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A generalised prey-predator type model of immunogenic cancer with the effect of immunotherapy

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Abstract

This paper deals with the qualitative analysis of the system of nonlinear ordinary differential equations describing the interaction between cancer and immune cells during immunotherapy. Mathematical analysis of the model equation with regard to boundedness of solutions, nature of equilibria and their local and global study is done. Numerical analysis is performed to support analytical findings. It is observed that cancer cell population decrease considerably due to proliferation of lymphocytes mediated by immunotherapy. It is found from our analysis that cancer population can be controlled easily if cancer is immunogenic that is, cancer cells possess distinctive surface markers called tumor-specific antigens. Further, time delay in production of immuno-agents due to the presence of antigenic cancer cells is studied and critical value of delay for which stability switch occurs is determined.

Keywords: Cancer cells, Immune Response, Hunting cells, Resting cells, Antigenicity

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1. Introduction

The generic word “cancer” denotes an entire family of high-mortality diseases each differing from the other, but all characterized by a remarkable lack of symptoms (Clark et al, 1990; Kolev, 2003; Loose, 2009; Marrari, 2007; Preziosi, 2003, Pekham, 1995; de Vito Jr., 2005). It may also be classified as nonlinear since it reflects a considerable number of intra-cellular and inter-cellular phenomena that are strongly nonlinear and time varying. Consequently, the behavior of “cancer” is anti-intuitive (Alberto d’Onofrio, 2008). This inherent nonlinearity is the main reason of deaths due to cancer despite the enormous strides in prevention and cure (D’Onofrio, 2008). For these reasons, methods of modern mathematical physics, and in particular the theory of finite and infinite dimensional dynamical systems, may play an important role in oncology of the 21st century, both from a theoretical point of view and also in the clinical practice, by means of appropriate model-based decision support systems (Alberto d’Onofrio, 2008).

Variety of the literature on mathematical modeling of cancer is present (Dunn et al., 2004; Bellomo et al., 1994, 2004, 2006, 2008; Bellomo and Bellouquid, 2006, 2007; Bellomo, 2008, Bianca and Bellomo, 2010; Bellomo, Li, and Bianca 2008; Paulsonn, 2005; Oden et al., 2010). In this paper, we shall focus on the interactions within the cancer cells and the cells of the immune system (Kolev, 2003, 2005, Banerjee, 2008, Kipp, 2007; McNeel, 2008; Nani and Freedman, 2000) with the effect of immunotherapy on it. The interactions between tumor and immune cells can be modeled by a nonlinear dynamical system which identifies the evolution of the number of cells belonging to different interacting populations, tumor cells and immune system cells, at different scales: molecular, cellular and macroscopic. Several authors (Bellomo et al., 2004, 2006, 2008; Bellomo and Bellouquid, 2006, 2007; Bellomo, 2008, Bianca and Bellomo, 2010) have applied the methods of the classical mathematical kinetic theory of gases to study the immune competition with special attention to cancer phenomena. In this approach, one has to take account of statistical averages and stochastic parameters, typical of macromodels. Other authors (D’Onofrio, 2005, 2006, 2007, 2008; Kuznetsov, et al., 1994, 2001; Stepanova, 1979; Tao, 2007) have proposed mathematical models based on nonlinear differential equations, which generalize the classical Lotka-Volterra equations. These equations, as known, follow from a deterministic approach on a microscale. In some recent papers (D’Onofrio, 2008; Cattani and Ciancio, 2007, (a and b), 2008;

Cattani, Ciancio and Lods, 2006), a hybrid model was proposed which can be considered as an alternative method between the above two approaches, aiming to mix the two scales into a unique set of equations, the hybrid model. In this model, a system of nonlinear ordinary differential equations are coupled with a stochastic parameter generated by the (kinetic) interaction between the tumor cells and the immune system (Cattani and Ciancio, 2008). Further, Dolfin and Criaco (2011) studied a macroscopic phenomenological model for the T cell mediated immune response due to a single type of antigen challenge is developed in the framework of the thermodynamic theory of fluid mixtures.

In our paper, we study a generalized mathematical model on cancer growth and its treatment as a deterministic model. The general framework of such types of models is proposed by Nani and Freedman (2000) and Alberto d'Onofrio, 2008 that is mainly a Lotka–Volterra-like prey-predator model and the assumption that there exists a cancer free equilibrium. We consider the predator is T-lymphocytes and cytotoxic macrophages/ natural killer cells of immune system that attacks, destroys or ingests the cancer cell. The preys are the cancer cells that are attacked and destroyed by the immune cells. The predator has two stages, hunting and resting through which it destroys the prey. The cancer cells are caught by macrophages which can be found in all tissues in the body and circulate round in the blood system (Sarkar and Banerjee, 2005; Dingli et al., 2006). Macrophages absorb tumor cells, eat them and release series of cytokines which activates the resting T-lymphocytes that coordinates the counter attack. The resting cells can also be directly simulated to interact with antigens. These resting cells cannot kill cancer cells, but they are converted to a special type of T-lymphocyte cells called natural killer or hunting cells and begin to multiply and release other cytokines that simulate more resting cells. This conversion between hunting and resting cells result in degradation of the resting cells and an activation of hunting cells. The process of natural immune attack against cancer cells is not always sustainable and therefore several techniques and methodologies have been developed to enhance natural immune response against cancer. This method of treatment of cancer is called immunotherapy.

We include the effect of immunotherapy in our paper as it has been approved for use in various types of cancers like breast cancer, melanoma, renal cell carcinoma, leukemia, and other hematologic and solid tumors (Rescigno, 2007). Freedman (2000) studied a general mathematical model of cancer treatment by immunotherapy. They discussed general principles of cancer immunotherapy and the model equations and hypotheses. Sandip Banerjee, Ram Rup Sarkar, 2008 also studied tumor immune interactions. They classified the immune system into two subclasses, namely, the hunting cells (cytotoxic T lymphocytes) and the resting cells (T Helper cells) to demonstrate underlying defense mechanism of the immune system. However, above-mentioned research papers did not consider the effect of presence of cancer cells in induction of primary immune response in the body. We, therefore, assume that proliferation of immune cells depends on the number of cancer cells in our model. Further, time delay in production of immuno-agents due to the presence of antigenic cancer cells is also studied as any process is not instantaneous and it is imperative to consider the effect of time delay on the dynamical system, which is the novel feature of our model. Keeping this in mind, we analyze a basic general mathematical model with three variables given by cancer cells $x(t)$, hunting cells $y(t)$ and resting cells $z(t)$ using a system of nonlinear ordinary differential equations.

2. Mathematical model

The immune system presents a very complex entwining of cells to formulate a mathematical model. We present a very basic and general mathematical model consisting of nonlinear ordinary differential equations to discuss the interaction among cancer and immune cells of the body. Our approach is developed at the super-macro-scale where heterogeneity at the cellular scale is neglected (Dolfin and Criaco, 2011). Our model consist of three variables namely cancer cells $x(t)$, hunting cells $y(t)$ and resting cells $z(t)$. Each equation of the system represents the rate of change of a variable with respect to time. Thus, the final form of mathematical model is

$$\begin{aligned}
&\frac{dx}{dt} = B(x) - D(x) - h(x,y)\\
&\frac{dy}{dt} = Q_1 + f(y,z) - \alpha_1 d_1(y) - \beta h(x,y)\\
&\frac{dz}{dt} = Q_2 + \theta(x) - \eta f(y,z) - \alpha_2 d_2(z)\\
&x(t_0) = x_0 \geq 0, \quad y(t_0) = y_0 \geq 0, \quad z(t_0) = z_0 \geq 0.
\end{aligned} \tag{2.1}$$

We assume that cancer cells are proliferating at the rate $B(x)$ defined as the birth rate and dying at the rate $D(x)$. Q_1 and Q_2 are the proliferation rate of hunting and resting cells respectively due to external infusion of immune cells during immunotherapy. α_1, α_2, η and β are the positive constants. In addition, our model is based on following hypothesis given below:

H1: There do not exist negative solutions $x(t)$, $y(t)$ and $z(t)$ for non-small t, since they are physically unacceptable, so that

$x(t) \geq 0$ $y(t) \geq 0$ and $z(t) \geq 0$ $\forall t$

H2:The term $f(y,z)$ represents the conversion of resting stage to hunting stage of lymphocytes and is characterized by

$f_y(y,z) > 0,\ y > 0, z > 0,\quad f_z(y,z) > 0,\ y > 0, z > 0,\quad f(0,z) = 0,\quad f(y,0) = 0$

H3: $h(x,y)$ represents the cancer cell destruction by hunting cells due to stimulation by resting cells. It may be assumed that

$h_x(x,y) > 0,\ x > 0, y > 0,\quad h_y(x,y) > 0,\ x > 0, y > 0,\ h_y(0,y) = 0,\ y > 0$

$h_x(0,y) \neq 0,\ y > 0,\qquad h(0,y) = 0,\quad h(x,0) = 0.$

H4: $d_1(y)$ and $d_2(z)$ represent the elimination of hunting and resting cells respectively.

$d_{1,2}(0) = 0,\quad d_1'(0) = 0, y > 0,\ d_2'(0) = 0, z > 0$

H5: $\theta(x)$ is the induction of primary immune response against cancer in resting cells that is assumed to be a function of cancer cells population in the body. It satisfies following conditions:

$\theta(0) = 0,\quad \theta'(x) > 0, x > 0,\ \theta'(x) \neq 0, x = 0.$

H6: The birth and death rates of cancer cells are based on following assumptions:

$B(0) = D(0),\ B'(x) > 0, D'(x) > 0,\ B'(0) > 0, D'(0) > 0,$ and there exist a value $K > 0$ such that

$B(K) = D(K)$ and $B'(K) < D'(K).$

3. Boundedness

Here we show that system (2.1) is bounded.

Theorem 3.1: All solutions of system (2.1) with initial values in R_+^3 are bounded in the region Ω defined by

$$\Omega = \left\{(x,y,z) \in R_+^3, 0 \leq x(t) \leq K, 0 \leq y(t) \leq -\frac{Q_1}{\eta_1}, \eta_1 < 0, 0 \leq z(t) \leq \frac{Q_2 + \theta(K)}{\eta_2}, \eta_2 > 0\right\}$$

Where,

$\eta_1 = \max\left(\max \tilde{f}(y,z) - \alpha_1 \min \tilde{d}_1(y)\right)$

$\eta_2 = \alpha_2 \min \tilde{d}_2(z) > 0$

Proof: Let $x_0 > 0$, considering first equation of model (2.1) we have

$$\frac{dx}{dt} = B(x) - D(x) - h(x,y)$$

$$\frac{dx}{dt} \leq B(x) - D(x)$$

But by hypothesis H6, there exist a value $K > 0$ such that $B(K) = D(K)$. Thus, $x(t) \leq \max(K, x_0)$

We note that $\frac{dx}{dt} < 0$ for $x > K$ and hence,

$\limsup_{t \to \infty} x(t) \leq K$

Let us now consider second equation of system (2.1)

$$\frac{dy}{dt} = Q_1 + f(y,z) - \alpha_1 d_1(y) - \beta h(x,y)$$

$$\frac{dy}{dt} < Q_1 + f(y,z) - \alpha_1 d_1(y)$$

$$< Q_1 + y \max \tilde{f}(y,z) - y\alpha_1 \min \tilde{d}_1(y)$$

where $f(y,z) = y\tilde{f}(y,z),\ d_1(y) = y\tilde{d}_1(y)$

Now, $\frac{dy}{dt} < Q_1 + y \max\left(\max \tilde{f}(y,z) - \alpha_1 \min \tilde{d}_1(y)\right)$

$\eta_1 = \max\left(\max \tilde{f}(y,z) - \alpha_1 \min \tilde{d}_1(y)\right)$

We assume that $\max \tilde{f}(y,z) < \alpha_1 \min \tilde{d}_1(y)$ or $\eta_1 = \max\left(\max \tilde{f}(y,z) - \alpha_1 \min \tilde{d}_1(y)\right)$

Thus, we have

$$y \le -\frac{Q_1}{\eta_1} + y_0 e^{\eta_1 t}$$

this implies that,

$$y \le \max\left(-\frac{Q_1}{\eta_1}, y_0\right)$$

or $\limsup_{t\to\infty} y(t) \le -\frac{Q_1}{\eta_1}$, $\eta_1 < 0, y_0 \ge 0.$

Similarly, if $z_0 > 0$, third equation of the model gives

$$\frac{dz}{dt} = Q_2 + \theta(x) - \eta f(y,z) - \alpha_2 d_2(z)$$

$$\frac{dz}{dt} < Q_2 + \theta(K) - \alpha_2 z \min \tilde{d}_2(z)$$

$$d_2(z) = z\tilde{d}_2(z).$$

Now, if $\eta_2 = \alpha_2 \min \tilde{d}_2(z) > 0$

we have,

$$z(t) \le \frac{Q_2 + \theta(K)}{\eta_2} + z_0 e^{-\eta_2 t}$$

this implies that $z(t) \le \max\left(\frac{Q_2 + \theta(K)}{\eta_2}, z_0\right)$

and hence,

$$\limsup_{t\to\infty} z(t) \le \frac{Q_2 + \theta(K)}{\eta_2}.$$

This proves the boundedness of the system

4. Equilibrium Analysis

Equilibrium is a constant solution of the system of differential equations. Geometrically, equilibrium is a point in the phase plane that is the orbit of a constant solution. There are two possible equilibria of the system (2.1):
$\bar{E}(0, \bar{y}, \bar{z})$ and $E^*(x^*, y^*, z^*)$

Equilibrium $\bar{E}(0, \bar{y}, \bar{z})$ is obtained by solving the following system of differential equations,

$$\begin{aligned} \frac{dy}{dt} &= Q_1 + f(y,z) - \alpha_1 d_1(y) \\ \frac{dz}{dt} &= Q_2 - \eta f(y,z) - \alpha_2 d_2(z) \\ y(t_0) &= y_0 \ge 0, \; z(t_0) = z_0 > 0. \end{aligned} \tag{4.1}$$

Theorem 4.1: Consider system (4.1), let

$$P_1 = \max f(y,z) \ge 0 \tag{4.2}$$

$$P_2 = \min\left(\alpha_1 \min d_1(y), \alpha_2 \min d_2(z)\right) > 0. \tag{4.3}$$

Then,

$$\limsup_{t\to\infty}\left(y(t) + z(t)\right) \le \frac{Q_1 + Q_2 + (1-\eta)P_1}{P_2}.$$

Proof: Let us choose a function

$$M = y + z. \tag{4.4}$$

Differentiating (4.4) with respect to t, we have

$$\frac{dM}{dt} = \frac{d(y+z)}{dt} = Q_1 + Q_2 + f(y,z) - \eta f(y,z) - \alpha_1 d_1(y) - \alpha_2 d_2(z)$$

$$\begin{aligned} &\le Q_1 + Q_2 + (1-\eta)\max f(y,z) - \alpha_1 y \min \tilde{d}_1(y) - \alpha_2 z \min \tilde{d}_2(z) \\ &\le Q_1 + Q_2 + (1-\eta)P_1 - (y+z)\left(\alpha_1 \min \tilde{d}_1(y), \alpha_2 \min \tilde{d}_2(z)\right) \\ &\le Q_1 + Q_2 + (1-\eta)P_1 - MP_2. \end{aligned}$$

This implies that

$$\limsup_{t\to\infty} M(t) \le \frac{Q_1 + Q_2 + (1-\eta)P_1}{P_2}$$

or

$$\limsup_{t\to\infty} \left(y(t) + z(t)\right) \le \frac{Q_1 + Q_2 + (1-\eta)P_1}{P_2}.$$

.

Thus we have shown that system (4.1) is dissipative under conditions (4.2) and (4.3) in Theorem 4.1.

Lemma 4.1: Equilibrium $\bar{E}(0,\bar{y},\bar{z})$ exists if

$$\left(Q_1 - \alpha_1 d_1(\bar{y})\right) + \frac{1}{\eta}\left(Q_2 - \alpha_2 d_2(\bar{z})\right) = 0 \text{ as } t \to \infty.$$

Proof: $\bar{E}(0,\bar{y},\bar{z})$ is the solution of the system (2.1) if it satisfies the right hand side of (4.1) that is,

$$Q_1 + f(\bar{y},\bar{z}) - \alpha_1 d_1(\bar{y}) = 0 \tag{4.5}$$

$$Q_2 - \eta f(\bar{y},\bar{z}) - \alpha_2 d_2(\bar{z}) = 0 \tag{4.6}$$

We have shown that system (4.1) is dissipative under conditions (4.2) and (4.3) in theorem (4.1).

Now from (4.5) and (4.6) we have,

$$\begin{aligned} f(\bar{y},\bar{z}) &= -\left(Q_1 - \alpha_1 d_1(\bar{y})\right) \\ &= \frac{1}{\eta}\left(Q_2 - \alpha_2 d_2(\bar{z})\right). \end{aligned} \tag{4.7}$$

Equation (4.7) gives $\left(Q_1 - \alpha_1 d_1(\bar{y})\right) + \frac{1}{\eta}\left(Q_2 - \alpha_2 d_2(\bar{z})\right) = 0$

This proves the lemma.

Existence of Interior Equilibrium $E^*(x^*,y^*,z^*)$:

Interior equilibrium $E^*(x^*,y^*,z^*)$ of system (2.1) exists if it satisfies the right hand side of its equations, that is

$$B(x^*) - D(x^*) - h(x^*,y^*) = 0 \tag{4.8}$$

$$Q_1 + f(y^*,z^*) - \alpha_1 d_1(y^*) - \beta h(x^*,y^*) = 0 \tag{4.9}$$

$$Q_2 + \theta(x^*) - \eta f(y^*,z^*) - \alpha_2 d_2(z^*) \tag{4.10}$$

within the region Ω.

We will prove the existence of $E^*(x^*,y^*,z^*)$ by persistence analysis in a subsequent section.

5. Stability Analysis of Equilibria

We now discuss local or linearized stability of system (2.1) about its equilibria. For this, we compute eigenvalues of the Jacobian matrix of linearized system of (2.1). Negative eigenvalues of the variational matrix about equilibrium implies local asymptotic stability of that equilibrium. The general variational matrix of the system about an arbitrary equilibrium is given by

$$V(E)=\begin{bmatrix} B'(x)-D'(x)-h_x(x,y) & -h_y(x,y) & 0 \\ -\beta h_x(x,y) & f_y(y,z)-\alpha_1 d_1'(y)-\beta h_y(x,y) & f_z(y,z) \\ \theta'(x) & -\eta f_y(y,z) & -\eta f_z(y,z)-\alpha_2 d_2'(z) \end{bmatrix}$$

5.1 Local Stability of Cancer Free Equilibrium $\overline{E}(0,\bar{y},\bar{z})$:

Using hypothesis H1-H6, the variational matrix of the system due to linearization of system (2.1) about $\overline{E}(0,\bar{y},\bar{z})$ is expressed as

$$V(\overline{E})=\begin{bmatrix} B'(0)-D'(0)-h_x(0,\bar{y}) & 0 & 0 \\ -\beta h_x(0,\bar{y}) & f_y(\bar{y},\bar{z})-\alpha_1 d_1'(\bar{y}) & f_z(\bar{y},\bar{z}) \\ \theta'(0) & -\eta f_y(\bar{y},\bar{z}) & -\eta f_z(\bar{y},\bar{z})-\alpha_2 d_2'(\bar{z}) \end{bmatrix}. \tag{5.1}$$

The eigenvalues of the variational matrix $V(\overline{E})$ are given by

$$\lambda_1 = B'(0)-D'(0)-h_x(0,\bar{y}), \tag{5.2}$$

and by the roots of the quadratic equation

$$\lambda^2+\lambda\left\{\eta f_z(\bar{y},\bar{z})+\alpha_1 d_1'(\bar{y})+\alpha_2 d_2'(\bar{z})-f_y(\bar{y},\bar{z})\right\}+\left(\eta f_z(\bar{y},\bar{z})+\alpha_2 d_2'(\bar{z})\right)\left(\alpha_1 d_1'(\bar{y})-f_y(\bar{y},\bar{z})\right)+\eta f_y(\bar{y},\bar{z})\,f_z(\bar{y},\bar{z})=0$$

By the Routh Hurwitz criteria (Gradshteyn and Ryzhik, 2000), the eigenvalues of variational matrix $V(\overline{E})$ have negative real parts if

$$\eta f_z(\bar{y},\bar{z})+\alpha_1 d_1'(\bar{y})+\alpha_2 d_2'(\bar{z})-f_y(\bar{y},\bar{z})>0 \tag{5.3}$$

$$\left(\eta f_z(\bar{y},\bar{z})+\alpha_2 d_2'(\bar{z})\right)\left(\alpha_1 d_1'(\bar{y})-f_y(\bar{y},\bar{z})\right)+\eta f_y(\bar{y},\bar{z})\,f_z(\bar{y},\bar{z})>0. \tag{5.4}$$

Thus, if conditions (5.2), (5.3) and (5.4) are satisfied then the equilibrium $\overline{E}(0,\bar{y},\bar{z})$ is locally asymptotically stable equilibrium.

Remark 1: We note that the equilibrium $\overline{E}(0,\bar{y},\bar{z})$ is a hyperbolic saddle point (Freedman and Mathsen, 1993) if $\lambda_1 = B'(0)-D'(0)-h_x(0,y)>0$ and λ_2 , $\lambda_3<0$. In other words, we can say that $\overline{E}(0,\bar{y},\bar{z})$ is repelling in the $x-$ direction in this case. And $\overline{E}(0,\bar{y},\bar{z})$ is a hyperbolic source if $\lambda_1 = B'(0)-D'(0)-h_x(0,y)>0$ and λ_2 , $\lambda_3>0$.

Remark 2: Equilibrium $\overline{E}(0,\bar{y},\bar{z})$ demonstrate the scenario in which all the cancer cells are killed. In this case, the immune system expels the cancer cells thoroughly out of the body.

Let us now determine the existence of an interior equilibrium, suppose equilibrium $\overline{E}(0,\bar{y},\bar{z})$ exists and is a unique hyperbolic point repelling in the $x-$ direction. Further assume that neither periodic nor homoclinic orbits exist in the planes of R_+^3 that is,

$$\int_0^T \left[B'(0)-D'(0)-h_x(0,y)\right]dt>0$$

and system (2.1) is bounded then by the definition of uniform persistence given by Butler et al, 1986; Freedman and Rai , 1987, 1995,

$$\liminf_{t\to\infty} x(t)>0$$

$$\liminf_{t\to\infty} y(t)>0$$

$$\liminf_{t\to\infty} z(t)>0.$$

In particular, the system (2.1) exhibit uniform persistence and a positive interior equilibrium of the form $E^*(x^*,y^*,z^*)$ exists. We now study the linearized stability of this equilibrium.

5.2 Local Stability of Interior Equilibrium $E^*(x^*,y^*,z^*)$:

Using assumptions H1-H6, the variational matrix of the system due to the linearization of the system (2.1) about $E^*(x^*,y^*,z^*)$ is expressed as

$$V(E^*)=\begin{bmatrix} B'(x^*)-D'(x^*)-h_x(x^*,y^*) & -h_y(x^*,y^*) & 0 \\ -\beta h_x(x^*,y^*) & f_y(y^*,z^*)-\alpha_1 d_1'(y^*) & f_z(y^*,z^*) \\ \theta'(x^*) & -\eta f_y(y^*,z^*) & -\eta f_z(y^*,z^*)-\alpha_2 d_2'(z^*) \end{bmatrix}. \tag{5.5}$$

The eigenvalues of the variational matrix $V(E^*)$ are given by the cubic equation

$$\lambda^3+A_1\lambda^2+A_2\lambda+A_3=0, \tag{5.6}$$

where,

$$A_1=-B'(x^*)+D'(x^*)+h_x(x^*,y^*)+\eta f_z(y^*,z^*)-f_y(y^*,z^*)+\beta h_y(x^*,y^*)+\alpha_1 d_1'(y^*)+\alpha_2 d_2'(z^*)$$

$$\begin{aligned} A_2=&\eta f_z(y^*,z^*)\left(\alpha_1 d_1'(y^*)+\beta h_y(x^*,y^*)\right)+\alpha_2 d_2'(z^*)\left(-f_y(y^*,z^*)+\alpha_1 d_1'(y^*)+\beta h_y(x^*,y^*)\right)\\ &+\left(-B'(x^*)+D'(x^*)\right)\left(\eta f_z(y^*,z^*)-f_y(y^*,z^*)+\alpha_1 d_1'(y^*)+\alpha_2 d_2'(z^*)+\beta h_y(x^*,y^*)\right)\\ &+h_x(x^*,y^*)\left(\eta f_z(y^*,z^*)-f_y(y^*,z^*)+\alpha_1 d_1'(y^*)+\alpha_2 d_2'(z^*)\right) \end{aligned}$$

$$\begin{aligned} A_3=&\left(-B'(x^*)+D'(x^*)+h_x(x^*,y^*)\right)\left\{\begin{array}{l}\left(\eta f_z(y^*,z^*)+\alpha_2 d_2'(z^*)\right)\left(\beta h_y(x^*,y^*)-f_y(y^*,z^*)+\alpha_1 d_1'(y^*)\right)\\ +\eta f_z(y^*,z^*)\,f_y(y^*,z^*)\end{array}\right\}\\ &-\beta h_x(x^*,y^*)h_y(x^*,y^*)\left(\eta f_z(y^*,z^*)+\alpha_2 d_2'(z^*)\right)+\theta'(x^*)\,f_z(y^*,z^*)h_y(x^*,y^*). \end{aligned}$$

By the Routh Hurwitz criteria (Gradshteyn and Ryzhik, 2000), the eigenvalues of variational matrix $V(E^*)$ have negative real parts if

$$A_1>0, A_3>0 \quad \text{and} \quad A_1A_2-A_3>0. \tag{5.7}$$

Thus, if condition (5.7) is satisfied then the interior equilibrium $E^*(x^*,y^*,z^*)$ is locally asymptotically stable.

Remark: Equilibrium $E^*(x^*,y^*,z^*)$ represents the scenario in which the immune system is unable to eliminate cancer cells but is able to control the lethal proliferation of cancer cells.

6. Global Stability Analysis

In this section, we derive global stability of the equilibria by choosing a Liapunov function and finding conditions for its derivative with respect to time to be negative definite. We use following two lemmas to prove global stability of the system used in by Nani and Freedman (2000).

Lemma 6.1: Let Liapunov function V be expressed as $V=X^TAX$ where,

$$X=\begin{bmatrix} x_1 \\ x_2 \\ . \\ . \\ x_n \end{bmatrix},\ X=\begin{bmatrix} x_1 & x_2 & . & . & x_n \end{bmatrix}\in R^n$$

and A be a symmetric $n\times n$ matrix over R is negative definite if

1. X^TAX is negative definite
2. X^TAX is negative if A is negative definite.
3. A is negative definite if the eigenvalues of polynomial $g(\lambda,A)=|A-\lambda I_n|=0$ has negative real parts.

Frobenius in 1876 gave an alternative method to prove V to be negative definite in the following lemma:

Lemma 6.2: (Frobenius 1876) Let

$$X=\begin{bmatrix} x_1 \\ x_2 \\ . \\ . \\ x_n \end{bmatrix},\ X=\begin{bmatrix} x_1 & x_2 & . & . & x_n \end{bmatrix}\in R^n$$

and let A be a symmetric $n \times n$ matrix over R. Then the real quadratic form $X^T AX$ is negative definite if A is negative definite. In particular, a necessary and sufficient condition for the real symmetric matrix A to be negative definite is that the principal minors of A starting with that of the first order be alternately negative and positive.

6.1 Global Stability of Cancer Free Equilibrium:

Let us choose the Liapunov function

$$V = x + \frac{1}{2}k_1(y-\bar{y})^2 + \frac{1}{2}k_2(z-\bar{z})^2 \tag{6.1}$$

The derivative of V with respect to time t is given by

$$\dot{V} = \dot{x} + k_1(y-\bar{y})\dot{y} + k_2(z-\bar{z})\dot{z}. \tag{6.2}$$

Using $B(x) - D(x) = xg(x)$,

$h(x,y) = xh_1(x,y)$,

$h_1(x,y) = yh_2(x,y)$ and equations of the system (2.1) in equation (6.2) we have,

$$\begin{aligned}\dot{V} &= x\big(g(x) - yh_2(x,y)\big) + k_1(y-\bar{y})\big(Q_1 + f(y,z) - \alpha_1 d_1(y) - \beta h(x,y)\big) + k_2(z-\bar{z})\big(Q_2 + \theta(x) - \eta f(y,z) - \alpha_2 d_2(z)\big)\\ &= x\big(g(x)\big) - x\big(yh_2(x,y) - \bar{y}h_2(x,\bar{y})\big) - x\bar{y}h_2(x,\bar{y}) + k_1(y-\bar{y})\big(f(y,z) - f(\bar{y},\bar{z})\big) + \alpha_1 k_1(y-\bar{y})\big(d_1(y) - d_1(\bar{y})\big)\\ &\quad - x\beta k_1(y-\bar{y})\big(yh_2(x,y) - \bar{y}h_2(x,\bar{y})\big) - x\beta k_1(y-\bar{y})\bar{y}h_2(x,\bar{y}) + \alpha_2 k_2(z-\bar{z})\big(d_2(z) - d_2(\bar{z})\big)\\ &\quad - \eta k_2(z-\bar{z})\big(f(y,z) - f(\bar{y},\bar{z})\big) + k_2(z-\bar{z})\theta(x).\end{aligned} \tag{6.3}$$

Writing (6.3) as $\dot{V} = X^T AX$ (6.4)

where $X = \begin{bmatrix} x \\ y-\bar{y} \\ z-\bar{z} \end{bmatrix}$, A is a real symmetric matrix defined by $A = \{a_{ij}\}_{1 \le i,j \le 3}$,

with $A = \begin{bmatrix} a_{11} & \frac{1}{2}a_{12} & \frac{1}{2}a_{13} \\ \frac{1}{2}a_{12} & a_{22} & \frac{1}{2}a_{23} \\ \frac{1}{2}a_{13} & \frac{1}{2}a_{23} & a_{33} \end{bmatrix}$

and $\dot{V} = a_{11}x^2 + a_{12}x(y-\bar{y}) + a_{13}x(z-\bar{z}) + a_{22}(y-\bar{y})^2 + a_{23}(y-\bar{y})(z-\bar{z}) + a_{33}(z-\bar{z})^2$

Where,

$$a_{11} = \frac{g(x) - \bar{y}h_2(x,\bar{y})}{x}$$

$$a_{12} = -\left(\frac{yh_2(x,y) - \bar{y}h_2(x,\bar{y})}{y-\bar{y}}\right) - \beta k_1 yh_2(x,y)$$

$$a_{13} = \frac{k_2\theta(x)}{x}$$

$$a_{22} = \frac{\alpha_1 k_1\big(d_1(y) - d_1(\bar{y})\big)}{y-\bar{y}}$$

$$a_{23} = \frac{k_1\big(f(y,z) - f(\bar{y},\bar{z})\big)}{z-\bar{z}} - \frac{\eta k_2\big(f(y,z) - f(\bar{y},\bar{z})\big)}{y-\bar{y}}$$

$$a_{33} = -\frac{\alpha_2 k_2\big(d_2(z) - d_2(\bar{z})\big)}{z-\bar{z}}.$$

Thus, by the Frobenius theorem (Nani and Freedman, 2000) and the hermiticity of matrix A, the matrix A and hence the quadratic form (6.4) is negative definite if the following criteria hold,

$$A_1 = a_{11} < 0,\quad A_2 = \begin{vmatrix} a_{11} & \frac{1}{2}a_{12} \\ \frac{1}{2}a_{12} & a_{22} \end{vmatrix} > 0 \text{ and } A_3 = \det A = \begin{vmatrix} a_{11} & \frac{1}{2}a_{12} & \frac{1}{2}a_{13} \\ \frac{1}{2}a_{12} & a_{22} & \frac{1}{2}a_{23} \\ \frac{1}{2}a_{13} & \frac{1}{2}a_{23} & a_{33} \end{vmatrix} < 0. \tag{6.5}$$

Thus, we have the following theorem for the global stability of the cancer free equilibrium:

Theorem 6.1: The cancer free equilibrium $\overline{E}(0,\bar{y},\bar{z})$ is globally asymptotically stable if conditions (6.5) are satisfied.

Remark: Global asymptotic stability of the cancer free equilibrium $\overline{E}(0,\bar{y},\bar{z})$ gives criteria for total success of therapy in eliminating cancer cells from human body. In such cases the immune system fights well with the cancer cells such that they are not able to proliferate and spread.

6.2 Global stability of Interior equilibrium

Let us consider a Liapunov function

$$V_1 = x - x^* - x^* \ln\frac{x}{x^*} + \frac{1}{2}l_1(y-y^*)^2 + \frac{1}{2}l_2(z-z^*)^2. \tag{6.6}$$

Derivative of V with respect to time t is given by

$$\dot{V}_1 = (x-x^*)\frac{\dot{x}}{x} + l_1(y-y^*)\dot{y} + l_2(z-z^*)\dot{z} \tag{6.7}$$

Again using

$B(x) - D(x) = xg(x)$,

$h(x,y) = xh_1(x,y)$,

$h_1(x,y) = yh_2(x,y)$ and equations of the system (2.1) in equation (6.7) we have,

$$\begin{aligned}\dot{V}_1 &= \frac{(x-x^*)}{x}\big(xg(x) - xh_1(x,y)\big) + l_1(y-y^*)\big(Q_1 + f(y,z) - \alpha_1 d_1(y) - \beta h(x,y)\big) \\ &\quad + l_2(z-z^*)\big(Q_2 + \theta(x) - \eta f(y,z) - \alpha_2 d_2(z)\big) \\ &= (x-x^*)\big(g(x)\big) - (x-x^*)\big(yh_2(x,y) - y^*h_2(x,y^*)\big) - (x-x^*)y^*h_2(x,y^*) + \alpha_1 l_1(y-y^*)\big(d_1(y) - d_1(y^*)\big) \\ &\quad - \beta l_1(y-y^*)\big(h(x,y) - h(x^*,y^*) + l_1(y-\bar{y})\big(f(y,z) - f(y^*,z^*)\big) + l_2(z-z^*)\big(\theta(x) - \theta(x^*)\big)\big) \\ &\quad - \alpha_2 l_2(z-z^*)\big(d_2(z) - d_2(z^*) - \eta l_2(z-z^*)\big(f(y,z) - f(y^*,z^*)\big)\big).\end{aligned} \tag{6.8}$$

Writing (6.8) as $\dot{V}_1 = X^T BX$ (6.9)

where, $X = \begin{bmatrix} x-x^* \\ y-y^* \\ z-z^* \end{bmatrix}$, B is a real symmetric matrix defined by $B = \{b_{ij}\}_{1\le i,j\le 3}$,

with

$$B = \begin{bmatrix} b_{11} & \frac{1}{2}b_{12} & \frac{1}{2}b_{13} \\ \frac{1}{2}b_{12} & b_{22} & \frac{1}{2}b_{23} \\ \frac{1}{2}b_{13} & \frac{1}{2}b_{23} & b_{33} \end{bmatrix}.$$

Equation (6.9) can be written as,

$$\dot{V}_1 = b_{11}(x-x^*)^2 + b_{12}(x-x^*)(y-y^*) + b_{13}(x-x^*)(z-z^*) + b_{22}(y-y^*)^2 + b_{23}(y-y^*)(z-z^*) + b_{33}(z-z^*)^2$$

where,

$$b_{11} = \frac{g(x) - y^*h_2(x,y^*)}{x-x^*}$$

$$b_{12} = -\left(\frac{yh_2(x,y) - y^* h_2(x,y^*)}{y - y^*}\right) - \beta l_1\left(\frac{h(x,y) - h(x^*,y^*)}{x - x^*}\right)$$
$$b_{13} = \frac{l_2\left(\theta(x) - \theta(x^*)\right)}{x - x^*}$$
$$b_{22} = -\frac{\alpha_1 l_1\left(d_1(y) - d_1(y^*)\right)}{y - y^*}$$
$$b_{23} = \frac{l_1\left(f(y,z) - f(y^*,z^*)\right)}{z - z^*} - \frac{\eta l_2\left(f(y,z) - f(y^*,z^*)\right)}{y - y^*}$$
$$b_{33} = -\frac{\alpha_2 l_2\left(d_2(z) - d_2(z^*)\right)}{z - z^*}.$$

Thus, by the Frobenius theorem and hermiticity of matrix B, the matrix B and hence the quadratic form (6.9) is negative definite if the following criteria hold,

$$B_1 = b_{11} < 0, \quad B_2 = \begin{vmatrix} b_{11} & \frac{1}{2}b_{12} \\ \frac{1}{2}b_{12} & b_{22} \end{vmatrix} > 0 \text{ and } B_3 = \det B = \begin{vmatrix} b_{11} & \frac{1}{2}b_{12} & \frac{1}{2}b_{13} \\ \frac{1}{2}b_{12} & b_{22} & \frac{1}{2}b_{23} \\ \frac{1}{2}b_{13} & \frac{1}{2}b_{23} & b_{33} \end{vmatrix} < 0. \tag{6.10}$$

From the above computations, we have the following theorem for the global stability of interior equilibrium:

Theorem 6.2: The interior equilibrium $E^*(x^*, y^*, z^*)$ is globally asymptotically stable if conditions (6.10) are satisfied.

Remark: Global stability of equilibrium $E^*(x^*, y^*, z^*)$ infers that cancer cells proliferate and attain a particular equilibrium level in the human body. In this case, although therapy is not able to eliminate cancer cells from the body yet it is effective in controlling the cancer cells and reducing them to a lowest possible limit. Thus, immunotherapy would be most effective in the case it is able to reduce the number of cancer cells in the body to lowest equilibrium value.

7. **Mathematical Model with Time Delay**

Time delay is the inherent property of the dynamical systems and plays an important role in almost all branches of science and particularly in biological sciences (e.g., population dynamics, epidemiology, etc.). The importance derives from the fact that many of the phenomena around us do not act instantaneously from the moment of their occurrence. There is always a time lag between the moment an action takes place and its effect is observed. Models that are more realistic should include some of the past states, i.e., a real system should be modeled by differential equations with time delays. Therefore, we consider time delay in production of immuno-agents due to the presence of antigenic cancer cells. Our model with time delay is as given below:

$$\begin{aligned} \frac{dx}{dt} &= B(x) - D(x) - h(x,y) \\ \frac{dy}{dt} &= Q_1 + f(y,z) - \alpha_1 d_1(y) - \beta h(x,y) \\ \frac{dz}{dt} &= Q_2 + \theta(x(t-\tau)) - \eta f(y,z) - \alpha_2 d_2(z) \end{aligned} \tag{7.1}$$

To determine stability of the system with delay we consider the following variational matrix of the system (7.1) at $E^*(x^*, y^*, z^*)$.

$$V(E^*) = \begin{bmatrix} B'(x^*) - D'(x^*) - h_x(x^*,y^*) & -h_y(x^*,y^*) & 0 \\ -\beta h_x(x^*,y^*) & f_y(y^*,z^*) - \alpha_1 d_1'(y^*) & f_z(y^*,z^*) \\ e^{-\lambda\tau}\theta'(x^*) & -\eta f_y(y^*,z^*) & -\eta f_z(y^*,z^*) - \alpha_2 d_2'(z^*) \end{bmatrix}$$

The characteristic equation for the variational matrix $V(E)$ is given by

$$\lambda^3 + \overline{A}_1\lambda^2 + \overline{A}_2\lambda + \overline{A}_3 + \overline{A}_4 e^{-\lambda\tau} = 0, \tag{7.2}$$

where,

$$\overline{A}_1 = A_1$$
$$\overline{A}_2 = A_2$$
$$\overline{A}_3 = A_3 - \overline{A}_4$$
$$\overline{A}_4 = \theta'(x^*) f_z(y^*, z^*) h_y(x^*, y^*)$$

The eigenvalues are the roots of the characteristics equation (7.2) of the system that has infinitely many solutions. We wish to find the periodic solutions of the system as existence of periodic solutions is relevant in cancer models. For the periodic solutions eigenvalues will be purely imaginary so we substitute $\lambda = i\omega$ in equation (7.2).We get the following system of transcendental equations on separating the real and imaginary parts of the resulting equation.

$$\overline{A}_1\omega^2 - \overline{A}_3 = \overline{A}_4 \cos\omega\tau \tag{7.3}$$

$$\overline{A}_2\omega - \omega^3 = \overline{A}_4 \sin\omega\tau \tag{7.4}$$

Eliminating τ between (7.3) and (7.4) we get

$$\omega^6 + \tilde{M}_1\omega^4 + \tilde{M}_2\omega^4 + \tilde{M}_3 = 0 \tag{7.5}$$

where.

$$\tilde{M}_1 = \overline{A}_1^2 - 2\overline{A}_2,$$
$$\tilde{M}_2 = \overline{A}_2^2 - 2\overline{A}_1\overline{A}_3,$$
$$\tilde{M}_3 = \overline{A}_3^2 - \overline{A}_4^2.$$

Substituting $\omega^2 = P$ in (7.5), we get a cubic equation given by

$$\phi(P) = P^3 + \tilde{M}_1P^2 + \tilde{M}_2P + \tilde{M}_3 = 0 \tag{7.6}$$

Now (7.6) will have a unique positive root if $\tilde{M}_1 > 0$ and $\tilde{M}_3 < 0.$ (7.7)

Since, the existence condition for interior equilibrium E holds true, we have the condition for $\tilde{M}_1$ to be positive and $\tilde{M}_3$ to be negative. The condition for the existence of positive root ensures that a purely imaginary root of (7.2) can be obtained and a stable periodic solution of the system can be observed in the presence of time delay. Thus, we can say that there is a unique positive root ω_0 satisfying (7.6), if (7.7) holds. Then, the characteristic equation (7.2) has a pair of purely imaginary roots of the form $\pm i\omega_0$.

From (7.3) we have,

$$\tau_0 = \frac{1}{\omega_0}\cos^{-1}\left[\frac{(\overline{A}_1\omega_0^2 - \overline{A}_3)}{\overline{A}_4}\right]. \tag{7.8}$$

For $\tau = 0,$ E^* is stable if (5.7) holds. Hence by Butler's lemma given in (Freedman and Rao, 1983), E^* remains stable for $\tau < \tau_0$

We also observe that the conditions for Hopf-bifurcation (Hale and Lunel, 1993)are satisfied if condition (7.7) holds, that is,

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

This signifies that there exists at least one eigenvalue with positive real part for $\tau > \tau_0$.

8. Numerical Simulation

Let us consider the following system to justify the analytical findings

$$\begin{aligned}
\frac{dx}{dt} &= rx(1-x) - a_1xy \\
\frac{dy}{dt} &= Q_1 + \frac{b_1yz}{b+z} - \alpha_1y - a_2xy \\
\frac{dz}{dt} &= Q_2 + \pi x - \frac{b_2yz}{b+z} - \alpha_2z
\end{aligned} \tag{8.1}$$

Hence,

$$\begin{aligned}
&B(x) - D(x) = rx(1-x), \quad h(x,y) = a_1xy, \quad f(y,z) = \frac{b_1yz}{b+z}, \\
&d_1(y) = y, \quad d_2(z) = z, \quad \theta(x) = \pi x, \quad a_1\beta = a_2, \quad b_1\eta = b_2
\end{aligned} \tag{8.2}$$

We note that all the hypothesis H1-H6 hold for the particular form of functions in (8.2).

Choosing the following set of hypothetical parameters to justify analytical findings in system (8.1),

$$r = 5, a_1 = 0.5, b_1 = 0.1, a_2 = 0.2, b_2 = 0.2, Q_1 = 1, Q_2 = 2, \pi = 0.8, \alpha_1 = 0.2, b = 0.01 \text{ and } \alpha_2 = 0.1, \quad (8.3)$$

We find that interior equilibrium of system (8.1) exist and is given by,

$E^*(x^*, y^*, z^*)$, where

$$x^* = 0.5004 \quad y^* = 4.9964 \quad z^* = 14.0171.$$

The characteristic equation (5.6) corresponding to E^* is given by

$$\lambda^3 + 2.8919\lambda^2 + 0.5216\lambda + 0.0401 = 0. \quad (8.4)$$

Roots of this equation are -2.7045, -0.0937+0.0778i, -0.0937-0.0778i. This implies that E^* is a locally asymptotically stable equilibrium owing to the negative real parts of the eigenvalues of characteristic equation. Further, we have found numerically that system exhibits bifurcation for $Q = 1.12174$ as two eigenvalues of the equation (8.4) are purely imaginary.

Further, to show changes occurring in populations with time under different conditions, figures have been plotted between dependent variables and time for different parameter values. In Fig. 1 and 2, global stability of the system is displayed by plotting the graphs in the $x - y$ plane and the $x - z$ plane respectively.

It is observed from the figures that whatever initial values of the equilibrium are taken, trajectory always moves towards the equilibrium. Thus, global stability of the system is ensured.

In Figure 3, the variation of cancer cell population with time for different proliferation rates of the hunting cells due to external infusion of immune cells is given. It is evident from the figure that the cancer cell population decreases as the proliferation rate of hunting cells, denoted by Q_1, increases and for a particular value of Q_1, the cancer population vanish. It may be because lymphocytes are cytotoxic to the cancer cells and increase in their proliferation causes reduction in number of the cancer cells as enhanced population of lymphocytes kill more cancer cells. In this way, cancer cell population can be reduced largely and hence can be controlled.

In Figure. 4, the variation of the cancer cell population with time in the presence and absence of recruitment of resting cells due to external infusion is determined. It is observed that the cancer cell population approach to a lower equilibrium level when external infusion of resting cells is done as compared to the case when no external infusion is considered.

Figure. 5 gives the variation of cancer cells with time for different rate of induction of primary immune response against cancer due to presence of antigenic cancer cells that is for different antigenicity of cancer cells. It is observed from the figure that the cancer cell population decrease with the increase in antigenicity of the cancer cells. Biologically, it implies that if the cancer cells possess distinctive surface markers called tumor-specific antigens, spontaneous immune response is possible against cancer cell population that reduces the number of cancer cells in the body. These types of cancer cells that possess such antigens are called immunogenic cancers. Thus, higher is the antigenicity of cancer cells easier is to control the cancer population.

We observed that there is no effect of delay in the system for above set of parameters given in (8.1). That is, (7.7) does not hold and system is stable for all the values of delay. Therefore, in order to study the effect of delay on the system (8.1) we consider another set of parameters as given below:

$$r = 5, a_1 = 0.6, b_1 = 0.1, a_2 = 0.1, b_2 = 0.449, Q_1 = 1.1, Q_2 = 2, \pi = 7, \alpha_1 = 0.2, b = 0.08 \text{ and } \alpha_2 = 0.1 \quad (8.5)$$

which satisfy corresponding model with time delay,

$$\begin{aligned} \frac{dx}{dt} &= rx(1-x) - a_1 xy \\ \frac{dy}{dt} &= Q_1 + \frac{b_1 yz}{b+z} - \alpha_1 y - a_2 xy \\ \frac{dz}{dt} &= Q_2 + \pi x(t-\tau) - \frac{b_2 yz}{b+z} - \alpha_2 z \end{aligned} \quad (8.6)$$

.

With this set of parameters, we observed there exists a unique interior equilibrium given by $x^* = 0.0512$, $y^* = 7.9066$, $z^* = 0.1553$. For this set of parameter, we found that $\tilde{M}_1 > 0$ and $\tilde{M}_3 < 0$, which indicates that there exist a unique positive root. We found a positive root $\omega_0 = 0.0303$, with this value of ω_0 we calculated the critical value of delay that was found to be $\tau_0 = 9.4935$. Critical value of delay implies the value of τ where stability switch may occur. Stability

switch in our case stands for switching from stable steady state to stable oscillatory state. Figure 6 shows the stable dynamics of the system for $\tau = 8(< \tau_0)$. Further, Figures 7 and 8 show large amplitude oscillations for long time for $\tau = 22(> \tau_0)$.

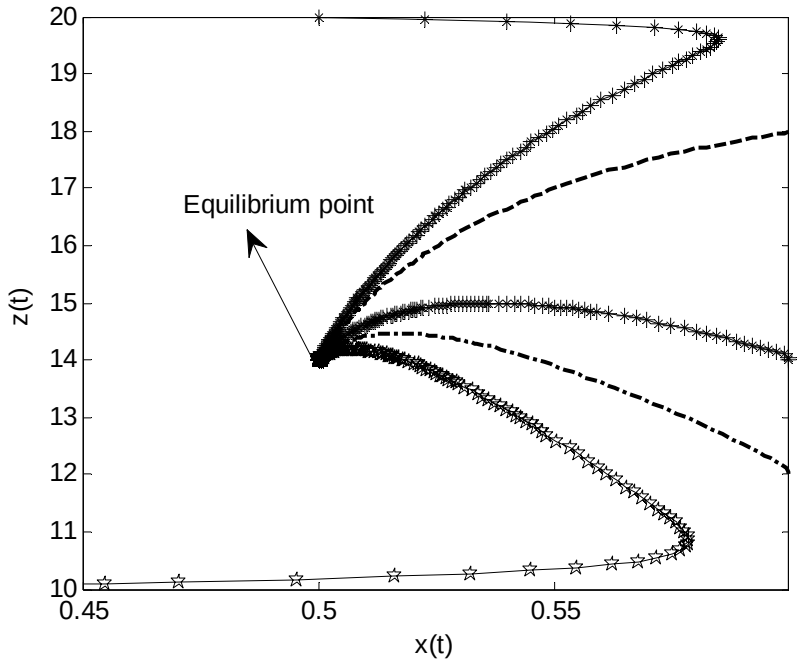

Figure 1: Graph of $x(t)$ versus $z(t)$ for different initial starts for the set of parameters same as (8.3)

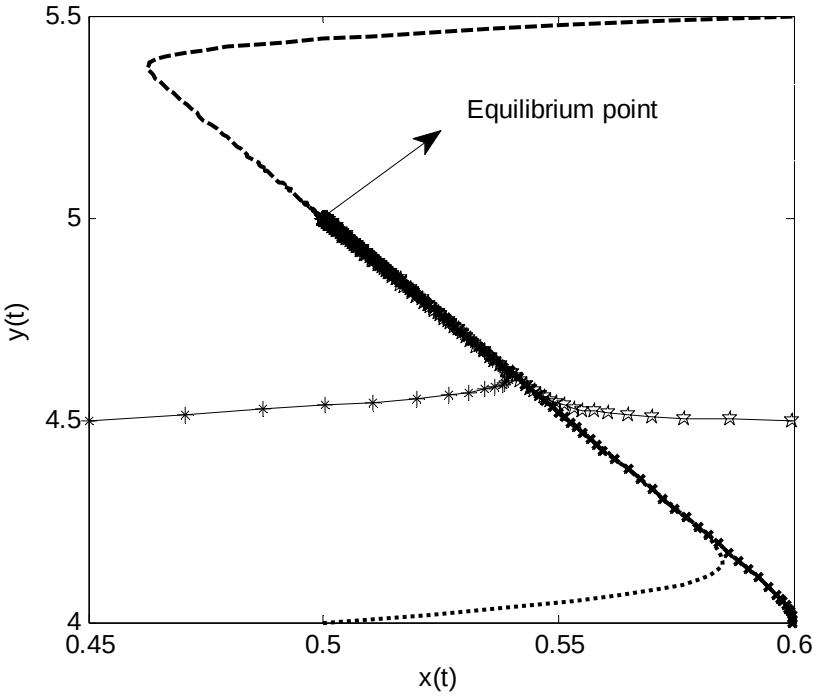

Figure 2: Graph of $x(t)$ versus $y(t)$ for different initial starts for the set of parameters same as (8.3)

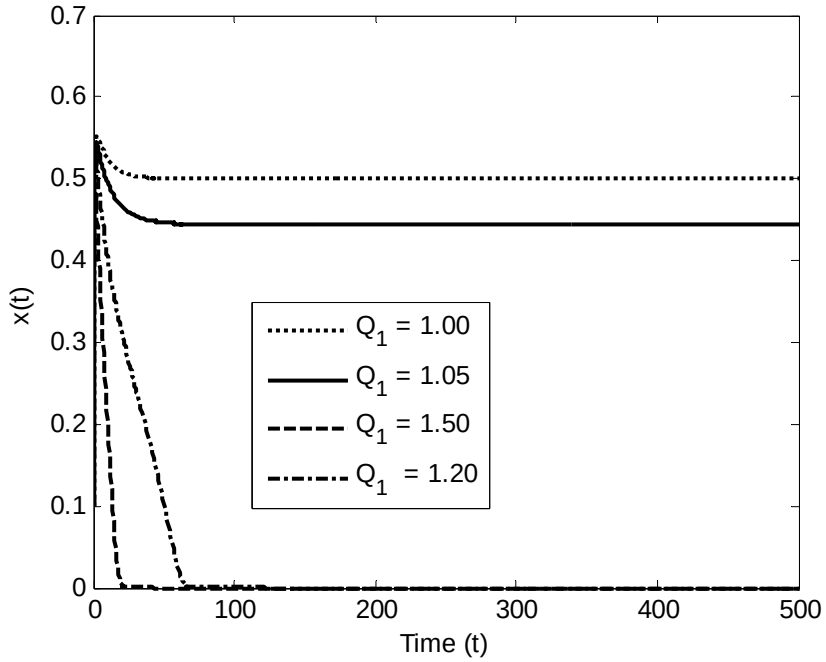

Figure 3**:** Graph of $x(t)$ versus t for different Q_1 and initial conditions $(0.10, 2.00, 10.00)$, other values of parameters are same as (8.3)

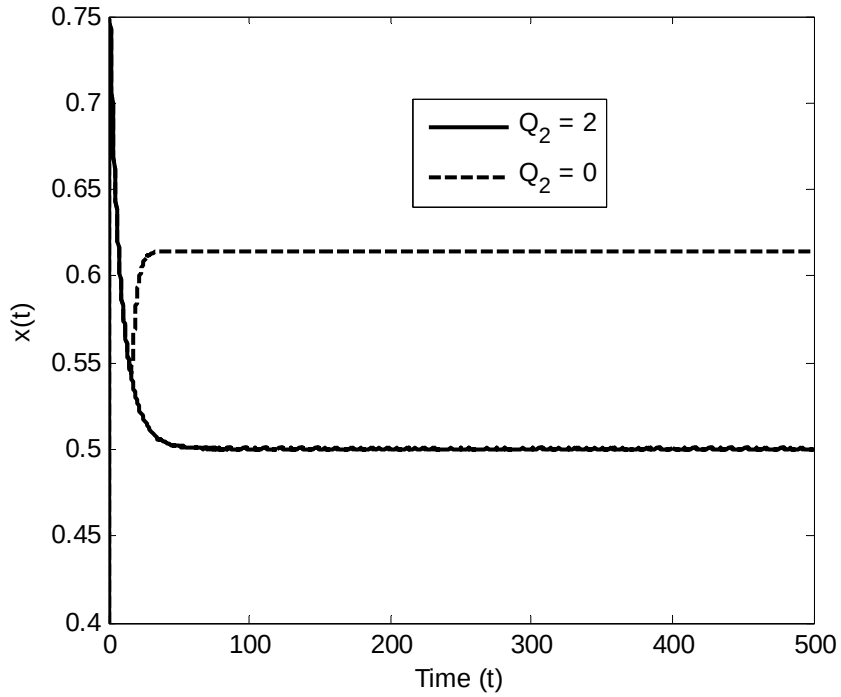

Figure 4: Graph of $x(t)$ versus t for different Q_2 and initial conditions $(0.10, 2.00, 10.00)$, other values of parameters are same as (8.3)

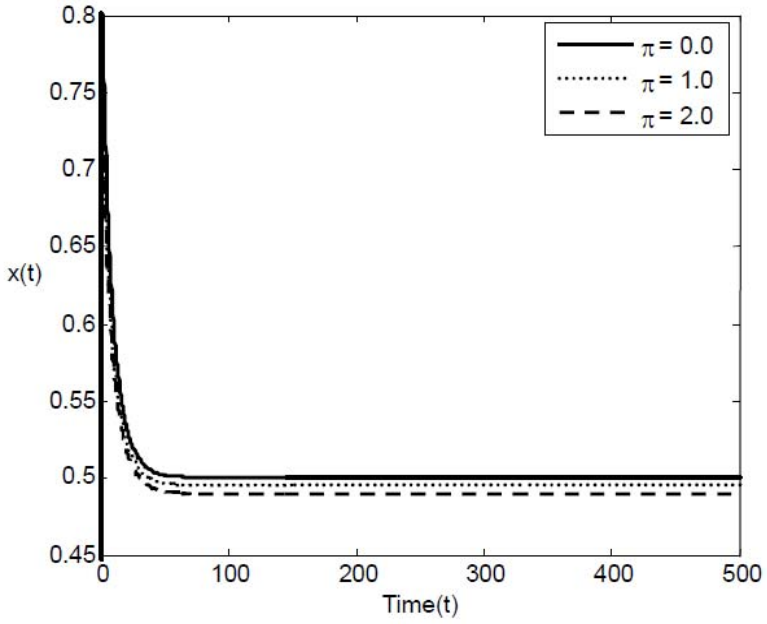

Figure 5: Graph of $x(t)$ versus t for different π and initial conditions $(0.10, 2.00, 10.00)$, other values of parameters are same as (8.3)

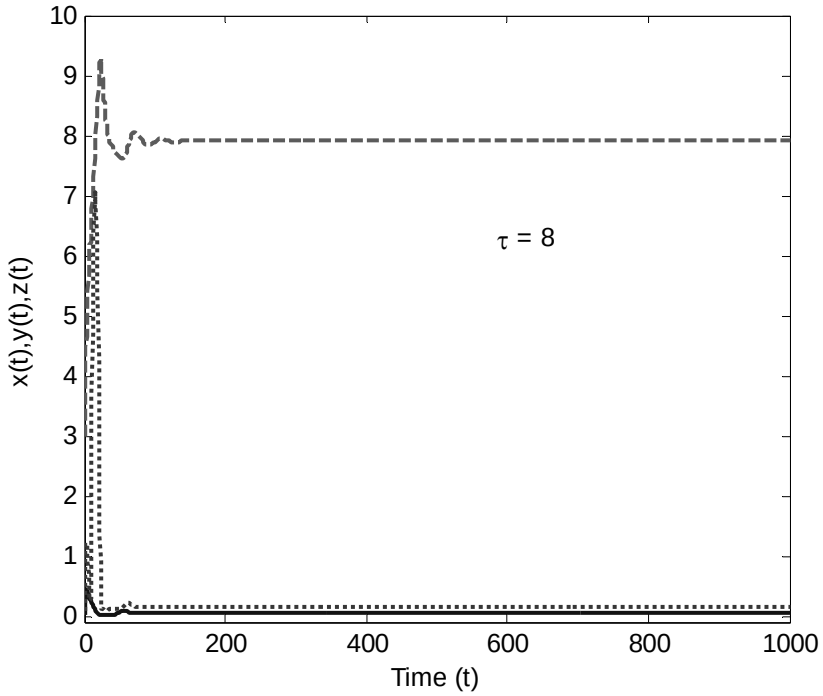

Figure 6: Graph of $x(t)$, $y(t)$, $z(t)$ versus t for $\tau = 8 < \tau_0$ and other values of parameters are same as (8.5) with initial conditions $(0.01, 3.00, 0.10)$

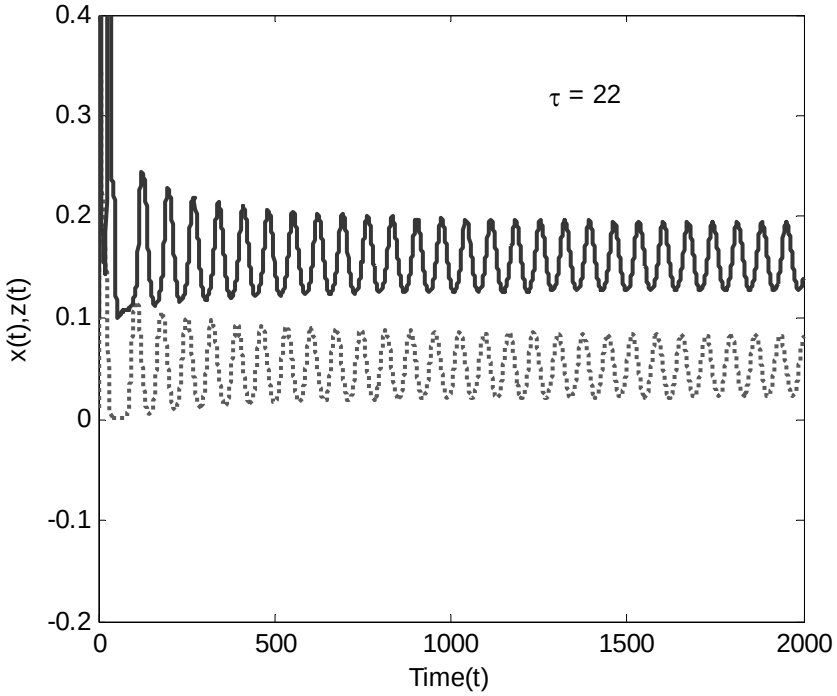

Figure 7: Graph of $x(t), z(t)$ versus t for $\tau = 22 > \tau_0$ and other values of parameters are same as (8.5) with initial conditions $(0.01, 3.00, 0.10)$

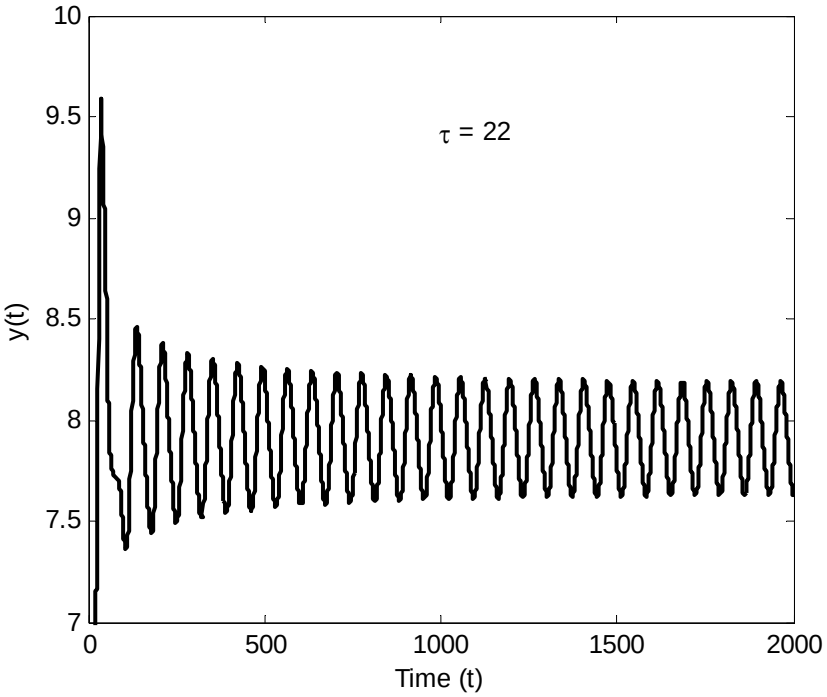

Figure 8: Graph of $y(t)$ versus t for $\tau = 22 > \tau_0$ and other values of parameters are same as (8.5) with initial conditions $(0.01, 3.00, 0.10)$

9. Conclusion

This paper considers a mathematical model to discuss the effect of immunotherapy on immunogenic cancer cells with prey predator dynamics using nonlinear ordinary differential equations. The model is analyzed using stability theory of differential equations and numerical simulations. It is found that the model has two equilibria. Conditions for local and global stability of these equilibria are determined. Cancer free equilibrium $\overline{E}(0,\overline{y},\overline{z})$ gives the criteria for total success of therapy in eliminating cancer cells from the body. This case implies that the immune system fights so well with the cancer cells that they are not able to proliferate and spread in the body and hence cancer can be cured. Interior equilibrium $E^*(x^*,y^*,z^*)$ demonstrates the case of how the cancer cells proliferate and attain a particular equilibrium level in the human body. In this case, although therapy is not able to eliminate cancer cells from the body yet it is effective in controlling the cancer cells and reducing them to a lowest possible level. Further, time delay in production of immuno-agents due to the presence of antigenic cancer cells is also studied as any process is not instantaneous and it is imperative to consider the effect of time delay on the dynamical system.

To substantiate the analytical findings, the model is studied numerically for a particular case using fourth order Runge-Kutta method. Local stability conditions are verified for a set of hypothetical parameter values. Further, to illustrate the global stability of the equilibria, numerical simulation is performed for different initial values and the results are displayed graphically. Numerically, it is observed that the cancer cell population is very sensitive to the proliferation rate of hunting cells due to external infusion of immune cell during immunotherapy. A little increase in the numerical value of proliferation rate of lymphocytes produces a considerable decrease in the equilibrium level of cancer cell population. It is further observed that cancer cell population decrease with an increase in induction of the immune response in resting cells due to cancer antigens. However, if antigenicity is zero i.e., cancer is non-immunogenic then cancer cell population rise to a large value. On the other hand, it is observed that if the rate of antigenicity is higher the cancer cell population can be controlled considerably to a lower level. Critical value of delay for the corresponding model with time delay is determined. Through figures, we have shown the stable dynamics of the system for the values of delay less than critical value of delay and large amplitude periodic oscillations for time delay larger than critical value of delay.

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