macroscopic scale and it is not to fit every
type of cancer (since each type represents different characteristics), but there are few features in our study (e.g., inclusion of delay, estimation of delay parameter for preserving stability, identification of different thresholds to obtain tumor free steady state as well as to control malignant cells when all types of cells are present, etc.) which are biologically very significant and observed clinically before. An alternative approach in this direction is to estimate the mean delay time and other parameters for population and use these statistics to compare with the model which may be helpful for a system level understanding. Also, there are many components in this model that may be regarded as stochastic rather than deterministic and these variations may significantly alter the dynamics of the system. We, therefore, suggest to convert the system given by (1) into a stochastic delay differential equations and study its dynamics, which we propose as our future work.

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Appendix A

A.1. Proofs for Lemmas 2 and 3

Proof of Lemma 2. We first consider \( Z(t) \geq k_2 \) for all \( t > 0 \). From the last two equations of (1) we get,

\[
\frac{d}{dt}[N(t) + Z(t)] = \frac{r_2}{k_2} Z[k_2 - Z] - d_1 N - \alpha_2 MN.
\]

(22)

Hence for all \( t \geq 0 \), we have \( \dot{N}(t) + \dot{Z}(t) \leq 0 \). Let

\[
\lim_{t \to \infty} [N(t) + Z(t)] = \eta.
\]

(23)

If \( \eta > k_2 \), then by the Barbálat lemma, we have,

\[
0 = \lim_{t \to \infty} \frac{d}{dt}[N(t) + Z(t)]
\]

\[
= \lim_{t \to \infty} \frac{r_2}{k_2} Z[k_2 - Z] - d_1 N - \alpha_2 MN.
\]

\[
= \lim_{t \to \infty} \frac{r_2}{k_2} Z[k_2 - Z] - d_1 N - \alpha_2 MN.
\]

\[
= \lim_{t \to \infty} \frac{r_2}{k_2} Z[k_2 - Z] - d_1 N - \alpha_2 MN
\]

\[
\leq - \min \left\{ \frac{r_2}{k_2} (\eta - k_2), d_1 \right\} \lim_{t \to \infty} [N(t) + Z(t)]
\]

\[
= -\eta \min \left\{ d_1, \frac{r_2}{k_2} (\eta - k_2) \right\} < 0.
\]

This contradiction shows that \( \eta = k_2 \), i.e.,

\[
\lim_{t \to \infty} [N(t) + Z(t)] = k_2.
\]

(24)

Let us denote by \( g(t) = N(t) + Z(t) \) for \( t \in [0, +\infty) \). Of course, \( g(t) \) is differentiable and \( g(t) \) uniformly continuous for \( t \in (0, +\infty) \). Thus with (24), all the assumptions of the Barbálat lemma hold true and, therefore

\[
\lim_{t \to \infty} \frac{d}{dt}[N(t) + Z(t)] = 0.
\]

(25)

Since from the last two equations of (1),

\[
\frac{d}{dt}[N(t) + Z(t)] = \frac{r_2}{k_2} Z[k_2 - Z] - d_1 N - \alpha_2 MN,
\]

then (24) implies that

\[
\lim_{t \to \infty} \frac{d}{dt}[N(t) + Z(t)] = -\lim_{t \to \infty} N(t)(d_1 + \alpha_2 M(t)).
\]

(27)

Hence (25) and (26) are in agreement if and only if \( \lim_{t \to \infty} N(t) = 0 \), which jointly with (24) implies \( \lim_{t \to \infty} Z(t) = k_2 \). From the first equation of (1), if \( N(t) \to 0 \) as \( t \to +\infty \), then for any given \( \epsilon_1 > 0 \) sufficiently small and satisfying \( \epsilon_1 < k_1 \), we have \( dM/dt \leq \epsilon_1 \), i.e.,

\[
\lim_{t \to \infty} M(t) = k_1.
\]

This completes the case (i).

Assume that assumption (i) is violated. Then there exists \( t_0 > 0 \) at which for the first time \( Z(t_0) + N(t_0) = k_2 \). According to (26), we have

\[
\frac{d}{dt}[N(t) + Z(t)]_{t=t_0} = -d_1 N(t_0) - \alpha_2 M(t_0) N(t_0) < 0.
\]

This implies that once a solution with \( N + Z \) has entered into the interval \((0, k_2)\), then it remains bounded for all \( t > t_0 \) i.e. \( N(t) + Z(t) < k_2 \) for all \( t > t_0 \).

Finally, if \( \psi_1(\theta) + \psi_2(\theta) < k_2 \), \( \theta \in [-\tau, 0] \), applying Lemma 1 and previous argument it follows that \( N(t) + Z(t) < k_2 \) for all \( t > 0 \), i.e. (iii) holds true. Hence the proof is complete. □

Proof of Lemma 3. Lemma 2 implies that for any \( (\psi_1, \psi_1, \psi_2) \in C_+ \) such that \( \psi_1(\theta) + \psi_2(\theta) \geq k_2, \theta \in [-\tau, 0] \), then either a time \( t_0 > 0 \) exists for which \( N(t_0) + Z(t_0) < k_2 \), for all \( t > t_0 \), or \( \lim_{t \to \infty} Z(t) = k_2 \), \( \lim_{t \to \infty} N(t) = 0 \), \( \lim_{t \to \infty} M(t) = k_1 \). Furthermore, if \( \psi_1(\theta) + \psi_2(\theta) \geq k_2 \) for all \( \theta \in [-\tau, 0] \), then either a time \( t_0 > 0 \) exists for which \( N(t_0) + Z(t_0) < k_2 \), for all \( t > t_0 \), or \( \lim_{t \to \infty} Z(t) = k_2 \), \( \lim_{t \to \infty} N(t) = 0 \), \( \lim_{t \to \infty} M(t) = k_1 \). Lastly, if \( \psi_1(\theta) + \psi_2(\theta) < k_2 \) for all \( \theta \in [-\tau, 0] \), then \( \lim_{t \to \infty} Z(t) = k_2 \), \( \lim_{t \to \infty} N(t) = 0 \), \( \lim_{t \to \infty} M(t) = k_1 \).

□
\( \psi_2(\theta) < k_2, \theta \in [-\tau, 0] \) then \( N(t) + Z(t) < k_2 \), for all \( t > 0 \). Hence in any case a non-negative time, say \( t^* \), exists such that \( N(t) < k_2 \), \( Z(t) < k_2 + \epsilon \), for all \( t > t^* \).

Set \( W = M(t) + N(t) + Z(t) \).

Calculating the derivative of \( W \) along the solution of system (1), we find for \( t > t^* \),

\[
W = r_1 M(t) \left( 1 - \frac{M(t)}{k_1} \right) - \alpha_1 M(t) N(t) - \alpha_2 M(t) N(t) - d_1 N(t) + r_2 Z(t) \left( 1 - \frac{Z(t)}{k_2} \right) \leq r_1 M(t) \left( 1 - \frac{M(t)}{k_1} \right) - d_1 N(t) + r_2 Z(t) \times \left( 1 - \frac{Z(t)}{k_2} \right) = -d_1 (M(t) + N(t) + Z(t)) + r_1 M(t) \left( \frac{d_1}{r_1} - \frac{M(t)}{k_1} \right) + r_2 Z(t) \left( \frac{d_1}{r_2} - \frac{Z(t)}{k_2} \right) \leq -d_1 W + \frac{k_1}{4r_1} (r_1 + d_1)^2 + \frac{k_2}{4r_2} (r_2 + d_1)^2,
\]

where \( (k_1/4r_1)(r_1 + d_1)^2 \) and \( (k_2/4r_2)(r_2 + d_1)^2 \) are the maximum values of the functions \( r_1 M(t) [1 + (d_1/r_1) - (M(t)/k_1)] \) and \( r_2 Z(t) [1 + (d_1/r_2) - (Z(t)/k_2)] \), respectively.

Hence \( W \leq -d_1 W + \tilde{k} \), where \( \tilde{k} = (k_1/4r_1)(r_1 + d_1)^2 + (k_2/4r_2)(r_2 + d_1)^2 \).

Thus there exists a positive constant, \( B \), such that \( W(t) < B \) for all large \( t \). The assertion of Lemma 3 now follows and the proof is completed. \( \square \)

**A.2. Calculation of \( a_1 a_2 - a_3 \)**

\[
a_1 a_2 - a_3 = \left( \frac{r_2}{k_2} Z^* + \frac{r_1}{k_1} M^* \right) \times \left( \frac{r_1 r_2}{k_1 k_2} M^* Z^* + \beta^2 N^* Z^* - \alpha_2 M^* N^* \right) \leq \left( \frac{r_1}{k_1} \beta^2 M^* N^* Z^* - \frac{r_1 r_2}{k_2} M^* N^* Z^* \right) = \frac{r_1 r_2}{k_1 k_2} M^* Z^* + \frac{\beta^2 r_2}{k_2} N^* Z^* + \frac{r_1^2 r_2}{k_1 k_2} M^* Z^* - \frac{\alpha_1 a_2}{k_1} M^* N^* = a_{11} M^* + a_{12} M^* + a_{13} M^* + a_{14}, \tag{28}
\]

where

\[
\begin{align*}
a_{11} &= \frac{r_1 r_2 \alpha_2}{\beta k_1 k_2} \left( \frac{r_1}{k_1} + \frac{r_2 \alpha_2}{\alpha_1} - \frac{\alpha_2 \beta}{r_1 k_2} \right), \\
a_{12} &= \frac{r_1 r_2 \alpha_2 d_1}{k_1 k_2 \beta^2} \times \left( \frac{2r_2}{k_2} - \frac{\beta^2}{\alpha_1} + \frac{\alpha_2 k_1 \beta^2}{d_1 \alpha_1} - \frac{r_1 k_2 \beta^2}{r_2 d_1} + \frac{r_1 \beta}{k_1 a_2} \right), \\
a_{13} &= \frac{r_1 r_2 d_1}{a_1 k_2} \left( 2\alpha_2 - \frac{d_1}{k_1} + \frac{d_1 r_2 a_1}{\beta^2 k_1 k_2} \right), \\
a_{14} &= \frac{r_1 r_2 d_1^2}{a_1 k_2} > 0.
\end{align*}
\]

Since, \( M^* \) and \( a_{14} \) are positive, clearly (27) will be positive if \( a_{11} > 0, a_{12} > 0 \) and \( a_{13} > 0 \). Therefore, we can say that the system is asymptotically stable around the positive interior equilibrium point \( E_* \) (provided the existence condition (6) holds true), if the following inequality holds true:

\[
a_1 > \max(x_3, x_4, x_6), \tag{29}
\]

where

\[
\begin{align*}
x_3 &= \frac{\alpha_2 \beta}{(r_1/k_1) + (r_2 a_2/\beta k_2) + (r_1 k_2 \beta/r_2 k_1)}, \\
x_4 &= \frac{\beta^2 (2 - (\alpha_2 k_1/d_1))}{(2r_2/k_2) - (r_1 k_2 \beta^2/r_2 d_1) + (r_1 \beta/k_1 a_2)}, \\
x_6 &= \frac{\beta^2 k_1 k_2 ((d_1/k_1) - 2\alpha_2)}{d_1 r_2}.
\end{align*}
\]

With our set of parameters (from Table 1), we see that \( x_3 = 1.66747 \times 10^{-11}, x_4 = 1.27902 \times 10^{-10}, x_6 = 1.43866 \times 10^{-8} \). As \( x_6 \) is maximum, we must have,

\[
a_1 > x_6 \text{(which is true, from Table 1)}
\]

which implies, \( a_1 > \frac{\beta^2 k_1 k_2 ((d_1/k_1) - 2\alpha_2)}{d_1 r_2} \).

**Appendix B**

**B.1. Theorem 1 in Cooke and van den Driessche (1986)**

Consider Eq. (7)(see, Cooke and van den Driessche (1986)), where \( P \) and \( Q \) are analytic functions in a right half-plane \( \text{Re} z > -\delta, \delta > 0 \), which satisfy the following conditions:
(i) \( P(z) \) and \( Q(z) \) have no common imaginary zero,
(ii) \( P(-iy) = P(iy), Q(-iy) = Q(iy) \), for real \( y \) (\( X \) denotes complex conjugate \( X \)),
(iii) \( P(0) + Q(0) \neq 0 \),
(iv) There are at most a finite number of roots of (7) in the right half-plane when \( T = 0 \),
(v) \( F(y) \equiv |P(iy)|^2 - |Q(iy)|^2 \) for real \( y \), has at most a finite number of real zeroes. Under these conditions, the following statements are true.

(a) Suppose that the equation \( F(y) = 0 \) has no positive roots. Then if (7) is stable at \( T = 0 \), it remains unstable for all \( T \geq 0 \).
(b) Suppose that the equation \( F(y) \) has at least one positive root and that each positive root is simple. As \( T \) increases, stability switches may occur. There exists a positive number \( T^* \) such that Eq. (7) is unstable for all \( T \geq T^* \). As \( T \) varies from 0 to \( T^* \), at most a finite number of stability switches may occur.

### B.2. Proof for Hopf-bifurcation

We first look for purely imaginary roots of \( \lambda = i\omega_0 \) of (14). Eq. (14) implies

\[
|P(i\omega_0)| = |Q(i\omega_0)|, \quad (30)
\]

Now, differentiating (14) with respect to \( \tau \), we get

\[
\begin{align*}
(3\lambda^2 + 2p_1\lambda + p_2 + e^{-\lambda\tau}(2q_1\lambda + q_2) - \tau e^{-\lambda\tau}(q_1\lambda^2 + q_2\lambda + q_3)) \frac{d\lambda}{d\tau} &= (q_1\lambda^2 + q_2\lambda + q_3) e^{-\lambda\tau}\lambda
\end{align*}
\]

which implies,

\[
\left( \frac{d\lambda}{d\tau} \right)^{-1} = \frac{3\lambda^2 + 2p_1\lambda + p_2}{\lambda e^{-\lambda\tau}(q_1\lambda^2 + q_2\lambda + q_3)} + \frac{2q_1\lambda + q_2}{\lambda(q_1\lambda^2 + q_2\lambda + q_3)} - \frac{\tau}{\lambda}
\]

\[
= \frac{3\lambda^2 + 2p_1\lambda + p_2}{-\lambda(\lambda^3 + p_1\lambda^2 + p_2\lambda + p_3)} + \frac{2q_1\lambda + q_2}{\lambda(q_1\lambda^2 + q_2\lambda + q_3)} - \frac{\tau}{\lambda}
\]

\[
= \frac{2\lambda^3 + p_1\lambda^2 - p_3}{-\lambda(\lambda^3 + p_1\lambda^2 + p_2\lambda + p_3)} + \frac{q_1\lambda^2 - q_3}{\lambda^2(q_1\lambda^2 + q_2\lambda + q_3)} - \frac{\tau}{\lambda}.
\]

Therefore

\[\Theta = \text{sign} \left[ Re \left( \frac{2\lambda^3 + p_1\lambda^2 - p_3}{-\lambda^2(\lambda^3 + p_1\lambda^2 + p_2\lambda + p_3)} + \frac{q_1\lambda^2 - q_3}{\lambda^2(q_1\lambda^2 + q_2\lambda + q_3)} - \frac{\tau}{\lambda} \right) \right]_{\lambda = i\omega_0}\]

\[
= \frac{1}{\omega_0} \text{sign} \left\{ Re \left[ \left( \frac{p_3 + p_1\omega_0^2}{(p_1\omega_0^2 - p_3) + i(\omega_0^2 - p_2\omega_0)} + \frac{q_1\omega_0^2 + q_3}{(q_3 - q_1\omega_0^2) + i(q_2\omega_0)} \right) \right] \right\}
\]

\[
= \frac{1}{\omega_0} \text{sign} \left\{ \left( \frac{p_3 + p_1\omega_0^2}{(p_1\omega_0^2 - p_3)^2 + (\omega_0^2 - p_2\omega_0)^2} + \frac{q_1\omega_0^2 + q_3}{(q_3 - q_1\omega_0^2)^2 + (q_2\omega_0)^2} \right) \right\}
\]

\[
= \frac{1}{\omega_0} \text{sign} \left\{ \left( \frac{2\omega_0^6 + (p_1^2 - 2p_2 - q_1^2)\omega_0^4 + (q_2^2 - p_3^2)}{(q_3 - q_1\omega_0^2)^2 + (q_2\omega_0)^2} \right) \right\}.
\]

This determines a set of possible eigenvalues of \( \omega_0 \). Our aim is to determine the direction of motion of \( \lambda \) as \( \tau \) is varied. That is, we determine

\[
\Theta = \text{sign} \left[ \text{Re} \left( \frac{d\lambda}{d\tau} \right) \right]_{\lambda = i\omega_0} = \text{sign} \left[ \text{Re} \left( \frac{d\lambda}{d\tau} \right)^{-1} \right]_{\lambda = i\omega_0}
\]

As \( p_1^2 - 2p_2 - q_1^2 \) and \( q_2^2 - p_3^2 \) are both positive by virtue of (18), we have

\[
\left[ \frac{d(\text{Re} \lambda)}{d\tau} \right]_{\omega = \omega_0, \tau = \tau_0} > 0.
\]

Therefore, the transversality condition holds and hence Hopf bifurcation occurs at \( \omega = \omega_0, \tau = \tau_0 \).
B.3. Nyquist Criterion

If $L$ is the arc length of a curve encircling the right half-plane, the curve $\bar{p}_J(L)$ will encircle the origin a number of times equal to the difference between the number of poles and the number of zeroes of $\bar{p}_J(L)$ in the right half-plane.

B.4. Proof for Estimation of the Length of Delay to Preserve Stability

We consider system (1) and the space of all real valued continuous functions defined in $C_+$ satisfying the initial conditions $M(\theta) > 0$, $N(\theta) > 0$, $Z(\theta) > 0$, $\theta \in C[-\tau, 0]$.

Taking laplace transform of the system given by (11)–(13), we get,

$$
\left(\frac{s + \frac{r_1}{k_1}M^*}{s + \frac{r_2}{k_2}N^* - \beta N^*}\right) u_1(s) = -\alpha_1 M^* u_2(s) + u_1(0),
$$

$$
s u_2(s) = -\alpha_2 N^* u_1(s) + \beta N^* e^{-st} u_3(s) + \beta N^* e^{-st} K(s) + u_2(0),
$$

$$
\left(\frac{s + \frac{r_2}{k_2}}{s + \frac{r_2}{k_2}N^* - \beta N^*}\right) u_3(s) = -\beta z^* u_2(s) - \beta N^* e^{-st} u_3(s) - \beta N^* e^{-st} K(s) + u_3(0),
$$

where

$$
K(s) = \int_0^\tau e^{-st} u_3(t) \, dt,
$$

and $\bar{u}_1(s)$, $\bar{u}_2(s)$ and $\bar{u}_3(s)$ are the Laplace transform of $u_1(t)$, $u_2(t)$ and $u_3(t)$, respectively.

Following the lines of Freedman et al. (1986) and using Nyquist criterion (see, Appendix B.2), it can be shown that the conditions for local asymptotic stability of $E_s(M^*, N^*, Z^*)$ are given by

$$\text{Im} H(i\eta_0) > 0, \quad \text{(31)}$$

$$\text{Re} H(i\eta_0) = 0, \quad \text{(32)}$$

where $H(s) = s^3 + p_1 s^2 + p_2 s + p_3 + e^{-st}(q_1 s^2 + q_2 s + q_3)$ and $\eta_0$ is the smallest positive root of (32).

We have already shown that $E_s(M^*, N^*, Z^*)$ is locally asymptotically stable in absence of delay (by virtue of (9)). Hence, by continuity, all eigenvalues will continue to have negative real parts for sufficiently small $\tau > 0$ provided one can guarantee that no eigenvalues with positive real parts bifurcates from infinity as $\tau$ increases from zero. This can be proved using Butler’s lemma (Freedman and Rao, 1983), already stated before.

In our case, (31) and (32) gives

$$p_2 \eta_0 - \eta_0^3 > -q_2 \eta_0 \cos(\eta_0 \tau) + q_3 \sin(\eta_0 \tau) - q_1 \eta_0^2 \sin(\eta_0 \tau), \quad \text{(33)}$$

$$p_3 - p_1 \eta_0^2 = q_1 \eta_0^2 \cos(\eta_0 \tau) - q_3 \cos(\eta_0 \tau) - q_2 \eta_0 \sin(\eta_0 \tau). \quad \text{(34)}$$

Now, Eqs. (33) and (34), if satisfy simultaneously, are sufficient conditions to guarantee stability. We shall utilize them to get an estimate on the length of delay. Our aim is to find an upper bound $\eta_+$ on $\eta_0$, independent of $\tau$ and then to estimate $\tau$ so that (33) holds true for all values of $\eta$, $0 \leq \eta \leq \eta_+$ and hence in particular at $\eta = \eta_0$.

We rewrite (34) as

$$p_1 \eta_0^2 = p_3 + q_3 \cos(\eta_0 \tau) - q_1 \eta_0^2 \cos(\eta_0 \tau) + q_2 \eta_0 \sin(\eta_0 \tau). \quad \text{(35)}$$

Maximizing $p_3 + q_3 \cos(\eta_0 \tau) - q_1 \eta_0^2 \cos(\eta_0 \tau) + q_2 \eta_0 \sin(\eta_0 \tau)$ subject to $|\sin(\eta_0 \tau)| \leq 1$, $|\cos(\eta_0 \tau)| \leq 1$ we obtain,

$$|p_1 \eta_0^2| \leq |p_3| + |q_3| + q_1 \eta_0^2 + q_2 \eta_0. \quad \text{(36)}$$

Hence, if

$$\eta_+ = \frac{1}{2(|p_1| - q_1)} \times \left[ q_2 + \sqrt{q_2^2 + 4(|p_1| - q_1)(|p_3| + q_3)} \right]. \quad \text{(37)}$$

then clearly from (36) we have $\eta_0 \leq \eta_+$.

From the inequality (33) we obtain

$$\eta_0^2 < p_2 + q_2 \cos(\eta_0 \tau) + q_1 \eta_0 \sin(\eta_0 \tau) - \frac{q_3 \sin(\eta_0 \tau)}{\eta_0}. \quad \text{(38)}$$

At $\tau = 0$, this inequality becomes $\eta_0^2 < p_2 + q_2$. But at $\tau = 0$ from (35) we have $p_1 \eta_0^2 = p_3 + q_3 - q_1 \eta_0^2$, i.e. $\eta_0^2 = (p_3 + q_3)/(p_1 + q_1)$. Therefore, $E_s(M^*, N^*, Z^*)$ is locally asymptotically stable for $\tau = 0$, if the condition $p_3 + q_3 < (p_1 + q_1)(p_2 + q_2)$ holds true and this has been also observed from the Routh–Hurwitz condition obtained in Appendix A.2. For sufficiently small $\tau > 0$,
inequality (38) will continue to hold. Substituting (35) in (38) and rearranging we get,
\[(q_3 - q_1\eta_0^2 - p_1q_2)[\cos(\eta_0\tau) - 1] + \left\{(q_2 - p_1q_1)\eta_0 + \frac{p_1q_3}{\eta_0}\right\} \sin(\eta_0\tau)
\leq p_1p_2 - p_3 - q_3 + q_1\eta_0^2 + p_1q_2,\]
or
\[(q_3 - q_1\eta_0^2 - p_1q_2)[\cos(\eta_0\tau) - 1] + \left\{(q_2 - p_1q_1)\eta_0 + \frac{p_1q_3}{\eta_0}\right\} \sin(\eta_0\tau)
\leq (p_1 + q_1)(p_2 + q_2) - (p_3 + q_3).\] \quad (39)

Using the bounds,
\[\frac{3}{2}\left(q_1\eta_0^2 + p_1q_2 - q_3\right)\sin^2\left(\frac{\eta_0\tau}{2}\right) \leq \frac{1}{2}(q_1\eta_0^2 + p_1q_2 - q_3)\eta_0^2\tau^2,\]
and
\[\left\{(q_2 - p_1q_1)\eta_0 + \frac{p_1q_3}{\eta_0}\right\} \sin(\eta_0\tau) \leq \{(q_2 - p_1q_1)\eta_0 + |p_1||q_3|\} \tau,\]
we obtain from (39)
\[L_1\tau^2 + L_2\tau \leq L_3,\] \quad (40)
where
\[L_1 = \frac{1}{2}(q_1\eta_0^2 + p_1q_2 - q_3)\eta_0^2,\]
\[L_2 = \{(q_2 - p_1q_1)\eta_0^2 + |p_1||q_3|\},\]
\[L_3 = (p_1 + q_1)(p_2 + q_2) - (p_3 + q_3).\]

Hence, if
\[\tau_+ = \frac{1}{2L_1}(-L_2 + \sqrt{L_2^2 + 4L_1L_3}),\] \quad (41)
then for \(0 \leq \tau < \tau_+\), the Nyquist criterion holds true and \(\tau_+\) estimates the maximum length of delay preserving the stability of the limit cycle.

References


