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A Mathematical Model of Vascular Tumor Treatment by Chemotherapy

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Abstract—From the viewpoint of biological stoichiometry, a mathematical model of vascular tumor treatment with chemotherapy techniques is proposed utilizing a system of delayed differential equations representing the change in mass of healthy cells, competing parenchyma cells, chemotherapy, and the number of blood vessels within the tumor. In the absence of treatment, mathematical analysis of the model equations with regard to invariance of nonnegativity, boundedness of solutions, nature of equilibria, permanence, and global stability are analyzed. It is shown that the system can be permanent, but whenever the boundary equilibrium is stable, the interior equilibrium of the system cannot be globally stable for at least small values of time delay. Further, in this case, persistence cannot occur at least for small values of the time delay. Necessary and sufficient conditions for Hopf bifurcation to occur are also obtained by using the time delay as a bifurcation parameter. Finally, based on all these qualitative behaviors of the model, a continuous treatment for tumor growth is considered. The analysis is carried out both analytically and numerically.

Keywords—Vascular tumor, Stoichiometry, Growth hypothesis, Permanence, Hopf bifurcation.

1. INTRODUCTION

Cancer is a multistage malignant disease in which certain cells proliferate in disregard of the regulatory mechanisms that act to regulate the growth of healthy cells. These cells then biotransform to stages of greater malignancy, characterized by oncogene activation/mutation, heterogeneity, invasion, and metastasis, [1–4]. In general, such a cellular proliferation is called neoplasia and, hence, cancer is sometimes referred to as a neoplastic disease. The term tumor which denotes swelling is commonly used to refer to neoplasm, while cancer is a general term for all malignant neoplasms. A malignant tumor or cancer is a configuration of neoplastic cells in an anatomic organ or tissue such that these cancer cells differ from healthy cells in histopathologic, morphologic, immunologic, and cytokinetic characteristics, [3,5].

Having a tumor has been known as a deadly disease of mankind. Studies in cell and molecular biology show some cancers coerce surrounding healthy cells into a servile role in the tumor stroma.

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Moreover, these same cancer cells not only compete with those healthy cells for resources, but also compete with each other and against healthy cells throughout the body for the same resources, including oxygen, nutrients, and space. One important resource over which cancer and healthy cells may compete is phosphorus. Many lines of evidence suggest that cancer cells up-regulate ribosome synthesis, a process that requires large amounts of phosphate, [6–8]. In addition, certain cancer-related genes, both tumor suppressors (gatekeepers) like p53 and oncogenes, including members of the myc family, are involved in regulating production of ribosomes, [9–11]. Additional studies indicate that cancer cells with larger, more active nucleoli proliferate more rapidly *in vivo*, [12]. Since the nucleolus is the site of rDNA transcription and the initial stages of ribosome formation, these results highlight ribosome biogenesis as a central process in tumor biology.

Biological stoichiometry is the study of the balance of energy and multiple chemical elements in biological systems [13]. The growth rate hypothesis proposes that ecologically significant variations in the relative requirements of an organism for C, N, and P are determined by its mass-specific growth rate because of the heavy demand for P-rich ribosomal RNA under rapid growth [14]. Numerous experimental data show that P-rich animals are usually sensitive to the P-content of their foods, suffering strong declines in growth and reproduction when consuming food low in P, making them vulnerable to erratic population dynamics and possible extinction in environments that do not supply sufficient P [13].

Biological stoichiometry and the growth rate hypothesis have strong relevance for tumor biology. The idea of modelling cancer interactions with healthy tissue from the viewpoint of biological stoichiometry and the growth rate hypothesis was first proposed by Kuang *et al.* [15]. However, their work did not consider treatment. Here, we incorporate chemotherapy treatment with the model developed in [15] (see [15] for the derivation of the model) and testify the effect of treatment on the tumor growth. Current therapeutic approaches centered on destroying individual cancer cells or slowing their reproduction, while increasingly successful for many cancers [16], may be inherently limited in their ability to defeat many forms of cancer [17]. However, by applying a stoichiometric perspective to better reflect the multivariate material demands and transactions of the players, we might be better able to turn the tables of competition in favor of the patient. It is within this context our studies of treatment for such tumor growth may be significant.

The organization of the paper is as follows. In the next section, we develop our model. In Section 3, we discuss the invariance of nonnegativity, boundedness of solutions, nature of equilibria, permanence, and global stability in the no treatment case. In the section that follows, we look at the continuous treatment case: we discuss the existence, local, and nonlocal stability of relevant equilibria, and check the effects of the time delay on the stability of solutions. These are done both analytically and numerically.

2. THE MODEL

The model consists of three ordinary differential equations and one-functional differential equation, altogether simulating the interactions between the normal cells, parenchyma (cancerous) cells, blood vessels within the tumor, and chemotherapy agents. Let $x(t)$ and $y(t)$ be the mass of healthy and cancer cells, $z(t)$ is the number of blood vessels within the tumor, and $u(t)$ is the mass of chemotherapy agents. Then, the model is given as

$$\begin{aligned}
\dot{x}(t) &= x(t)\left[a\min\left(1,\frac{P_e}{nk_hf}\right) - d_x - (a-d_x)\frac{x(t)+y(t)+z(t)}{k_h}\right] - \frac{p_1x(t)u(t)}{a_1+x(t)},\\
\dot{y}(t) &= y(t)\left[b\min\left(1,\frac{P_e}{mk_hf}\right)\min(1,L) - d_y - (b-d_y)\frac{y(t)+z(t)}{k_t}\right] - \frac{p_2y(t)u(t)}{a_2+y(t)}, \qquad (1)\\
\dot{z}(t) &= cy(t-\tau) - d_zz(t) - \frac{p_3z(t)u(t)}{a_3+z(t)},
\end{aligned}$$

$$\begin{aligned}
\dot{u}(t) &= \Delta - \left[\xi + \frac{c_1 x(t)}{a_1 + x(t)} + \frac{c_2 y(t)}{a_2 + y(t)} + \frac{c_3 z(t)}{a_3 + z(t)}\right] u(t), \\
L &= \frac{g(z - \alpha y)}{y}, \\
P_e &= P - (nx + my + nz),
\end{aligned} \tag{1}(\text{cont.})$$

with initial conditions

$$\begin{gathered}
x(t) = \phi_1(\theta) = x(0) > 0, \qquad y(t) = \phi_2(\theta) \geq 0, \\
z(t) = \phi_3(\theta) = z(0) \geq 0, \qquad -\tau \leq \theta \leq 0, \\
u(0) = u_0 \geq 0.
\end{gathered}$$

Here, the chemotherapy is the combination of several chemical agents, which acts like a predator on both healthy and cancer cells. The growth rate of heathy tissue decelerates as the mass of both the healthy and tumor tissue approaches k_h. A similar situation does not apply to the tumor. The tumor growth rate is only modified by the relationship between tumor mass and tumor carrying capacity, k_t; mass of healthy tissue has no effect on the tumor. The parameters in the model can be interpreted as follows:

- a,b are the maximum per capita rates at which healthy cells and tumor cells proliferate, respectively, in a phosphorus-rich environment.
- k_h,k_t are respective carrying capacities of healthy cells and tumor cells.
- d_x,d_y represent the respective constant per capita mortality of healthy cells and tumor cells.
- p_i, $i = 1, 2, 3$ are the predation coefficients of u on x, y, and z.
- a_i, $i = 1, 2, 3$ determine the rate at which x, y, z, in the absence of competition and predation, reach carrying capacities.
- c_i, $i = 1, 2, 3$ represent the combination rates of the chemotherapy agent with the cells. Hence, they are proportional to p_i, $i = 1, 2, 3$.
- P is the homeostatically regulated total amount of phosphorus within the organ.
- m represents the mean amount of phosphorus (g) per kilogram of parenchyma cells.
- n is the mean amount of phosphorus per kilogram of healthy cells, including both healthy organ tissue and vascular endothelial cells within the tumor stroma.
- Δ represents the continuous infusion rate of chemotherapy.
- ξ is the washout rate of chemotherapy at the site.
- τ represents the time it takes for vascular endothelial cells to respond to angiogenic growth factors, divide, degrade their basement membranes, migrate to the site of growth and mature into working endothelium.
- α is the mass of cancer cells that one unit of blood vessel can just barely be maintained.
- g measures the sensitivity of tumor tissue to the lack of blood.

All constants are positive. To make this model more realistic, we impose certain inequalities among the parameters. It is well known that cancer cells grow at a much faster rate than normal cells. The chemotherapy agents must be considerably more effective in killing cancer cells than in killing normal cells in order for the treatment to be effective. This leads to the inequalities

$$b > a, \qquad p_2 \gg p_1.$$

At this point, we establish some important properties of system (1).

LEMMA 1. *All solutions with positive initial values remain positive.*

PROOF. By uniqueness of solutions, since $x \equiv 0$ is a solution of the first equation of (1), no solution with $x(t) > 0$ at any time $t \geq 0$ can become zero in finite time. Similarly, the same is true for $y(t)$. Since $\dot{u}(0) = \Delta > 0$, no solution $u(t)$ of (1) with $u(t) > 0$ can become zero. With the same argument as in [18], $z(t)$ must remain positive provided that $y(t)$ is positive on $t \geq -\tau$, which it is. ∎

THEOREM 1. *System (1) is dissipative provided that there exists an $M > 0$ such that $\|\phi_2\| \leq M$.*

PROOF. Since the initial conditions are nonnegative, then so are the solutions. From (1), we have

$$\frac{dx}{dt} \leq x(a_0 - a_1 x), \qquad \frac{dy}{dt} \leq y(b_0 - b_2 y).$$

It follows from standard comparison theory that

$$\lim_{t\to\infty} \sup x(t) \leq a_1^{-1} a_0, \qquad \lim_{t\to\infty} \sup y(t) \leq b_2^{-1} b_0.$$

Let T be so large that $0 \leq y(t) \leq b_0^{-1} b_2$ for $t \geq T$. Then, we have

$$\frac{dz}{dt} \leq b_2^{-1} b_0 c - d_z z,$$

which then implies, again using a comparison theorem and after some computations, that

$$\lim_{t\to\infty} \sup z(t) \leq d_z^{-1} b_2^{-1} b_0 c,$$

where

$$a_0 = \frac{aP}{nk_h f} - d_x, \qquad a_1 = \frac{a}{k_h f} + \frac{a - d_x}{k_h}, \qquad b_0 = \frac{bP}{mk_h f} - d_y, \qquad b_2 = \frac{b}{k_h f} + \frac{b - d_y}{k_t}.$$

Now, we have that

$$\frac{du}{dt} \leq \Delta - \xi u$$

giving

$$\lim_{t\to\infty} \sup u(t) \leq \xi^{-1} \Delta.$$

Hence, the region $\Re = \{(x, y, z, u) \in R_+^4 : 0 \leq x \leq a_1^{-1} a_0, 0 \leq y \leq b_2^{-1} b_0, 0 \leq z \leq d_z^{-1} b_2^{-1} b_0 c, 0 \leq u \leq \xi^{-1} \Delta\}$ is an attracting invariant region proving the property. ∎

3. THE NO TREATMENT CASE

Depending on the initial conditions, a trajectory can either converge to an attractor, or diverge to infinity. In our system, the attractor may be an equilibrium, a limit cycle, or a higher-dimensional subset of phase space. Knowing the conditions for which we can obtain all these possibilities, enables us to better understand the long term behavior of our system that is crucial to the outcome of therapy. We first determine the type of dynamics that can arise in the system without the presence of the drug and then study the case with drugs. The rationale behind this is to use the information about the drug-free system when designing chemotherapeutic protocols. When we stop the treatment, we would like the patient to be "cured", or to be inside the basin of attraction of the cancer-free fixed points of this new drug-free system. It is also of interest to study how the delay τ affects the behavior of our system and how each element contributes to the overall stability. Here, the model is modified to the form

$$\begin{aligned}
\dot{x}(t) &= x(t)\left[a \min\left(1, \frac{P_e}{nk_h f}\right) - d_x - (a - d_x)\frac{x(t) + y(t) + z(t)}{k_h}\right], \\
\dot{y}(t) &= y(t)\left[b \min\left(1, \frac{P_e}{mk_h f}\right) \min(1, L) - d_y - (b - d_y)\frac{y(t) + z(t)}{k_t}\right], \\
\dot{z}(t) &= cy(t - \tau) - d_z z(t),
\end{aligned} \tag{2}$$

with initial conditions

$$x(t) = \phi_1(\theta) = x(0) > 0, \quad y(t) = \phi_2(\theta) \geq 0, \quad z(t) = \phi_3(\theta) = z(0) \geq 0, \qquad -\tau \leq \theta \leq 0.$$

The growth rate is limited by nutrients and decreases whenever the concentration of extracellular phosphorus drops below n. The same applies to tumor cells. Therefore, our analysis throughout the paper is simplified by the assumption that

$$\frac{P_e}{nk_hf} < 1, \qquad L > 1. \tag{3}$$

Clearly, equation (3) implies that

$$\frac{P_e}{mk_hf} < 1.$$

3.1. Asymptotic Behavior and Hopf Bifurcation

3.1.1. Equilibria

System (2) has a trivial equilibrium $E_0(0,0,0)$ and a one-dimensional equilibrium $E_1(\bar{x},0,0)$. The two-dimensional equilibrium is $E_2(0,\hat{y},\hat{z})$. Finally, a possible interior equilibrium is $E_3(x^*, y^*, z^*)$.

By solving the algebraic equation

$$\frac{a(P-nx)}{nk_hf} - d_x - (a-d_x)\frac{x}{k_h} = 0,$$

we obtain

$$\bar{x} = \frac{aP - nk_hfd_x}{n[a+(a-d_x)f]}.$$

Similarly, solving the algebraic system with $x = 0$

$$\begin{aligned} \frac{b(P-my-nz)}{mk_hf} - d_y - (b-d_y)\frac{y+z}{k_t} &= 0, \\ cy - d_z z &= 0, \end{aligned}$$

gives

$$\hat{y} = \frac{k_td_z(bP - mk_hfd_y)}{bk_t(md_z+nc) + mk_hf(b-d_y)(c+d_z)}, \qquad \hat{z} = \frac{c}{d_z}\hat{y}.$$

Again, by solving the system

$$\begin{aligned} \frac{a(P-nx-my-nz)}{nk_hf} - d_x(a-d_x)\frac{x+y+z}{k_h} &= 0, \\ \frac{b(P-nx-my-nz)}{mk_hf} - d_y - (b-d_y)\frac{y+z}{k_t} &= 0, \\ cy - d_z z &= 0, \end{aligned}$$

we have

$$\begin{aligned} x^* &= \frac{a_0}{a_1} - \left(\frac{a_2}{a_1} + \frac{c}{d_z}\right) y^*, \\ y^* &= \frac{(a_0b_1 - a_1b_0)\, d_z}{(a_2b_1 - a_1b_2)\, d_z + (a_3b_1 - a_1b_3)c}, \\ z^* &= \frac{cy^*}{d_z}, \end{aligned}$$

where

$$a_2 = \frac{ma}{fnk_h} + \frac{a-d_x}{k_h}, \qquad a_3 = \frac{a}{fk_h} + \frac{a-d_x}{k_h}, \qquad b_1 = \frac{nb}{mfk_h}, \qquad b_3 = \frac{nbk_t + mfk_h(b-d_y)}{mfk_hk_t}.$$

3.1.2. Characteristic equation

In order to determine the stability of an equilibrium $E(x, y, z)$, we linearize system (2) about E and obtain

$$w'(t) = Aw(t) + Bw(t - \tau),$$

where

$$w(t) = (x(t), y(t), z(t))^\top,$$
$$A = \begin{bmatrix} a_0 - 2a_1x - a_2y - a_3z & -a_2x & -a_3x \\ -b_1y & b_0 - b_1x - 2b_2y - b_3z & -b_3y \\ 0 & 0 & -d_z \end{bmatrix},$$
$$B = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & c & 0 \end{bmatrix},$$

where matrices A and B are computed at the equilibrium under consideration. The stability is determined by computing the roots of the characteristic equation

$$\det\left(A + Be^{-\lambda\tau} - \lambda I\right) = 0. \tag{4}$$

3.1.3. Nonpersistence

THEOREM 2. *Suppose the interior equilibrium $E_3(x^*, y^*, z^*)$ exists. Whenever either, (or both)*

(i) $a_0 < a_2\hat{y} + a_3\hat{z}$, *or*
(ii) $b_0 < b_1\bar{x}$,

then system (2) is nonpersistent for all $\tau \geq 0$ provided $d_z(2b_2\hat{y} + b_3\hat{z} - b_0) > cb_3\hat{z}$. On the other hand, if $d_z(2b_2\hat{y} + b_3\hat{z} - b_0) < cb_3\hat{z}$, then system (2) is nonpersistent at least for small values of the time delay.

PROOF. Clearly, the trivial equilibrium is a hyperbolic saddle point. The characteristic equation about $E_1(\bar{x}, 0, 0)$ is given by

$$\begin{vmatrix} a_0 - 2a_1\bar{x} - \lambda & -a_2\bar{x} & -a_3\bar{x} \\ 0 & b_0 - b_1\bar{x} - \lambda & 0 \\ 0 & ce^{-\lambda\tau} & -d_z - \lambda \end{vmatrix} = 0.$$

Hence, the eigenvalues are

$$\lambda_1 = a_0 - 2a_1\bar{x} = -\frac{aP - nfk_hd_x}{nfk_h} < 0,$$
$$\lambda_2 = b_0 - b_1\bar{x} = \frac{nbd_xk_h + bP(a - d_x)}{mk_h[a + (a - d_x)f]} - d_y,$$
$$\lambda_3 = -d_z < 0.$$

In the case $b_0 < b_1\bar{x}$, all eigenvalues are negative and E_1 is asymptotically stable for all $\tau \geq 0$. Therefore, a necessary condition for the tumor growth is $b_0 > b_1\bar{x}$, i.e.,

$$P > [b(a - d_x)]^{-1}[(a - d_x)mfk_hd_y + (amd_y - bnd_x)k_h].$$

Let (i) hold. Evaluating the Jacobian matrix about $E_2(0, \hat{y}, \hat{z})$, gives

$$J = \begin{bmatrix} a_0 - a_2\hat{y} - a_3\hat{z} & 0 & 0 \\ -b_1\hat{y} & b_0 - 2b_2\hat{y} - b_3\hat{z} & -b_3\hat{z} \\ 0 & ce^{-\lambda\tau} & -d_z \end{bmatrix}.$$

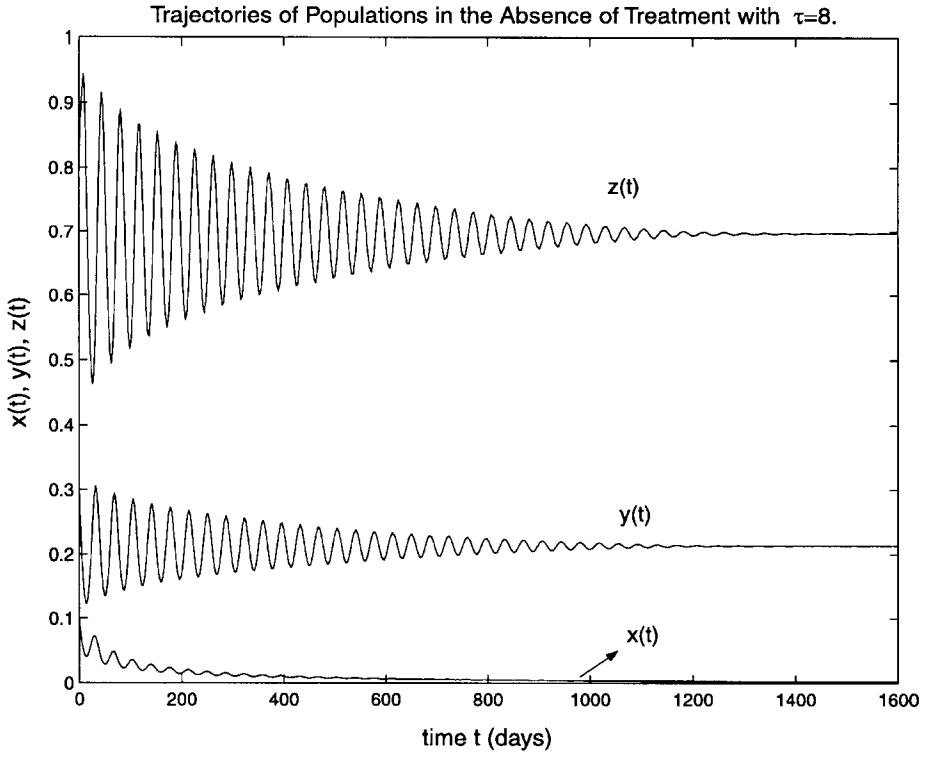

Figure 1. A solution for model (2) with $a = 3$, $p = 60$, $f = 0.67$, $n = 10$, $k_h = 20$, $k_t = 10$, $b = 3.01$, $d_x = 1$, $d_y = 0.3$, $m = 20$, $d_z = 0.2$, $c = 0.654$. Here, $E_2(0, 0.213, 0.698)$ is locally stable at least for $\tau < 8.4$. The interior equilibrium $E_3(0.002, 0.231, 0.698)$ cannot be globally stable and system (2) is nonpersistent at least for $\tau < 8.4$.

Hence, one of the eigenvalues is

$$\lambda = a_0 - a_2\hat{y} - a_3\hat{z},$$

which is negative by assumption. The other roots satisfy

$$\lambda^2 - (b_0 - 2b_2\hat{y} - b_3\hat{z} - d_z)\,\lambda - (b_0 - 2b_2\hat{y} - b_3\hat{z})\,d_z + cb_3\hat{z}e^{-\lambda\tau} = 0. \tag{5}$$

It follows from Freedman and Rao [19] that equation (5) has all roots with negative real parts for $\tau \geq 0$ if $d_z(2b_2\hat{y} + b_3\hat{z} - b_0) > cb_3\hat{z}$. On the other hand, if $d_z(2b_2\hat{y} + b_3\hat{z} - b_0) < cb_3\hat{z}$, then E_2 is asymptotically stable for $0 \leq \tau \leq d_z(2b_2\hat{y} + b_3\hat{z} - b_0)/cb_3\hat{z}$.

COROLLARY 1. *Whenever E_2 is stable in the x-direction, then the interior equilibrium E_3 cannot be globally stable for system (2), at least for small time delays.*

PROOF. It follows from Theorem 2 that stability of E_2 implies nonpersistence, at least for small values of delay. Hence, global stability cannot hold as it implies persistence of the system under consideration.

3.1.4. Permanence

In this section, we shall prove that the instability of boundary equilibria implies that system (2) is permanent. Thus, we prove the open problem in [15]. Before starting our theorem, we give some definitions.

Let $\Omega = \{(x, y, z) \in R^3_+ : 0 \leq x \leq a_1^{-1}a_0,\ 0 \leq y \leq b_2^{-1}b_0,\ 0 \leq z \leq d_z^{-1}b_2^{-1}b_0c\}$. Then, it is easy to show that Ω is an attracting invariant region for system (2).

DEFINITION 1. *System (2) is said to be uniformly persistent if there is an $\eta > 0$ (independent of initial data) such that every solution $(x(t), y(t), z(t))$ with nonnegative initial conditions satisfies*

$$\liminf_{t\to\infty} x(t) \geq \eta, \qquad \liminf_{t\to\infty} y(t) \geq \eta, \qquad \liminf_{t\to\infty} z(t) \geq \eta.$$

DEFINITION 2. *System (2) is said to be permanent if there exists a compact region $\Omega_0 \in \operatorname{int}\Omega$ such that every solution of equation (2) with nonnegative initial conditions will eventually enter and remain in region Ω_0.*

Clearly for a dissipative system uniform persistence is equivalent to permanence.

THEOREM 3. *System (2) is permanent provided*

$$\frac{a_2 d_z + a_3 c}{b_2 d_z + b_3 c} < \frac{a_0}{b_0} < \frac{a_1}{b_1}.$$

PROOF. Since we have uniform boundedness of solutions of system (2), we only need to show system (2) is uniformly persistent. It follows from Definition 1 that uniform persistence means strictly positive solutions are eventually uniformly bounded away from the boundary. To obtain persistence, two techniques have been employed: verifying that invariant sets in the boundary of the feasible region are not attractors and constructing Lyapunov-like functions. We shall analyze the boundary flow following techniques established in [20]. The basic idea of proving Theorem 3 is to show that all dynamics are trivial on the boundaries of R^3_+, that all equilibria are hyperbolic and acyclic, and that no equilibrium is asymptotically stable. By acyclicity, we mean that equilibria which are connected to other equilibria through a chain of saddle connectors are not eventually connected to themselves (see [21] for a formal definition).

For the convenience of description, we first present the uniform persistence theory for infinite-dimensional systems from [20]. Let X be a complete metric space. Suppose that X^0 is open, dense in X and $X^0 \subset X$, $X_0 \subset X$, $X_0 \cup X^0 = X$, $X_0 \cap X^0 = \emptyset$. Assume that $S(t)$ is a C^0 semigroup on X satisfying

$$S(t) : \begin{cases} X^0 \to X^0, \\ X_0 \to X_0. \end{cases} \tag{6}$$

Let $S_b(t) = S(t)|_{X_0}$ and let A_b be the global attractor for $S_b(t)$.

LEMMA 2. *Suppose that $S(t)$ satisfies equation (4) and we have the following:*

(i) *there is a $t_0 \geq 0$ such that $S(t)$ is compact for $t > t_0$,*
(ii) *$S(t)$ is point dissipative in X,*
(iii) *$\hat{A}_b = \bigcup_{x\in A_b} \omega(x)$ is isolated and has an acyclic covering $\hat{M}$, where $\hat{M} = \{M_1, M_2, \ldots, M_n\}$,*
(iv) *$W^s(M_i) \cap X^0 = \emptyset$ for $i = 1, 2, \ldots, n$.*

Then, X_0 is a uniform repellor with respect to X^0, i.e., there is an $\epsilon > 0$ such that for any $x \in X^0$, $\liminf_{t\to\infty} d(S(t)x, X_0) \geq \epsilon$, where d is the distance of $S(t)x$ from X_0.

Now we sketch a proof that the boundary planes of R^3_+ repel the positive solutions of system (2) uniformly. Let us define

$$C_1 = \left\{(\phi_1, \phi_2, \phi_3) \in C\left([-\tau, 0], R^3_+\right) : \phi_1(\theta) = 0, \phi_2(\theta) = 0, \theta \in [-\tau, 0]\right\},$$

$$C_2 = \left\{(\phi_1, \phi_2, \phi_3) \in C\left([-\tau, 0], R^3_+\right) : \phi_1(\theta) = 0, \phi_2(\theta)\phi_3(\theta) \neq 0, \theta \in [-\tau, 0]\right\},$$

$$C_3 = \left\{(\phi_1, \phi_2, \phi_3) \in C\left([-\tau, 0], R^3_+\right) : \phi_1(\theta) \neq 0, \phi_2(\theta) = 0, \theta \in [-\tau, 0]\right\}.$$

If $C_0 = C_1 \cup C_2 \cup C_3$ and $C^0 = \operatorname{int} C([-\tau, 0], R^3_+)$, it suffices to show that there exists an $\epsilon_0 > 0$ such that for any solution u_t of system (2) initiating from C^0, $\liminf_{t\to+\infty} d(u_t, C_0) \geq \epsilon_0$. To this end, we verify below that the conditions of Lemma 2 are satisfied. It is easy to see that C^0

and C_0 are positively invariant. Moreover, Conditions (i) and (ii) of Lemma 2 are clearly satisfied. Thus, we only need to verify Conditions (iii) and (iv). There are three constant solutions E_0, E_1, and E_2 in C_0, corresponding, respectively, to $x(t) = y(t) = z(t) = 0$; $x = \bar{x}$, $y(t) = z(t) = 0$; and $x(t) = 0$, $y(t) = \hat{y}$, $z(t) = \hat{z}(t)$.

In the following, we shall show that if invariant sets E_0, E_1, and E_2 are isolated, then $\{E_0, E_1, E_2\}$ is isolated and is an acyclic covering. To do this, we need to prove that any solution of system (2) initiating from C_i will remain in C_i, $i = 1, 2, 3$, which is easily shown. It is obvious that E_0 is isolated invariant. The proof of isolated invariance of E_1 and E_2 will follow.

We show that $W^s(E_i) \cap C^0 = \emptyset$, $i = 0, 1, 2$. Taking the case of $i = 1$ as an example to show the method, we assume the contrary, i.e., $W^s(E_1) \cap C^0 \neq \emptyset$. Then, there exists a positive solution $(x(t), y(t), z(t))$ of system (2) such that

$$(x(t), y(t), z(t)) \to \left(\frac{a_0}{a_1}, 0, 0\right), \qquad \text{as } t \to +\infty.$$

Let $t_0 > 0$ be sufficiently large such that

$$\begin{aligned} \frac{a_0}{a_1} - \epsilon_0 < x(t) < \frac{a_0}{a_1} + \epsilon_0, \\ -\epsilon_0 < z(t) < \epsilon_0, \qquad \text{for } t > t_0, \end{aligned}$$

where $\epsilon_0 > 0$ is sufficiently small. Then,

$$\frac{dy(t)}{dt} > y\left[b_0 - b_1\left(\frac{a_0}{a_1} + \epsilon_0\right) - b_2 y - b_3\epsilon_0\right].$$

Hence, we have

$$\liminf_{t\to+\infty} y(t) \geq \frac{b_0 b_1}{a_1 b_2}\left[\frac{a_1}{b_1} - \frac{a_0}{b_0} - \left(\frac{b_1 + b_3}{b_0 b_1}\right)\epsilon_0\right] > 0,$$

which contradicts $\lim_{t\to+\infty} y(t) = 0$. Hence, $W^s(E_1) \cap C^0 = \emptyset$. Therefore, we are able to conclude from Lemma 2 that C_0 repels the positive solutions of system (2) uniformly, and hence, the conclusion of Theorem 3 follows.

3.1.5. Global stability

Here, we consider the problem of global stability of the interior equilibrium E_3 defined in the previous section. We use ideas similar to Shukla [22]. However, we note that his proof is incomplete as he did not establish the boundedness of the solutions. For an arbitrary solution of (2), we define a positive definite function V by

$$\begin{aligned} V(x(t), y(t), z(t)) = \alpha_1\left[x(t) - x^* - x^* \ln\left(\frac{x(t)}{x^*}\right)\right] + \alpha_2\left[y(t) - y^* - y^* \ln\left(\frac{y(t)}{y^*}\right)\right] \\ + \frac{1}{2}\alpha_2 b_2 \int_{-\tau}^{0} [y(t+s) - y^*]^2\, ds + \frac{1}{2}\left(z(t) - z^*\right)^2, \end{aligned} \tag{7}$$

where α_1, α_2 are positive constants to be determined later.
The time derivative of V along the solutions of (2) is given by

$$\begin{aligned} \dot{V} = \alpha_1(x - x^*)(a_0 - a_1 x - a_2 y - a_3 z) + \alpha_2(y - y^*)(b_0 - b_1 x - b_2 y - b_3 z) \\ + \frac{1}{2} b_2 \alpha_2 \left[(y - y^*)^2 - (y(t-\tau) - y^*)^2\right] + (z - z^*)(cy(t-\tau) - d_z z). \end{aligned}$$

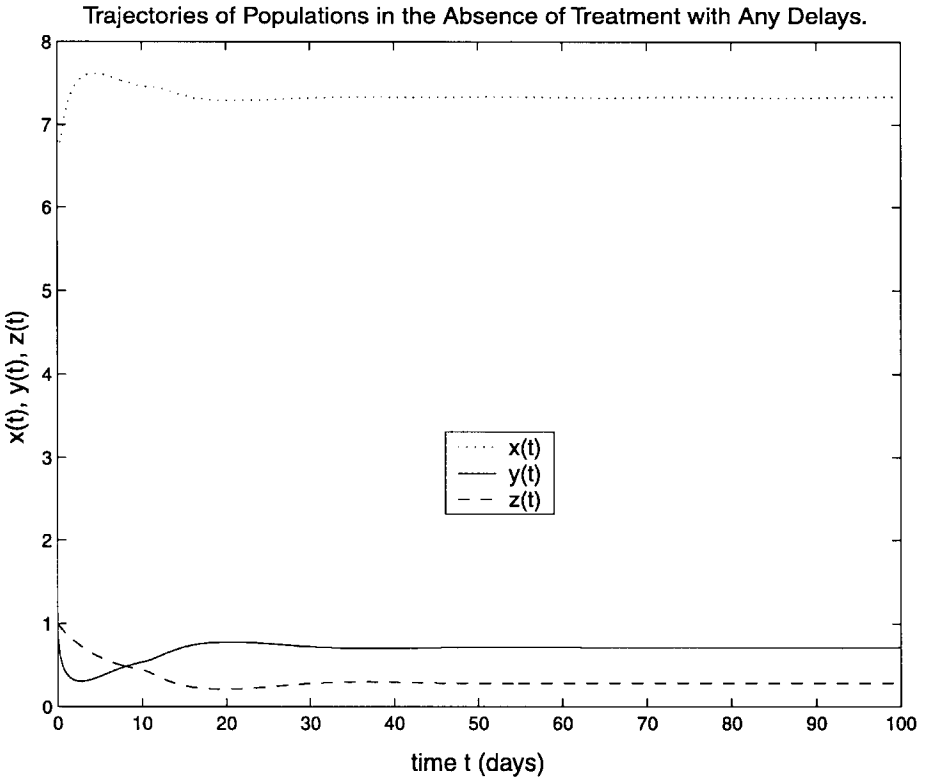

Figure 2. A solution for model (2) with $a = 3$, $p = 150$, $f = 0.67$, $n = 10$, $k_h = 10$, $k_t = 3$, $b = 6$, $d_x = d_y = 1$, $m = 20$, $d_z = 0.2$, $c = 0.08$. Here, $E_1(8.825, 0, 0)$ and $E_2(0, 1.677, 0.671)$ are unstable. System (2) is permanent and the interior equilibrium $E_3(7.342, 0.714, 0.286)$ is globally stable, independent of the delay.

After some algebraic manipulations, we obtain

$$\begin{aligned}\dot{V} = &-(x-x^*, y-y^*, z-z^*)\frac{1}{2}M(x-x^*, y-y^*, z-z^*)^\top \\ &-\frac{1}{2}b_2\alpha_2\left[(y(t-\tau)-y^*) - \frac{c}{b_2\alpha_2}(z-z^*)\right]^2,\end{aligned} \tag{8}$$

where the vector $(x-x^*, y-y^*, z-z^*)^\top$ denotes the transformation of vector $(x-x^*, y-y^*, z-z^*)$ and

$$M = \begin{bmatrix} 2a_1\alpha_1 & a_2\alpha_1 + b_1\alpha_2 & a_3\alpha_1 \\ a_2\alpha_1 + b_1\alpha_2 & b_2\alpha_2 & b_3\alpha_2 \\ a_3\alpha_1 & b_3\alpha_2 & 2\left(d_z - (2b_2\alpha_2)^{-1}c^2\right) \end{bmatrix}.$$

To ensure that $\dot{V}$ is negative definite along the solutions, we shall choose α_1,α_2 such that M is positive definite. As a result, we have the following theorem.

THEOREM 4. *The interior equilibrium $E_3(x^*, y^*, z^*)$ for system (2) is globally stable provided there exist $\alpha_1 > 0$, $\alpha_2 > 0$ such that M is positive definite.*

3.1.6. Stability and Hopf bifurcation

As shown in the previous section, a stable boundary equilibrium implies $E_3(x^*, y^*, z^*)$ cannot be globally stable, at least for small τ and that the system is nonpersistent for such a delay. Thus, it is of interest to know if E_3 can be locally stable. We now address ourselves to this question.

Computing the characteristic polynomial (4) about E_3, we obtain

$$H(\lambda) =: P(\lambda) + Q(\lambda)e^{-\lambda\tau} = \lambda^3 + p_2\lambda^2 + p_1\lambda + p_0 + (q_1\lambda + q_0)e^{-\lambda\tau} = 0, \tag{9}$$

where

$$\begin{aligned} p_1 &= (a_0 - 2a_1x^* - a_2y^* - a_1z^*)(b_0 - b_1x^* - 2b_2y^* - b_3z^*) - d_z(d_z - p_2) - a_2b_1x^*y^*, \\ p_2 &= d_z - a_0 - b_0 + (2a_1 + b_1)x^* + (a_2 + 2b_2)y^* + (a_1 + b_3)z^*, \\ p_0 &= d_z(p_1 + d_z(d_z - p_2)), \\ q_1 &= cb - 3y^*, \\ q_0 &= -c(a_1b_1 + a_2b_3)x^*y^*. \end{aligned} \tag{10}$$

Note that when the delay $\tau = 0$, equation (9) becomes

$$\lambda^3 + p_2\lambda^2 + (p_1 + q_1)\lambda + p_0 + q_0 = 0. \tag{11}$$

By the Routh-Hurwitz criteria, necessary and sufficient conditions for solutions λ to have negative real parts are

$$p_0 + q_0 > 0, \qquad p_1 + q_1 > 0, \qquad p_2(p_1 + q_1) > p_0 + q_0. \tag{12}$$

When $\tau \neq 0$, there are many ways in which we can determine if there is a root of the characteristic equation (9) with a positive real part. Geometric arguments can be used to establish the stability of an equilibrium, such as those used by Mahaffy in [23], where the argument principle is used to count the number of zeroes of the characteristic equation (9) on the right-hand side of the complex plane. However, in this case, we will resort to some results by Cooke and van den Driessche in Theorem 1 of [24].

They define the function

$$F(y) = |P(iy)|^2 - |Q(iy)|^2,$$

and analyze the function $F(y)$, giving conditions under which equation (9) is stable as a function of τ. They also gives conditions under which stability changes may occur as the delay τ is increased and show that in these cases the equilibrium is unstable for large enough τ. In short, they showed: (a) suppose that if $F(y) = 0$ has no positive roots, then if (9) is stable at $\tau = 0$, it remains stable for all $\tau \geq 0$, whereas if it is unstable at $\tau = 0$, it remains unstable for all $\tau \geq 0$, (b) if $F(y) = 0$ has at least one positive root and each positive root is simple, then as τ increases, stability switches may occur, and there exists a positive $\bar{\tau}$ such that (9) is unstable for all $\tau > \bar{\tau}$, and as τ varies from 0 to $\bar{\tau}$, at most a finite number of stability switches may occur.

Following the steps in this theorem, it is straightforward to check the stability of the equilibrium and find conditions for cancer growth. In this case, $F(y)$ is found to be

$$F(y) = y^6 + m_2y^4 + m_1y^2 + m_0,$$

where

$$m_2 = {p_2}^2 - 2p_1, \qquad m_1 = {p_1}^2 - 2p_0p_1 - {q_1}^2, \qquad m_0 = {p_0}^2 - {q_0}^2.$$

Let $y^2 = x$. Then, $F(y)$ becomes

$$F_1(x) = x^3 + m_2x^2 + m_1x + m_0. \tag{13}$$

Now, we will employ a lemma from [25] which we state here.

LEMMA 3. *Define*

$$\gamma = \frac{4}{27}{m_1}^3 - \frac{1}{27}{m_2}^2{m_1}^2 + \frac{4}{27}{m_2}^3m_0 - \frac{2}{3}m_2m_1m_0 + {m_0}^2.$$

Suppose that $m_0 > 0$. *Then,*

(I) *necessary and sufficient conditions for cubic equation (13) to have at least one simple positive root for* x *are:*
  (i) *either*
    (a) $m_2 < 0$, $m_1 \geq 0$, *and* $m_2{}^2 > 3m_1$, *or*
    (b) $m_1 < 0$, *and*
  (ii) $\gamma < 0$;

(II) *necessary and sufficient conditions for cubic equation (13) to have no positive real roots for* x *are either of the following,*
  (i) $3m_1 > m_2{}^2$,
  (ii) $3m_1 = m_2{}^2$,
  (iii) $m_2{}^2 > 3m_1$, *and* $\gamma > 0$ *or*
  (iv) $m_2{}^2 > 3m_1$ *and* $\gamma \leq 0$, $m_2 > 0$, *and* $m_1 > 0$.

Based on Lemmas 1 and 2 and methods in [24], we obtain the following stability theorems.

THEOREM 5. *Suppose that* $m_2{}^2 > 3m_1$, $\gamma \leq 0$, $m_2 > 0$, *and* $m_1 > 0$. *Then,*

1. *if* $p_0 + q_0 > 0$, $p_1 + q_1 > 0$, $p_2(p_1 + q_1) > p_0 + q_0$, *the stability of equilibrium* E_3 *is independent of delay* τ *and it remains stable for all* $\tau \geq 0$,
2. *if* $p_0 + q_0 \leq 0$, *or* $p_1 + q_1 \leq 0$, *or* $p_2(p_1 + q_1) \leq p_0 + q_0$, *the stability of equilibrium* E_3 *does not depend on* τ *and it remains unstable for all* $\tau \geq 0$.

THEOREM 6. *Suppose that* $m_2{}^2 > 3m_1$, $\gamma \geq 0$. *Then,*

1. *if (12) holds, the stability of equilibrium* E_3 *is independent of delay* τ *and it remains stable for all* $\tau \geq 0$,
2. *if (12) does not hold,* E_3 *remains unstable for all* $\tau \geq 0$.

THEOREM 7. *Assume that either (a)* $m_2 < 0$, $m_1 \geq 0$, *and* $m_2{}^2 > 3m_1$, *or (b)* $m_1 < 0$ *and* $\gamma < 0$. *Then, there exists a positive* $\bar{\tau}$ *such that*

1. *if* $p_0 + q_0 > 0$, $p_1 + q_1 > 0$, $p_2(p_1 + q_1) > p_0 + q_0$, *the equilibrium* E_3 *remains stable for* $0 \leq \tau \leq \bar{\tau}$, *and becomes unstable for all* $\tau \geq \bar{\tau}$,
2. *if* $p_0 + q_0 \leq 0$, *or* $p_1 + q_1 \leq 0$, *or* $p_2(p_1 + q_1) \leq p_0 + q_0$, *the equilibrium* E_3 *remains unstable for all* $\tau \geq \bar{\tau}$. *As* τ *varies from 0 to* $\bar{\tau}$, *at most a finite number of stability switches may occur.*

In cancer chemotherapy, stability switching is a very important issue in the design of a drug protocol. We must keep in mind that in many cases the drugs can prevent vascular endothelial precursor cells from continuing through their immigration, maturation into vascular endothelia cells, thus, trapping them at some points, where the cells die from natural cause. This effect can be interpreted as an increase in the delay τ. But as we have seen here, this trapping may have adverse effects, since it may cause a fixed point to become unstable when it was stable initially (Theorem 7). On the other hand, the same properties can be used to the clinicians advantage, if we are certain that our parameters are in the stability switching region and the equilibrium is unstable. In this case, it may be possible to use the same trapping mechanism to stabilize the cancer-free equilibrium.

Now by applying Theorem 1 in [24], it is also straightforward to check for possible Hopf bifurcations when we increase the delay τ. The importance of Hopf bifurcations in this context is that at the bifurcation point a limit cycle is formed around the fixed point, thus, resulting in stable periodic solutions. The existence of periodic solutions is of significance in cancer models because it implies that the cancer levels may oscillate around a fixed point even in the absence of any treatment. Such a phenomenon has been observed clinically and is known as "Jeff's Phenomenon" [25]. In this section, we will prove that such a Hopf bifurcation can occur. Here,

we are interested in the bifurcation of the coexistence of three populations. Hence, we consider the characteristic equation (9) and rewrite it as

$$\lambda^3 + p_2\lambda^2 + p_1\lambda + p_0 + (q_1\lambda + q_0)e^{-\lambda\tau} = 0. \tag{14}$$

Let $\lambda = u + iv (u, v \in R)$ and rewrite (14) in terms of its real and imaginary parts as

$$\begin{aligned} u^3 - 3uv^2 + p_2\left(u^2 - v^2\right) + p_1u + p_0 &= e^{-u\tau}[q_1v\sin(v\tau) + (q_1u + q_0)\cos(v\tau)], \\ 3u^2v - v^3 + 2p_2uv + p_1v &= e^{-u\tau}[(q_1u + q_0)\sin(v\tau) - q_1v\cos(v\tau)]. \end{aligned} \tag{15}$$

Let $\bar{\tau}$ be such that $u(\bar{\tau}) = 0$. Then, the above equations reduce to

$$\begin{aligned} p_2\bar{v}^2 - p_0 &= q_1\bar{v}\sin(\bar{v}\bar{\tau}) + q_0\cos(\bar{v}\bar{\tau}), \\ -\bar{v}^3 + p_1\bar{v} &= q_0\sin(\bar{v}\bar{\tau}) - q_1\bar{v}\cos(\bar{v}\bar{\tau}). \end{aligned} \tag{16}$$

It follows by taking the sum of squares that

$$\bar{v}^6 + \left({p_2}^2 - 2p_1\right)\bar{v}^4 + \left({p_1}^2 - 2p_0p_2 - {q_1}^2\right)\bar{v}^2 + {p_0}^2 - {q_0}^2 = 0. \tag{17}$$

Suppose that $\bar{v}_1$ is the last positive simple root of equation (17). We now show that with this value of $\bar{v}_1$, there is a $\bar{\tau}_1$ such that $u(\bar{\tau}_1) = 0$ and $v(\bar{\tau}_1) = \bar{v}_1$. Given $\bar{v}_1$, equation (16) can be written as

$$\begin{aligned} A\cos(\bar{\tau}_1\bar{v}_1) + B\sin(\bar{\tau}_1\bar{v}_1) &= C, \\ A\sin(\bar{\tau}_1\bar{v}_1) - B\cos(\bar{\tau}_1\bar{v}_1) &= D, \end{aligned} \tag{18}$$

where $C^2 + D^2 = A^2 + B^2 = G^2$, say, where $G > 0$. The equations

$$\begin{aligned} A &= G\cos\alpha, \\ B &= G\sin\alpha \end{aligned} \tag{19}$$

determine a unique $\alpha \in [0, 2\pi]$. With this value of α, we have

$$\begin{aligned} G\cos(\bar{\tau}_1\bar{v}_1)\cos\alpha + G\sin(\bar{\tau}_1\bar{v}_1)\sin\alpha &= C, \\ G\sin(\bar{\tau}_1\bar{v}_1)\cos\alpha - G\cos(\bar{\tau}_1\bar{v}_1)\sin\alpha &= D. \end{aligned} \tag{20}$$

Hence,

$$G\cos(\bar{\tau}_1\bar{v}_1 - \alpha) = C, \qquad G\sin(\bar{\tau}_1\bar{v}_1 - \alpha) = D. \tag{21}$$

These equations determine $\bar{\tau}_1\bar{v}_1 - \alpha$ uniquely in $[\alpha/\bar{v}_1, (\alpha + 2\pi)/\bar{v}_1]$. To apply the Hopf bifurcation theorem as stated in [26], we state and prove the following theorem.

THEOREM 8. *Suppose that equation (17) has at least one simple positive root and $\bar{v}_1$ is the last such root. Then, $iv(\bar{\tau}_1) = i\bar{v}_1$ is a simple root of equation (14) and $u(\tau) + iv(\tau)$ is differentiable with respect to τ in a neighborhood of $\tau = \bar{\tau}_1$.*

PROOF. To show that $iv(\bar{\tau}_1) = i\bar{v}_1$ is a simple root, we investigate equation (14)

$$H(\lambda) = \lambda^3 + p_2\lambda^2 + p_1\lambda + p_0 + (q_1\lambda + q_0)e^{-\lambda\tau} = 0.$$

Any double root λ satisfies

$$H(\lambda) = 0, \qquad \dot{H}(\lambda) = 0,$$

where

$$\dot{H}(\lambda) = 3\lambda^2 + 2p_2\lambda + p_1 + (q_1 - \tau q_1\lambda - \tau q_0)e^{-\lambda\tau}. \tag{22}$$

Substituting $\lambda = i\bar{v}_1$ and $\tau = \bar{\tau}_1$ into (14),(22) and equating real and imaginary parts, if $i\bar{v}_1$ is a double root, we obtain

$$\begin{aligned} p_2\bar{v}_1^2 - p_0 &= q_1\bar{v}_1 \sin(\bar{v}_1\bar{\tau}_1) + q_0 \cos(\bar{v}_1\bar{\tau}_1), \\ p_1\bar{v}_1 - \bar{v}_1^3 &= -q_1\bar{v}_1 \cos(\bar{v}_1\bar{\tau}_1) + q_0 \sin(\bar{v}_1\bar{\tau}_1), \end{aligned} \tag{23}$$

and

$$\begin{aligned} 3\bar{v}_1^2 - p_1 &= (q_1 - \bar{\tau}_1 q_0)\cos(\bar{v}_1\bar{\tau}_1) + \bar{v}_1\bar{\tau}_1 q_1 \sin(\bar{v}_1\bar{\tau}_1), \\ 2p_2\bar{v}_1 &= (q_1 - \bar{\tau}_1 q_0)\sin(\bar{v}_1\bar{\tau}) + \bar{v}_1\bar{\tau}_1 q_1 \cos(\bar{v}_1\bar{\tau}_1). \end{aligned} \tag{24}$$

Now, equation (16) can be written as $h(\bar{v}_1) = 0$, where

$$h(v) = \left(p_2 v^2 - p_0\right)^2 + \left(p_1 v - v^3\right)^2 - q_1^2 v^2 - {q_0}^2, \tag{25}$$

$$\dot{h}(v) = 2\left(p_1 v^2 - p_0\right) 2p_2 v + 2\left(p_1 v - v^3\right)\left(p_1 - 3v^2\right) - 2v{q_1}^2. \tag{26}$$

By substituting (23) and (24) into (25),(26), we obtain

$$h(\bar{v}_1) = \dot{h}(\bar{v}_1) = 0.$$

It follows that $\bar{v}_1$ is a double root of equation (25) and that $h(\bar{v}_1) = \dot{h}(\bar{v}_1) = 0$, which is a contradiction since we have assumed that $\bar{v}_1$ is a simple root of (17). Hence, $i\bar{v}_1$ is a simple root of equation (14), which is an analytic equation. By using the analytic version of the implicit function theorem [27], we can see that $u(\tau) + iv(\tau)$ is defined and analytic in a neighborhood of $\tau = \bar{\tau}_1$. The proof is complete! ∎

Next, to establish Hopf bifurcation at $\tau = \bar{\tau}_1$, we need to verify the transversality condition

$$\left.\frac{du}{d\tau}\right|_{\tau=\bar{\tau}_1} \neq 0.$$

By differentiating equations (15) with respect to τ and setting $u = 0$ and $v = \bar{v}_1$, we obtain

$$\begin{aligned} A_1 \left.\frac{du}{d\tau}\right|_{\tau=\bar{\tau}_1} - B_1 \left.\frac{dv}{d\tau}\right|_{\tau=\bar{\tau}_1} &= p_0\bar{v}_1 \sin(\bar{v}_1\bar{\tau}_1) - p_1\bar{v}_1^2 \cos(\bar{v}_1\bar{\tau}_1), \\ B_1 \left.\frac{du}{d\tau}\right|_{\tau=\bar{\tau}_1} + A_1 \left.\frac{dv}{d\tau}\right|_{\tau=\bar{\tau}_1} &= p_1\bar{v}_1^2 \sin(\bar{v}_1\bar{\tau}_1) + p_0\bar{v}_1 \cos(\bar{v}_1\bar{\tau}_1), \end{aligned} \tag{27}$$

where

$$\begin{aligned} A_1 &= p_1 - 3\bar{v}_1^2 + \bar{\tau}_1[q_1 \cos(\bar{v}_1\bar{\tau}_1) - q_1\bar{v}_1 \sin(\bar{v}_1\bar{\tau}_1) - q_0 \cos(\bar{v}_1\bar{\tau}_1)], \\ B_1 &= 2p_2\bar{v}_1 + \bar{\tau}_1[q_0 \sin(\bar{v}_1\bar{\tau}_1) - q_1\bar{v}_1 \cos(\bar{v}_1\bar{\tau}_1) - q_1 \sin(\bar{v}_1\bar{\tau}_1)]. \end{aligned} \tag{28}$$

Solving for $\frac{du}{d\tau}$, $\frac{dv}{d\tau}$ from (27) with the help of (16), we have

$$\left.\frac{du}{d\tau}\right|_{\tau=\bar{\tau}_1} = \frac{\bar{v}_1^2\left[3\bar{v}_1^4 + 2\left({p_2}^2 - 2p_1\right)\bar{v}_1^2 + {p_1}^2 - 2p_2p_0 - {q_1}^2\right]}{{A_1}^2 + {B_1}^2}. \tag{29}$$

Let $z = \bar{v}_1^2$. Then, equation (17) reduces to

$$\Phi(z) = z^3 + \left({p_2}^2 - 2p_1\right)z^2 + \left({p_1}^2 - 2p_2p_0 - {q_1}^2\right)z + {p_0}^2 - {q_0}^2.$$

Hence,

$$\frac{d\Phi}{dz} = 3z^2 + 2\left({p_2}^2 - 2p_1\right)z + {p_1}^2 - 2p_2p_0 - {q_1}^2.$$

As $\bar{v}_1^2$ is the last positive single root of equation (17), then

$$\left.\frac{d\Phi}{dz}\right|_{z=\bar{v}_1^2} > 0.$$

Therefore,

$$\left.\frac{du}{d\tau}\right|_{\tau=\bar{\tau}_1} = \frac{\bar{v}_1^2}{{A_1}^2 + {B_1}^2}\left.\frac{d\Phi}{dz}\right|_{z=\bar{v}_1^2} > 0.$$

We summarize the preceding details in the following theorem.

THEOREM 9. *Suppose that (17) has at least one simple positive root and $\bar{v}_1$ is the last such root. Then, a Hopf bifurcation occurs as τ passes through $\bar{\tau}_1$. On the other hand, if (17) has no positive real roots, then the interior equilibrium E^* is locally asymptotically sable for all values of τ.*

4. THE CONTINUOUS TREATMENT CASE

Here, we consider the full model (1). Again equilibria are derived and listed. We study the local stability of some relevant equilibria by analytical and numerical methods.

4.1. Equilibria

In this case, we denote the equilibria by variations on F and again some of them are physiologically nonfeasible. As in the no treatment case, the trivial equilibrium $F_0(0,0,0,\xi^{-1}\Delta)$ always exists. The following equilibria may or may not exist:

$$F_1(\bar{x},0,0,\bar{u}), \qquad F_2(0,\hat{y},\hat{z},\hat{u}), \qquad F_3(x^*,y^*,z^*,u^*).$$

Here, the symbols that are the same as in the no treatment case may have different values.

Equilibrium F_1 exists provided that the algebraic system

$$\begin{aligned} \frac{aP_e}{nfk_h} - d_x - (a-d_x)\frac{x}{k_h} - \frac{p_1 u}{a_1+x} &= 0, \\ \Delta - \left[\xi + \frac{c_1 x}{a_1+x}\right] u &= 0 \end{aligned} \tag{30}$$

has a positive solution. System (30) has a positive solution provided that the quadratic equation

$$a_1(\xi+c_1)x^2 + \left({a_1}^2\xi - a_0\xi - a_0c_1\right)x + p_1\Delta - a_0a_1\xi = 0 \tag{31}$$

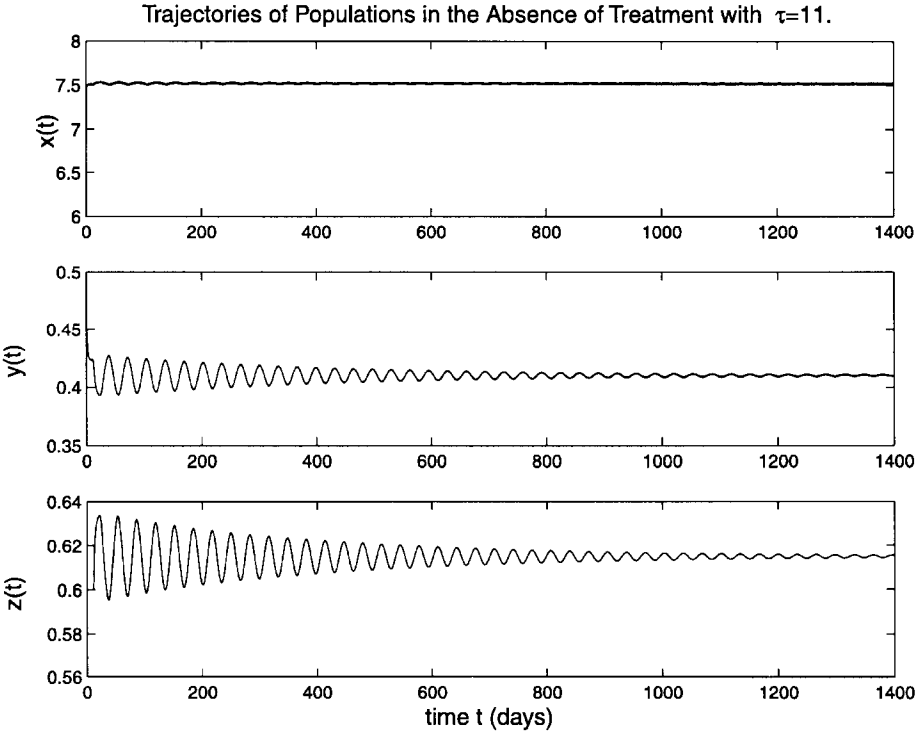

Figure 3. A solution for model (2) with $a = 3$, $p = 150$, $f = 0.67$, $n = 10$, $k_h = 10$, $k_t = 3$, $b = 6$, $d_x = d_y = 1$, $m = 20$, $d_z = 0.2$, $c = 0.3$. Here, the interior equilibrium $E_3(7.679, 0.397, 0.5955)$ is locally stable when the delay $\tau < 12.14$.

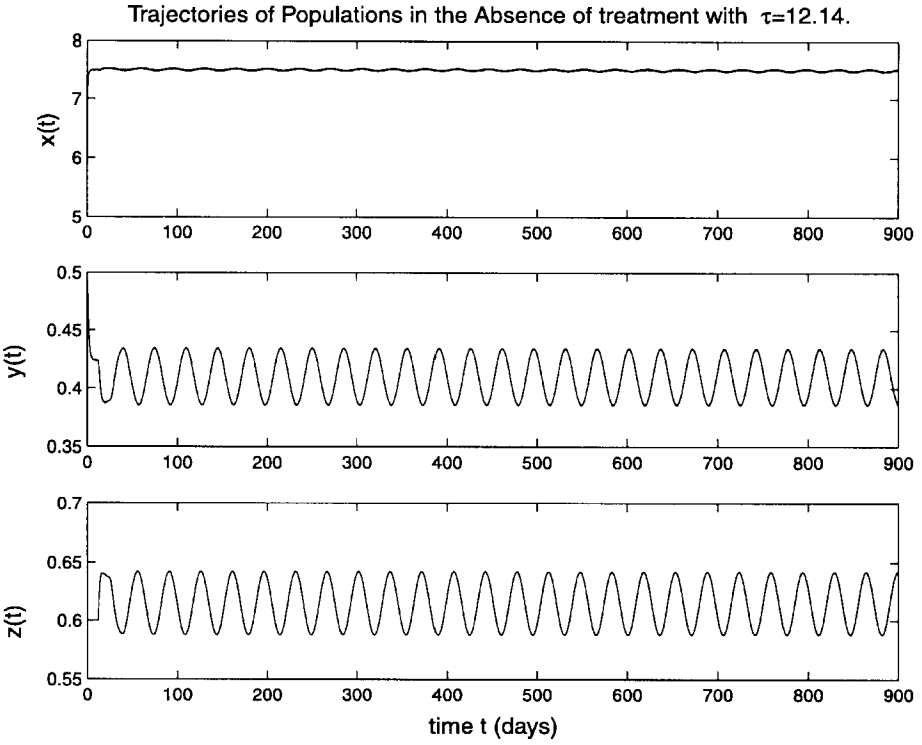

Figure 4. A solution for model (2) with $a = 3$, $p = 40$, $f = 0.67$, $n = 10$, $k_h = 10$, $k_t = 5$, $b = 4$, $d_x = d_y = 1$, $m = 15$, $d_z = 0.2$, $c = 0.3$. Here, the interior equilibrium $E_3(1.027, 0.068, 0.102)$ bifurcates at $\tau = 12.14$ and periodic solutions occur.

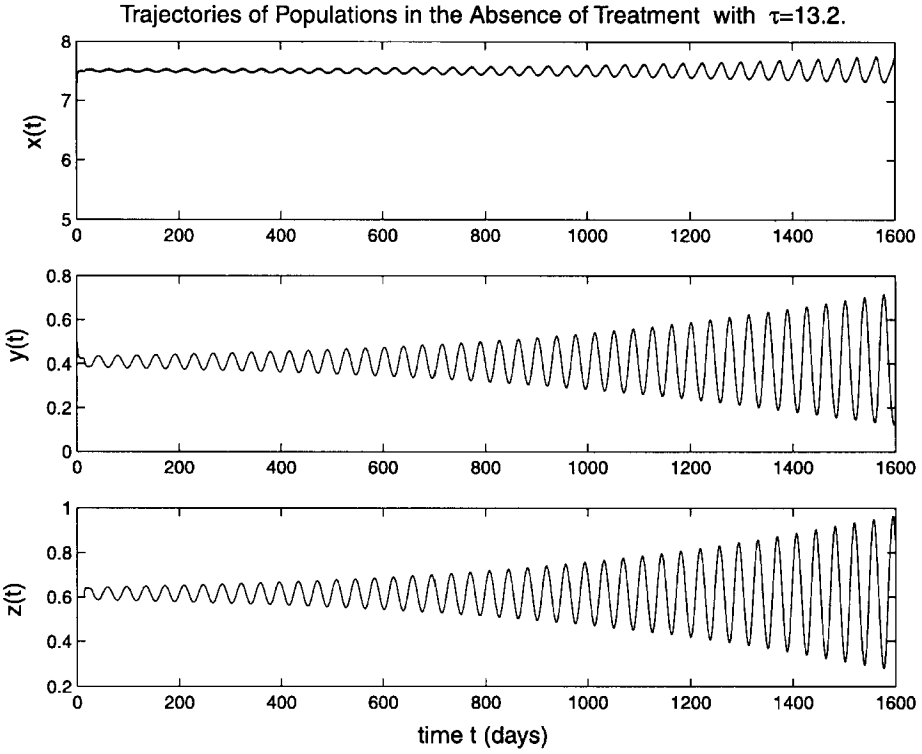

Figure 5. A solution for model (2) with $a = 3$, $p = 150$, $f = 0.67$, $n = 10$, $k_h = 10$, $k_t = 3$, $b = 6$, $d_x = d_y = 1$, $m = 20$,$d_z = 0.2$, $c = 0.3$. Here, the interior equilibrium $E_3(7.679, 0.397, 0.5955)$ becomes unstable when $\tau > 12.14$.

has a positive solution. Here, a_0, a_1 are defined in the previous section. If

$$p_1\Delta < a_0 a_1 \xi, \tag{32}$$

then equation (31) has a unique positive solution. Necessary and sufficient conditions for (31) to have two positive solutions are

$$\begin{aligned} &{a_1}^2\xi < a_0\left(\xi + c_1\right), \\ &a_0 a_1 \xi < p_1\Delta < \frac{\left({a_1}^2\xi - a_0\xi - a_0 c_1\right)^2}{4a_1\left(\xi + c_1\right)}. \end{aligned} \tag{33}$$

From the above, we have proved the following lemma.

LEMMA 4. *If (32) holds, then F_1 exists uniquely. If (33) holds, then there exist two distinct equilibria of type F_1.*

Although the other equilibria F_2 and F_3 may exist, sufficient conditions for their existence are not easily obtained. In Section 4.3.2, we will present some numerical examples to illustrate cases when these equilibria exist.

4.2. Local Stability

Here, the Jacobian matrix around a general equilibrium $F(x, y, z, u)$ is

$$M = \begin{bmatrix} a_{11} & -a_2 x & -a_3 x & -\dfrac{p_1 x}{a_1 + x} \\ -b_1 y & a_{22} & -b_3 y & -\dfrac{p_2 y}{a_2 + y} \\ 0 & e^{-\lambda\tau} & -d_z & -\dfrac{p_3 z}{a_3 + z} \\ -\dfrac{a_1 c_1 u}{(a_1 + x)^2} & -\dfrac{a_2 c_2 u}{(a_2 + y)^2} & -\dfrac{a_3 c_3 u}{(a_3 + z)^2} & a_{33} \end{bmatrix},$$

where

$$\begin{aligned} a_{11} &= a_0 - 2a_1 x - a_2 y - a_3 z - \frac{p_1 a_1 u}{(a_1 + x)^2}, \\ a_{22} &= b_0 - b_1 x - 2b_2 y - b_3 z - \frac{p_2 a_2 u}{(a_2 + y)^2}, \\ a_{33} &= -\left(\xi + \frac{c_1 x}{a_1 + x} + \frac{c_2 y}{a_2 + y} + \frac{c_3 z}{a_3 + z}\right). \end{aligned}$$

4.2.1. Analysis of F_0

It is quite easy to get the eigenvalues associated with the trivial equilibrium F_0 which are

$$\begin{aligned} \lambda_1^{(0)} &= a_0 > 0, \\ \lambda_2^{(0)} &= b_0 > 0, \\ \lambda_3^{(0)} &= -d_z < 0, \\ \lambda_4^{(0)} &= -\xi < 0. \end{aligned}$$

Hence, F_0 is a hyperbolic saddle point.

4.2.2. Analysis of F_1

In this case, the Jacobian matrix is given by

$$M_1 = \begin{bmatrix} a_0 - 2a_1\bar{x} - \dfrac{p_1a_1\bar{u}}{(a_1+\bar{x})^2} & -a_2\bar{x} & -a_3\bar{x} & -\dfrac{p_1\bar{x}}{a_1+\bar{x}} \\ 0 & b_0 - b_1\bar{x} & 0 & 0 \\ 0 & e^{-\lambda\tau} & -d_z & 0 \\ -\dfrac{a_1c_1\bar{u}}{(a_1+\bar{x})^2} & -a_2^{-1}c_2\bar{u} & -a_3^{-1}c_3\bar{u} & -\left(\xi + \dfrac{c_1\bar{x}}{a_1+\bar{x}}\right) \end{bmatrix}.$$

Hence, two eigenvalues are

$$\lambda_2^{(1)} = b_0 - b_1\bar{x}, \qquad \lambda_3^{(1)} = -d_z.$$

Other eigenvalues satisfy

$$\sigma(A) = \left\{\lambda_i^{(1)} \mid \lambda^2 - \operatorname{Tr}(A)\lambda + \det(A) = 0,\ i = 1,4\right\},$$

where

$$A = \begin{bmatrix} a_0 - 2a_1\bar{x} - \dfrac{p_1a_1\bar{u}}{(a_1+\bar{x})^2} & -\dfrac{p_1\bar{x}}{a_1+\bar{x}} \\ -\dfrac{a_1c_1\bar{u}}{(a_1+\bar{x})^2} & -\left(\xi + \dfrac{c_1\bar{x}}{a_1+\bar{x}}\right) \end{bmatrix}.$$

By the Routh-Hurwitz criteria [28], if $\operatorname{Tr}(A) < 0$ and $\det(A) > 0$, then the eigenvalues of A have negative real parts. If $\bar{x} > a_0/2a_1$, then

$$\operatorname{Tr}(A) = a_0 - 2a_1\bar{x} - \left[\frac{p_1a_1\bar{u}}{(a_1+\bar{x})^2} + \xi + \frac{c_1\bar{x}}{a-1+\bar{x}}\right] < 0,$$

$$\det(A) = \frac{p_1a_1\xi\bar{x}}{(a_1+\bar{x})^2} + (2a_1\bar{x} - a_0)\left(\xi + \frac{c_1\bar{x}}{a_1+\bar{x}}\right) > 0.$$

As a result, we have the following lemma.

LEMMA 5. *If $\bar{x} > a_0/2a_1$, then the real parts of eigenvalues $\lambda_1^{(1)}$ and $\lambda_4^{(1)}$ are negative.*

Based on Lemma 5, we obtain the following theorem.

THEOREM 10. *Suppose that $\bar{x} > a_0/2a_1$ and $b_0 \neq b_1\bar{x}$. If $b_0 > b_1\bar{x}$, then F_1 is a hyperbolic saddle point. On the other hand, if $b_0 < b_1\bar{x}$, then F_1 is asymptotically stable.*

4.2.3. Analysis of F_2

In this case, the Jacobian matrix is given by

$$M_2 = \begin{bmatrix} M_{11}^{(2)} & 0 & 0 & 0 \\ -b_1\hat{y} & M_{22}^{(2)} & -b_3\hat{y} & -M_{24}^{(2)} \\ 0 & e^{-\lambda\tau} & -d_z & -M_{34}^{(2)} \\ -a_1^{-1}c_1\hat{u} & -M_{42}^{(2)} & -M_{43}^{(2)} & -M_{44}^{(2)} \end{bmatrix},$$

where

$$M_{11}^{(2)} = a_0 - a_2\hat{y} - a_3\hat{z} - a_1^{-1}p_1\hat{u}, \qquad M_{22}^{(2)} = b_0 - 2b_2\hat{y} - b_3\hat{z} - \frac{p_2a_2\hat{u}}{(a_2+\hat{u})^2},$$

$$M_{24}^{(2)} = \frac{p_2\hat{y}}{a_2+\hat{y}}, \qquad M_{34}^{(2)} = \frac{p_3\hat{z}}{a_3+\hat{z}}, \qquad M_{44}^{(2)} = -\left(\xi + \frac{c_2\hat{y}}{a_2+\hat{y}} + \frac{c_3\hat{z}}{a_3+\hat{z}}\right),$$

$$M_{42}^{(2)} = \frac{a_2c_2\hat{u}}{(a_2+\hat{y})^2}, \qquad M_{43}^{(2)} = \frac{a_3c_3\hat{u}}{(a_3+\hat{z})^2}.$$

Hence, one of the eigenvalues is

$$\lambda_1^{(2)} = a_0 - a_2\hat{y} - a_3\hat{z} - a_1^{-1}p_1\hat{u}.$$

Other eigenvalues satisfy

$$\lambda^3 + p_2\lambda^2 + p_1\lambda + p_0 + (q_1\lambda + q_0)\, e^{-\lambda\tau} = 0, \tag{34}$$

where

$$\begin{aligned}
p_2 &= d_z - M_{22}^{(2)} - M_{44}^{(2)},\\
p_1 &= M_{22}^{(2)}M_{44}^{(2)} - d_z\left(M_{22}^{(2)} + M_{44}^{(2)}\right) - M_{34}^{(2)}M_{43}^{(2)} - M_{24}^{(2)}M_{42}^{(2)},\\
p_0 &= d_z M_{22}^{(2)}M_{44}^{(2)} - d_z M_{24}^{(2)}M_{42}^{(2)} + M_{34}^{(2)}M_{43}^{(2)}M_{22}^{(2)},\\
q_1 &= b_3\hat{y},\\
q_0 &= -b_3 M_{44}^{(2)}\hat{y} - M_{24}^{(2)}M_{42}^{(2)}.
\end{aligned}$$

Equation (34) is the characteristic polynomial (9) in the previous section with new coefficient values. Computing γ, m_2, m_1, m_0 and employing the same arguments as before, we have the following theorems.

THEOREM 11. *Suppose that* ${m_2}^2 > 3m_1$, $\gamma \le 0$, $m_2 > 0$, *and* $m_1 > 0$. *Then,*

1. *if* $p_0 + q_0 > 0$, $p_1 + q_1 > 0$, $p_2(p_1 + q_1) > p_0 + q_0$, *the stability of equilibrium* F_2 *is independent of delay* τ *and it remains stable for all* $\tau \ge 0$, *provided that* $a_0 < a_2\hat{y} + a_3\hat{z} + a_1^{-1}p_1\hat{u}$,
2. *if* $p_0 + q_0 \le 0$, *or* $p_1 + q_1 \le 0$, *or* $p_2(p_1 + q_1) \le p_0 + q_0$, *the stability of equilibrium* F_2 *does not depend on* τ *and it remains unstable for all* $\tau \ge 0$.

THEOREM 12. *Assume that either (a)* $m_2 < 0$, $m_1 \ge 0$, *and* ${m_2}^2 > 3m_1$, *or (b)* $m_1 < 0$ *and* $\gamma < 0$. *Then, there exists a positive* $\bar{\tau}$ *such that*

1. *if* $p_0 + q_0 > 0$, $p_1 + q_1 > 0$, $p_2(p_1 + q_1) > p_0 + q_0$, *equilibrium* F_2 *remains stable for* $0 \le \tau \le \bar{\tau}$ *when* $a_0 < a_2\hat{y} + a_3\hat{z} + a_1^{-1}p_1\hat{u}$, *and becomes unstable for all* $\tau \ge \bar{\tau}$,
2. *if* $p_0 + q_0 \le 0$, *or* $p_1 + q_1 \le 0$, *or* $p_2(p_1 + q_1) \le p_0 + q_0$, *equilibrium* F_2 *remains unstable for all* $\tau \ge \bar{\tau}$. *As* τ *varies from* 0 *to* $\bar{\tau}$, *at most a finite number of stability switches may occur.*

4.3. Global Stability

Note that if F_1 is achieved, then healthy cells eventually win the competition with the cancer cells, which is the most desirable result. F_3 represents the coexistence of all four populations. In this section, we derive criteria for the global stabilities of F_1 and F_3 with respect to solutions initiating in $\operatorname{int}\mathbf{R}_+^4$.

4.3.1. Global stability of F_1

In $\operatorname{int}\mathbf{R}_+^4$, we choose the Liapunov function,

$$\begin{aligned}
V(x(t), y(t), z(t), u(t)) = \alpha_1\left[x(t) - \bar{x} - \bar{x}\ln\left(\frac{x(t)}{\bar{x}}\right)\right] + \alpha_2 y(t) + \frac{1}{2}z^2(t)\\
+\frac{1}{2}\alpha_2 b_2\int_{-\tau}^{0}[y(t+s)]^2\,ds + \frac{1}{2}\alpha_3(u(t) - \bar{u})^2,
\end{aligned} \tag{35}$$

where α_1, α_2, α_3 are positive constants to be determined later. The derivative of (35) along solutions of (1) is given by

$$\begin{aligned}\dot{V} &= \alpha_1(x-\bar{x})\left[a_0 - a_1x - a_2y - a_3z - \frac{p_1ux}{a_1+x}\right]\\ &\quad +\alpha_2 y\left[b_0 - b_1x - b_2y - b_3z - \frac{p_2uy}{a_2+y}\right]\\ &\quad +\frac{1}{2}\alpha_2 b_2[y^2 - (y(t-\tau))^2] + z\left(cy(t-\tau) - d_zz - \frac{p_3uz}{a_3+z}\right)\\ &\quad +\alpha_3(u-\bar{u})\left[\Delta - \left(\xi + \frac{c_1x}{a_1+x} + \frac{c_2y}{a_2+y} + \frac{c_3z}{a_3+z}\right)u\right].\end{aligned} \tag{36}$$

After some computing, we obtain

$$\begin{aligned}\dot{V} &= -\alpha_1(a_1-a_{11})(x-\bar{x})^2 - \alpha_2\left(\frac{1}{2}b_2 - a_{22}\right)y^2 - (d_z+a_{33})z^2\\ &\quad -\frac{1}{2}b_2\alpha_2\left[(y(t-\tau) - c(b_2\alpha_2)^{-1}z\right]^2 - \alpha_3(\xi+a_{44})(u-\bar{u})^2\\ &\quad -\Big\{(a_2\alpha_1 + b_1\alpha_2)(x-\bar{x})y + (a_{12}\alpha_1 + a_{21}\alpha_3)(u-\bar{u})(x-\bar{x}) + b_3\alpha_2yz\\ &\quad +a_3\alpha_1(x-\bar{x})z + a_{14}\alpha_3z(u-\bar{u}) + \left(\frac{\alpha_2p_2}{a_2} + a_{13}\alpha_3\right)y(u-\bar{u})\Big\},\end{aligned}$$

where

$$\begin{aligned}a_{11} &= \frac{p_1u}{(a_1+\bar{x})(a_1+x)}, \quad a_{12} = \frac{p_1}{a_1+\bar{x}}, \quad a_{13} = \frac{c_2u}{a_2+y}, \quad a_{22} = \frac{p_2u}{a_2(a_2+y)},\\ a_{21} &= \frac{a_1c_1u}{(a_1+\bar{x})(a_1+x)}, \quad a_{14} = \frac{c_3u}{a_3+z}, \quad a_{33} = \frac{p_3u}{(a_3+z)} - \frac{c^2}{2\alpha_2b_2}, \quad a_{44} = \frac{c_1\bar{x}}{a_2+\bar{x}}.\end{aligned}$$

Therefore, we have

$$\dot{V} = -(x-\bar{x}, y, z, u-\bar{u})\frac{1}{2}\bar{M}_1(x-\bar{x}, y, z, u-\bar{u})^\top - \frac{1}{2}b_2\alpha_2\left[y(t-\tau) - \frac{c}{b_2\alpha_2}z\right]^2, \tag{37}$$

where

$$\bar{M}_1 = \begin{bmatrix} 2(a_1-a_{11})\alpha_1 & a_2\alpha_1 + b_1\alpha_2 & a_3\alpha_1 & a_{12}\alpha_1 + a_{21}\alpha_3\\ a_2\alpha_1 + b_1\alpha_2 & 2\left(\frac{1}{2}b_2 - a_{22}\right)\alpha_2 & b_3\alpha_2 & p_2a_2^{-1}\alpha_2 + a_{13}\alpha_3\\ a_3\alpha_1 & b_3\alpha_2 & 2(d_z+a_{33}) & a_{14}\\ a_{12}\alpha_1 + a_{21}\alpha_3 & p_2a_2^{-1}\alpha_2 + a_{13}\alpha_3 & a_{14} & 2(\xi+a_{44}) \end{bmatrix}.$$

To ensure that $\dot{V}$ is negative definite along the solutions, we shall choose α_1, α_2, α_3 such that the terms $\bar{M}_1$ is positive definite. As a result, we have the following theorem.

THEOREM 13. *Suppose that the interior equilibrium F_1 exists. Then, F_1 is globally stable provided there exist α_1, α_2, α_3 such that $\bar{M}_1$ is positive definite.*

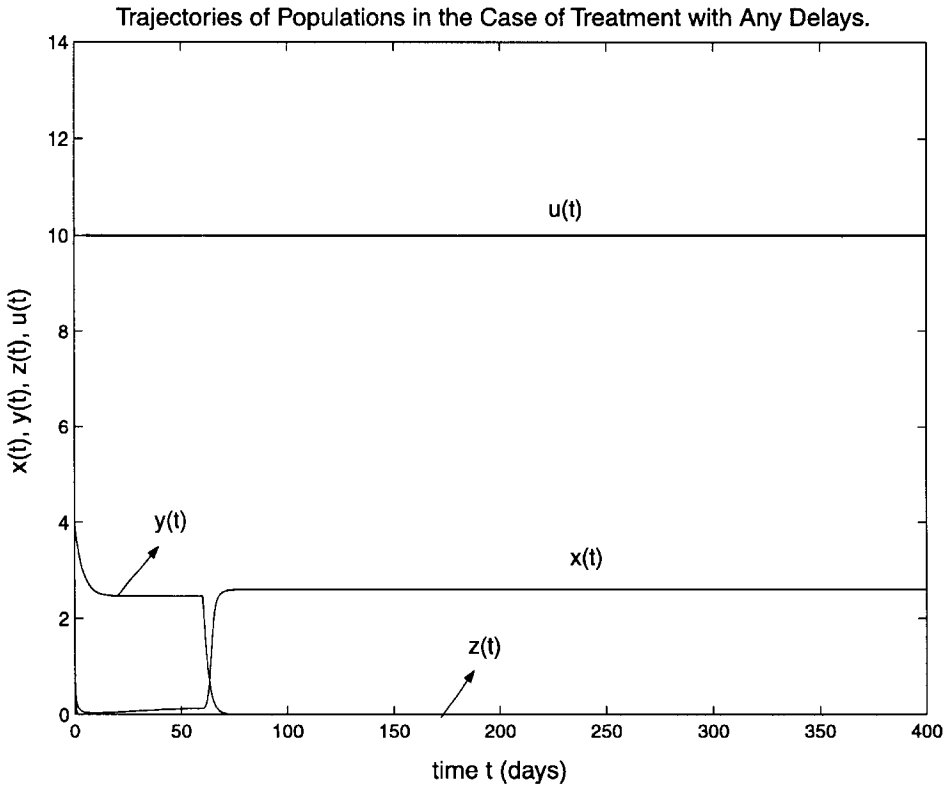

Figure 6. A solution for model (1) with $a = 3$, $P = 60$, $f = 0.67$, $n = 10$, $k_h = 10$, $k_t = 3$, $b = 6$, $d_x = d_y = 1$, $m = 20$, $d_z = 0.2$, $c = 0.3$, $p_1 = 0.0008$, $p_2 = 0.08$, $p_3 = 0.09$, $a_1 = 2$, $a_2 = a_3 = 3$, $c_1 = 0.0024$, $c_2 = 0.04$, $c_3 = 0.03$, $\Delta = 200$, $\xi = 20$. Here, $F_1(2.6015, 0, 0, 9.9887)$ is globally stable, independent of delay. The number of blood vessels drops to zero very fast from the beginning of the treatment. The initial conditions are $x(0) = 1$, $\phi_2(\theta) = 3$, $-\tau \le \theta \le 0$, $z(0) = 4$, $u(0) = 14$.

4.3.2. Global stability of F_3

In $\operatorname{int} \mathbf{R}^4_+$, we choose the Liapunov function,

$$V(x(t), y(t), z(t), u(t)) = \alpha_1 \left[x(t) - x^* - x^* \ln \left(\frac{x(t)}{x^*} \right) \right] + \alpha_2 \left[y(t) - y^* - y^* \ln \left(\frac{y(t)}{y^*} \right) \right]$$
$$+ \frac{1}{2} \alpha_2 b_2 \int_{-\tau}^{0} [y(t+s) - y^*]^2 \, ds + \frac{1}{2} (z(t) - z^*)^2 + \frac{1}{2} (u(t) - u^*)^2, \tag{38}$$

where α_1, α_2 are positive constants to be determined later. The derivative of (35) along solutions of (1) is given by

$$\dot{V} = \alpha_1 (x - x^*) \left[a_0 - a_1 x - a_2 y - a_3 z - \frac{p_1 u x}{a_1 + x} \right] + \alpha_2 (y - y^*) \left[b_0 - b_1 x - b_2 y - b_3 z - \frac{p_2 u y}{a_2 + y} \right]$$
$$+ \frac{1}{2} \alpha_2 b_2 \left[(y - y^*)^2 - (y(t - \tau) - y^*)^2 \right] + (z - z^*) \left(c y(t - \tau) - d_z z - \frac{p_3 u z}{a_3 + z} \right) \tag{39}$$
$$+ (u - u^*) \left[\Delta - \left(\xi + \frac{c_1 x}{a_1 + x} + \frac{c_2 y}{a_2 + y} + \frac{c_3 z}{a_3 + z} \right) u \right].$$

After some computing, we obtain

$$\dot{V} = -\alpha_1 (a_1 - b_{11}) (x - x^*)^2 - \alpha_2 \left(\frac{1}{2} b_2 - b_{22}\right) (y - y^*)^2 - (d_z + b_{33}) (z - z^*)^2$$

$$-\frac{1}{2} b_2 \alpha_2 \left[(y(t-\tau) - y^*) - c (b_2 \alpha_2)^{-1} (z - z^*)\right]^2 - (\xi + b_{31} + b_{41} + b_{51}) (u - u^*)^2$$

$$- \{a_3 \alpha_1 (x - x^*) (z - z^*) + (b_{12} \alpha_1 + b_{32}) (u - u^*) (x - x^*) + (b_{34} + b_{52}) (z - z^*) (u - u^*)$$

$$+ (a_2 \alpha_1 + b_1 \alpha_2) (x - x^*) (y - y^*) + b_3 \alpha_2 (y - y^*) (z - z^*) + (b_{21} \alpha_2 + b_{42}) (y - y^*) (u - u^*)\},$$

where

$$b_{11} = \frac{p_1 u}{(a_1 + x^*)(a_1 + x)}, \qquad b_{12} = \frac{p_1}{a_1 + x^*}, \qquad b_{21} = \frac{p_2}{a_2 + y^*},$$

$$b_{22} = \frac{p_2 u}{(a_2 + y^*)(a_2 + y)}, \qquad b_{31} = \frac{c_1 x^*}{a_1 + x^*}, \qquad b_{32} = \frac{a_1 c_1 u}{(a_1 + x^*)(a_1 + x)},$$

$$b_{33} = \frac{a_3 p_3 u}{(a_3 + z^*)(a_3 + z)} - \frac{c^2}{2 b_2 \alpha_2}, \qquad b_{34} = \frac{p_3 z^*}{a_3 + z^*}, \qquad b_{41} = \frac{c_2 y^*}{a_2 + y^*},$$

$$b_{42} = \frac{a_2 c_2 u}{(a_2 + y^*)(a_2 + y)}, \qquad b_{51} = \frac{c_3 z^*}{a_3 + z^*}, \qquad b_{52} = \frac{a_3 c_3 u}{(a_3 + z^*)(a_3 + z)}.$$

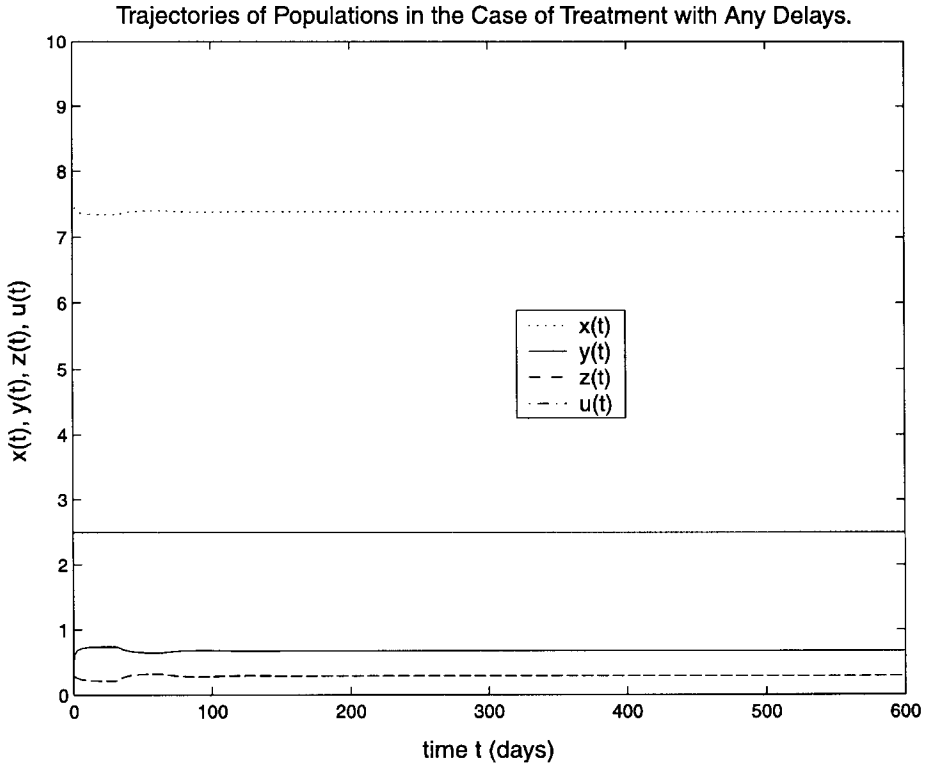

Figure 7. A solution for model (1) with $a = 3$, $P = 150$, $f = 0.67$, $n = 10$, $k_h = 10$, $k_t = 3$, $b = 6$, $d_x = d_y = 1$, $m = 20$, $d_z = 0.2$, $c = 0.09$, $p_1 = 0.0005$, $p_2 = 18$, $p_3 = 2$, $a_1 = 20$, $a_2 = a_3 = 800$, $c_1 = 0.01$,$c_2 = 36$, $c_3 = 8$, $\Delta = 200$, $\xi = 80$. Here, the interior equilibrium $F_3(7.238, 0.9224, 0.5, 2.4986)$ is globally stable, independent of delay. The initial conditions are $x(0) = 7.5$, $\phi_2(\theta) = 0.5$, $-\tau \leq \theta \leq 0$, $z(0) = 0.3$, $u(0) = 10$.

Therefore, we have

$$\dot{V} = -(x-x^*, y-y^*, z-z^*, u-u^*)\frac{1}{2}\bar{M}_2(x-x^*, y-y^*, z-z^*, u-u^*)^\top$$
$$-\frac{1}{2}b_2\alpha_2\left[(y(t-\tau)-y^*) - \frac{c}{b_2\alpha_2}(z-z^*)\right]^2, \tag{40}$$

where

$$\bar{M}_2 = \begin{bmatrix} 2(a_1-b_{11})\alpha_1 & a_2\alpha_1+b_1\alpha_2 & a_3\alpha_1 & b_{32}+b_{12}\alpha_1 \\ a_2\alpha_1+b_1\alpha_2 & 2\left(\frac{1}{2}b_2-b_{22}\right)\alpha_2 & b_3\alpha_2 & b_{42}+b_{21}\alpha_2 \\ a_3\alpha_1 & b_3\alpha_2 & 2(d_z+b_{33}) & b_{34}+b_{52} \\ b_{32}+b_{12}\alpha_1 & b_{42}+b_{21}\alpha_2 & b_{34}+b_{52} & 2(\xi+b_{31}+b_{41}+b_{51}) \end{bmatrix}.$$

To ensure that $\dot{V}$ is negative definite along the solutions, we shall choose α_1,α_2 such that the terms $\bar{M}_2$ is positive definite. As a result, we have the following theorem.

THEOREM 14. *Suppose that the interior equilibrium F_3 exists. Then, F_3 is globally stable provided there exist α_1,α_2 such that $\bar{M}_2$ is positive definite.*

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