

Hopf bifurcation Analysis and Stochastic Influence of a cancer Therapy Model

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ABSTRACT

In this paper, we intend a model for the treatment of tumor using chemotherapy and oncolytic virotherapy. This model describes the interactions among infected tumor cells, uninfected tumor cells, chemotherapy and oncolytic virotherapy. Existing of the positive equilibrium points and its stability are examined. Analytical results revealed that, the system is conditionally stable at the equilibrium points. Hopf bifurcation analyzed around the interior equilibrium point and also stochastic stability investigated. The reduced tumor cells in virotherapy are reduces the concentration of chemotherapy used. The numerical simulations illustrate the analytical results.

Key words: Tumor, Stability analysis, chemotherapy, virotherapy, Hopf bifurcation, stochastic stability

Mathematics Subject Classification: 37G, 92D, 60H, 70K, 92B

Journal of Economic literature classification: C60, C62

1. INTRODUCTION

Cancer is the one of the most dangerous disease causing deaths every year. It is characterised by an uncontrolled cell growth. The individuals are affected by this disease through genetic, alcoholism, environmental factors, radiation and others [1]. Till now, for the treatment of tumor great efforts have been carried out. However, the treatments are not able to reduce the spread of cancer in the human body but controlled medically and avoid surgery [2]. Traditional treatments not only kill the tumor cells but also damage the healthy cells. The side effects of these treatments involve weakness, hair loss and decrease blood cell count [3]. The critical assumption underlying the treatment of cancer is the specific attack on malignant cells and not damaging the healthy cells [4, 5]. Genetic researchers created virus which infects only tumor cells and normal cells are free of infection. Moreover the immune system could not suppress the infection at the stage of first injection. These types of viruses are called as oncolytic viruses and recreated in Infected tumor cells. While an Infected tumor cell is lysed, it could outburst accumulation of fresh viruses. The first oncolytic virus drug 'Oncorine'

approved by the Chinese state FDA [6, 7, 8]. virotherapy is the best treatment with low cost. Chemotherapy is the usage of drugs to kill the tumor cells, mitigate pain symptoms and control the growth [9]. For the enhancement of therapeutic efficacy, oncolytic virotherapy combined with the standard therapy like chemotherapy [10].

Mathematical models are used to find advisable treatment procedures for patients. A simple mathematical model can also play vital role in various drug therapies [11]. The communications between tumor, virus and drug concentration of chemotherapy are complex .Random fluctuations are very useful to development of Infected and UnInfected tumor cells dynamics [17]. Wodarz intended a model,which explain the interactions of uninfected and infected tumor cells with bilinear incidence rate [12], Novozhilov et.al altered this model by changing the incidence rate [13].

Many authors modified the model, which is proposed by wodarz by including their assumptions [14, 15]. A. Ashyan modified M. Agarwal proposed model by changing the incidence rate [16]. In this article, we modified A. Ashyan model by adding the chemotherapy drug in treatment strategy and added the delay in the death rate. Dynamical noise is introduced in our model. Combination of vrotherapy and chemo therapy is effective to eliminate the tumor. We assumed that chemotherapy is used after first or second injection of virotherapy.

2. MATHEMATICAL MODEL

Consider a mathematical model, which express the system of differential equations

$$\begin{aligned}\frac{dx}{dt} &= r_1 x \left[1 - \frac{x+y}{k} \right] - \beta_1 xy - \alpha_1 z \\ \frac{dy}{dt} &= r_2 y \left[1 - \frac{x+y}{k} \right] + \beta_1 xy - dy \\ \frac{dz}{dt} &= V - \gamma z\end{aligned}\tag{1}$$

Where $x(0)=x_0>0$, $y(0)=y_0>0$, $z(0)=z_0>0$

$y(t)$, $x(t)$ and $z(t)$ represents the virus infected tumor cells, Uninfected tumor cells and drug concentrations. r_2 and r_1 are the per capita growth rates of Infected & uninfected tumor cells respectively. carrying capacity is k , β_1 is Infection spread rate, α_1 is the parts of uninfected tumor cells destroyed by Chemotherapy, infected tumor cells death rate is d , γ is the drug concentration decay rate, V is drug dosage.

Once tumor cells infected with virus then that infected tumor cells cannot die immediately, it undergoes a certain period of time. Time delay in death rate of infected tumor cell is also play vital role in treatment strategies.

Time delay incorporated in equation (1) as

$$\begin{aligned}\frac{dx}{dt} &= r_1 x \left[1 - \frac{x+y}{k} \right] - \beta_1 xy - \alpha_1 z \\ \frac{dy}{dt} &= r_2 y \left[1 - \frac{x+y}{k} \right] + \beta_1 xy - d y(t-\tau) \\ \frac{dz}{dt} &= V - \gamma z\end{aligned}\quad (2)$$

Where τ is time delay, dynamical performance of (2) examined the local stability of the system by using Hopf bifurcation analysis. Considering white noise in the microenvironment of tumor then system (1) exists.

$$\begin{aligned}\frac{dx}{dt} &= r_1 x \left[1 - \frac{x+y}{k} \right] - \beta_1 xy - \alpha_1 z + \sigma_1 (x - x^*) d\xi_1 \\ \frac{dy}{dt} &= r_2 y \left[1 - \frac{x+y}{k} \right] + \beta_1 xy - d y + \sigma_2 (y - y^*) d\xi_2 \\ \frac{dz}{dt} &= V - \gamma z + \sigma_3 (z - z^*) d\xi_3\end{aligned}\quad (3)$$

$\sigma_1, \sigma_2, \sigma_3$ are constants which give out the fluctuations in the micro environment of tumor, ξ_1, ξ_2, ξ_3 are independent of each other with respect to standard wiener conditions

3. EXISTENCE OF EQUILIBRIUM POINTS

(i) It states that the uninfected & infected tumor cells are in same state. If tumor is completely eliminated then the trivial equilibrium point $E_0(0,0,0)$ is exists. It signifies that virus Infected and uninfected tumors cells could be abolished with respect to time. By using chemotherapy and virotherapy absolute recovery is possible.

(ii) If the treatment of virotherapy and chemotherapy fails then the existence of equilibrium point $E_1(k,0,0)$ is possible

(iii) Equilibrium point $E_2(0, \bar{y}, \bar{z})$ is exists if $r_2 > d$. In the initial stage, if tumor is detected then it can be reduced to lower size by using virotherapy and chemotherapy at $\bar{y} = \frac{k(r_2 - d)}{r_2}, \bar{z} = \frac{V}{\gamma}, r_2 > d$ If

treatment is successful then tumor eliminated. Biological point of view we are interested in steady states of E^* since uninfected, Infected and chemo drug exists.

(iv) Let $E^*(x^*, y^*, z^*)$ be the interior equilibrium point, x^*, y^*, z^* are non negative solutions of system

(1). To check the existence algebraic equations of system (1) are equate to zero.

$$\begin{aligned}
 rx \left[1 - \frac{x+y}{k} \right] - \beta_1 xy - \alpha_1 z &= 0 \\
 r_2 y \left[1 - \frac{x+y}{k} \right] + \beta_1 xy - dy &= 0 \quad V - \gamma z = 0 \\
 z^* = \frac{V}{\gamma}, \quad x^* = \frac{-m_2 + \sqrt{m_2^2 - 4m_1 m_2}}{2m_1}, \quad m_2^2 - 4m_1 m_2 &> 0 \\
 m_1 = r_1 r_2 + (r_1 + k\beta_1)(k\beta_1 - r_2), \quad m_2 = (r_1 + k\beta_1)(k(r_2 - d)) - kr_1 r_2, \quad m_3 = \frac{kr_2 \alpha_1 V}{\gamma} \\
 y^* = \frac{k(r_2 - d) + (k\beta_1 - r_2)x^*}{r_2}, \quad r_2 > d, k\beta_1 > r_2
 \end{aligned} \tag{4}$$

4. STABILITY ANALYSIS OF THE SYSTEM

Equilibrium point is said to be locally asymptotically stable (LAS) if solutions of the system approach to it as $t \rightarrow \infty$

4.1 Stability analysis at the equilibrium point $E_1(k, 0, 0)$

Jacobian matrix $J(E_1) = \begin{bmatrix} -r_1 & -r_1 - \beta_1 k & 0 \\ 0 & \beta_1 k - d & 0 \\ 0 & 0 & -\gamma \end{bmatrix}$

Characteristic equation is

$$(-r_1 - \lambda)((\beta_1 k - d) - \lambda)(-\gamma - \lambda) = 0 \tag{5}$$

$$\lambda_1 = -r_1, \lambda_2 = -(d - \beta_1 k), \lambda_3 = -\gamma$$

$$\beta_1 k < d \tag{6}$$

If $\beta_1 k < d$ then all the eigen values are negative real parts, by Routh-Hurwitz criteria E_1 is locally asymptotically stable. If $\beta_1 k > d$ then E_1 is a saddle point.

4.2 Stability analysis at the equilibrium $E_2(0, \bar{y}, \bar{z})$

Jacobian matrix at $E_2(0, \bar{y}, \bar{z})$

$$\bar{y} = \frac{k(r_2 - d)}{r_2}, \bar{z} = \frac{V}{\gamma}$$

$$J(E_2) = \begin{bmatrix} r_1(1 - \frac{\bar{y}}{k}) - \beta_1 \bar{y} & 0 & 0 \\ -\frac{r_2 \bar{y}}{k} + \beta_1 \bar{y} & r_2 - d - \frac{2r_2 \bar{y}}{k} & 0 \\ 0 & 0 & -\gamma \end{bmatrix}$$

Characteristic equation is

$$\left((r_1(1 - \frac{\bar{y}}{k}) - \beta_1 \bar{y}) - \lambda \right) \left((r_2 - d - \frac{2r_2 \bar{y}}{k}) - \lambda \right) (-\gamma - \lambda) = 0 \quad (7)$$

$$[r_1 d - \beta_1 k(r_2 - d) - \lambda](d - r_2 - \lambda)(-\gamma - \lambda) = 0$$

$$\frac{\beta_1 k(r_2 - d)}{r_1 d} < 1 \quad \lambda_2 = -(r_2 - d), \lambda_3 = -\gamma$$

Define Basic reproduction number $R_0 = \frac{\beta_1 k(r_2 - d)}{r_1 d}$

If $R_0 < 1$ and $r_2 > d$ then $E_2(0, \bar{y}, \bar{z})$ is LAS by Routh-hurwitz criteria. If $R_0 > 1$ then equilibrium point is not stable and Interior equilibrium point exists.

4.3 Stability analysis at $E^*(x^*, y^*, z^*)$

Jacobian matrix of the system (2) at the equilibrium point $E^*(x^*, y^*, z^*)$ is

$$J(E^*) = \begin{bmatrix} r_1 - \frac{r_1(2x^* + y^*)}{k} - \beta_1 y^* & -\frac{r_1 x^*}{k} - \beta_1 x^* & 0 \\ -\frac{r_2 y^*}{k} + \beta_1 y^* & (r_2 - d) + \beta_1 x^* - \frac{r_2(2y^* + x^*)}{k} - de^{-\lambda \tau} & 0 \\ 0 & 0 & -\gamma \end{bmatrix}$$

$$[r_1 - \beta_1 y^* - \frac{r_1}{k}(2x^* + y) - \lambda][r_2 + \beta_1 x^* - \frac{r_2}{k}(2y^* + x^*) - de^{-\lambda \tau} - \lambda] \quad (8)$$

$$(-\gamma - \lambda) - (-\frac{r_1 x^*}{k} - \beta_1 x^*)[(\gamma - \lambda)(\frac{r_2 y^*}{k} + \beta_1 y^*)] = 0$$

Case (i) there is no delay in the system, and then the characteristic equation is

$$(-\gamma - \lambda)(\lambda^2 + p_{11}\lambda + p_{12}) = 0$$

$$p_{11} = \beta_1 y^* + \frac{r_1}{k}(2x^* + y) + \frac{r_2}{k}(2y^* + x^*) + d - (r_1 + r_2 + \beta_1 x^*)$$

$$p_{12} = \left(r_1 - \frac{r_1}{k}(2x^* + y) - \beta_1 y^* \right) \left(r_2 + \beta_1 x^* + \frac{r_2}{k}(2y^* + x^*) \right) + (\beta_1^2 + (\frac{r_1}{k} - \frac{r_2}{k})\beta_1 - r_1 r_2) x^* y^*$$

are positive. By Routh-hurwitz criteria system is locally asymptotically stable at $E^*(x^*, y^*, z^*)$.

Case (ii) If $\tau > 0$ then the transcendental equation (8) has infinite number of solutions, but we consider periodic solutions of (2).

$$\lambda^3 + a_{11}\lambda^2 + a_{12}\lambda + a_{13} + e^{-\lambda\tau}(b_{11}\lambda^2 + b_{12}\lambda + b_{13}) = 0 \quad (9)$$

$$a_{11} = \frac{r_1}{k}(2x^* + y^*) + \frac{r_2}{k}(2y^* + x^*) + \beta_1(x^* + y^*) + \gamma - (r_1 + r_2)$$

$$a_{12} = \gamma \left(\frac{r_1}{k}(2x^* + y^*) + \frac{r_2}{k}(2y^* + x^*) + \beta_1 x^* \right) + (r_1 - \beta_1 y^* - \frac{r_1}{k}(2x^* + y^*)) \left(-\frac{r_2}{k}(x^* + 2y^*) + \right.$$

$$\left. \beta_1 x^* + r_2 \right) + (\frac{r_1}{k} + \beta_1) x^* \left(-\frac{r_2}{k} + \beta_1 \right) y^*$$

$$a_{13} = (r_1 - \beta_1 y^* - \frac{r_1}{k}(2x^* + y^*)) \left(r_2 + \beta_1 x^* + \frac{r_2}{k}(2y^* + x^*) \right) - \gamma \left(\frac{r_1}{k} + \beta_1 \right) x^* \left(-\frac{r_2}{k} + \beta_1 \right) y^*$$

$$b_{11} = d, b_{12} = \gamma d - r_1 d + \beta_1 d y^* + \frac{r_1}{k}(2x^* + y^*) d, b_{13} = d \gamma \left(\frac{r_1}{k}(2x^* + y^*) + \beta_1 - r_1 \right)$$

Assume that $\lambda = i\omega$ is the root of the equation (9)

$$-i\omega^3 - \omega^2 a_{11} + a_{12} i\omega + a_{13} + (\cos \omega\tau - i \sin \omega\tau)(-\omega^2 b_{11} + i\omega b_{12} + b_{13}) = 0$$

$$(\omega^2 b_{11} - b_{13})^2 + \omega^2 b_{12}^2 = (\omega^2 a_{11} - a_{13})^2 + (\omega^3 - a_{12} \omega)^2$$

$$\omega^6 + c_{11}\omega^4 + c_{12}\omega^2 + c_{13} = 0 \quad (10)$$

$$c_{11} = a_{11}^2 - 2a_{12} + b_{11}^2, c_{12} = a_{12}^2 - 2a_{11}a_{13} + 2b_{11}b_{13} + b_{12}^2, c_{13} = a_{13}^2 - b_{13}^2$$

In equation (10) function $f(\omega)$ can be written as $f(\omega) = h(\omega^2)$

Put $z = \omega^2$

$$h(z) = z^3 + c_{11}z^2 + c_{12}z + c_{13} = 0 \quad (11)$$

If c_{11}, c_{12}, c_{13} are positive then there is no positive root of equation (11).

$$\begin{aligned}\frac{dh}{dz} &= 3z^2 + 2c_{11}z + c_{12} \\ 3z^2 + 2c_{11}z + c_{12} &= 0 \\ z &= \frac{-c_{11} \pm \sqrt{(c_{11}^2 - 3c_{12})}}{3}\end{aligned}$$

If $c_{12} > 0$ then $\sqrt{(c_{11}^2 - 3c_{12})} < c_{12}$. So either Z_1 or Z_2 not positive. Thus (10) does not have positive roots and $h(0) = c_{13} > 0$, it shows that (11) has no non negative roots.

There is no such ω , $i\omega$ is characteristic value of (10). Hence eigen values are having negative real parts for $\tau \geq 0$.

If $c_{12} < 0$ or $c_{13} < 0$ then $\exists$ a unique non negative ω_0 satisfy equation (10).

If $c_{13} > 0$ then $h(0) < 0$ & $\lim_{z \rightarrow \infty} h(z) = \infty$. Thus (11) has at least one positive root, denoted by Z_0 and then (10) has positive root denoted by ω_0 .

If $c_{12} < 0$ then $\sqrt{(c_{11}^2 - 3c_{12})} > c_{12}$ and (10) has positive root ω_0 . This means (8) has purely imaginary pair of roots. Let $\lambda(\tau) = \phi(\tau) + i\omega(\tau)$ be an Eigen value of (9) such that $\phi(\tau_0) = 0$, $\omega(\tau_0) = \omega_0$.

From (9)

$$\tau_k = \frac{1}{\omega_k} \left(\arccos \left(\frac{(b_{12} - a_{11}b_{11})\omega^4 + (a_{13}b_{11} + a_{11}b_{13} - a_{12}b_{12})\omega^2 + a_{13}b_{13}}{(b_{11}\omega^2 - b_{13})^2 + b_{12}^2\omega^2} \right) + 2k\pi \right), k = 0, 1, 2, \dots$$

E^* is stable for $\tau < \tau_0$ if transversality condition $\left. \frac{d\operatorname{Re}(\lambda)}{d\tau} \right|_{\tau=\tau_0} > 0$ holds. There will be at least one

eigen value with non negative real part for $\tau > \tau_0$.

i.e to prove $\left. \operatorname{sign} \left(\frac{d\operatorname{Re}(\lambda)}{d\tau} \right) \right|_{\tau=\tau_0} = \operatorname{sign} \left(\operatorname{Re} \left[\frac{d\lambda}{d\tau} \right]^{-1} \right) \Big|_{\tau=\tau_0}$

Consider $\lambda^3 + a_{11}\lambda^2 + a_{12}\lambda + a_{13} + (b_{11}\lambda^2 + b_{12}\lambda + b_{13})e^{-\lambda\tau} = 0$

Differentiate with respect to τ

$$\left((3\lambda^2 + 2a_{11}\lambda + a_{12} + (2b_{11}\lambda + b_{12}))e^{-\lambda\tau} - \tau(b_{11}\lambda^2 + b_{12}\lambda + b_{13})e^{-\lambda\tau} \right) \frac{d\lambda}{d\tau} = \lambda e^{-\lambda\tau} (b_{11}\lambda^2 + b_{12}\lambda + b_{13})$$

$$\left(\frac{d\lambda}{d\tau}\right)^{-1} = \frac{3\lambda^2 + 2a_{11}\lambda + a_{12}}{\lambda e^{-\lambda\tau}(b_{11}\lambda^2 + b_{12}\lambda + b_{13})} + \frac{(2b_{11}\lambda + b_{12})}{(b_{11}\lambda^2 + b_{12}\lambda + b_{13})\lambda} - \frac{\tau}{\lambda}$$

$$\text{Put } \lambda = i\omega_0$$

$$\operatorname{Re}\left(\frac{d\lambda}{d\tau}\right)^{-1} = \operatorname{Re}\left[\frac{-3\omega_0^2 + a_{12} + 2a_{11}i\omega_0}{-\omega_0^4 + a_{11}\omega_0^2 + i(a_{11}\omega_0^3 + a_{13}\omega_0)} + \frac{b_{12} + 2b_{11}i\omega_0}{-b_{12}\omega_0^2 + i(b_{11}\omega_0^3 + b_{13}\omega_0)}\right]$$

$$\operatorname{Re}\left(\frac{d\lambda}{d\tau}\right)^{-1} = \operatorname{Re}\left[\frac{u_1 + iv_1}{u_2 + iv_2} + \frac{u_3 + iv_3}{u_4 + iv_4}\right]$$

$$u_1 = -3\omega_0^2 + a_{12}, v_1 = 2a_{11}\omega_0, u_2 = -\omega_0^4 + a_{11}\omega_0^2, v_2 = a_{11}\omega_0^3 + a_{13}\omega_0, u_3 = b_{12}$$

$$v_3 = 2b_{11}\omega_0, u_4 = -b_{12}\omega_0^2, v_4 = b_{11}\omega_0^3 + b_{13}\omega_0$$

$$\operatorname{Re}\left(\frac{d\lambda}{d\tau}\right)^{-1} = \operatorname{Re}\left[\frac{u_1u_2 + v_1v_2}{u_2^2 + v_2^2} + \frac{u_3u_4 + v_3v_4}{u_4^2 + v_4^2}\right]$$

$$\text{Under this condition } u_1u_2 + v_1v_2 > 0 \text{ and } u_3u_4 + v_3v_4 > 0, \left.\frac{d\operatorname{Re}(\lambda)}{d\tau}\right|_{\lambda=i\omega_0} > 0$$

Hopf bifurcation occurred at $\tau = \tau_0, \omega = \omega_0$

5. Stochastic influence at interior equilibrium point

Random fluctuations are essential to more or less all biological phenomena. To observe the random fluctuations generated on model (1) by micro environmental factors, perturbations are presumed to occur as white noise, which are in proportion to the distance of X, Y, Z from their equilibrium points.

Change of variables of stochastic system (3) at E^* is

$$M_1 = x - x^*, M_2 = y - y^*, M_3 = z - z^*$$

$$\text{Linearized system at } E^* \text{ is } dM(t) = f_1(M(t))dt + g_1(M(t))d\xi(t) \quad (12)$$

Where $M(t) = \operatorname{col}[M_1(t), M_2(t), M_3(t)]$

$$f_1(M(t)) = \begin{bmatrix} r_1(1 - \frac{2x^* + y^*}{k}) - \beta_1 y^* & -\frac{r_1 x^*}{k} - \beta_1 x^* & 0 \\ -r_2 y^* + \beta_1 y^* & \beta_1 x^* - d + r_2(1 - \frac{2y^* + x^*}{k}) & 0 \\ 0 & 0 & -\gamma \end{bmatrix}$$

$$g_1(M(t)) = \begin{bmatrix} \sigma_1 M_1 & 0 & 0 \\ 0 & \sigma_2 M_2 & 0 \\ 0 & 0 & \sigma_3 M_3 \end{bmatrix}$$

Let $C^{1,2}([0, +\infty) \times R^2, R^+)$ be the family of positive functions, $\psi(t, M)$ defined on $[0, +\infty) \times R^2$,

It is continuously differentiable function. Define a differential operator L for a function $\psi(t, M)$

$$L(\psi(t, M)) = \frac{\partial \psi(t, M)}{\partial t} + f_1^T(M) \frac{\partial \psi(t, M)}{\partial M} + \frac{1}{2} Tr \left[g_1^T(M) \frac{\partial^2 \psi(t, M)}{\partial M^2} g_1(M) \right] \quad (13)$$

$$\frac{\partial \psi}{\partial M} = \begin{bmatrix} \frac{\partial \psi}{\partial M_1} \\ \frac{\partial \psi}{\partial M_2} \\ \frac{\partial \psi}{\partial M_3} \end{bmatrix} \quad \text{and} \quad \frac{\partial^2 \psi}{\partial M^2} = \frac{\partial^2 \psi}{\partial M_i \partial M_j}; i, j = 1, 2, \dots$$

Theorem: If there exists a function $\psi(t, M) \in C^{1,2}([0, +\infty) \times R^2, R^+)$ which satisfies

$$K_1 |M|^p \leq \psi(t, M) \leq K_2 |M|^p$$

$$L\psi(t, M) \leq -K_3 |M|^p \quad (14)$$

Where K_1, K_2, K_3 and P are non negative constants then the trivial solution of (12) is exponentially p -stable for $t \geq 0$ [18,19]. Moreover the trivial solution of (12) is globally asymptotically stable if $p = 2$ in (14).

Theorem: suppose the inequalities

$$\sigma_1^2 \leq 2 \left[\frac{r_1}{k} (2x^* + y^*) + \beta_1 y^* - r_1 \right]$$

$$\sigma_2^2 \leq 2 \left[\frac{r_2}{k} (x^* + 2y^*) - \beta_1 x^* + d - r_2 \right]$$

$$\sigma_3^2 \leq 2\gamma^2$$

Are true then trivial solution of (12) is asymptotically mean square stable.

Proof:

$$\text{Choose a Lyapunov function} \quad \psi(M) = \frac{1}{2} [\psi_1 M_1^2 + \psi_2 M_2^2 + \psi_3 M_3^2] \quad (15)$$

where ψ_1, ψ_2, ψ_3 positive constants . It is easy to verify (14) for $p=2$

$$\begin{aligned}
 L(\psi(M)) = & \psi_1 \left[-\left(\frac{r_1}{k}(2x^* + y^*) + \beta_1 y^* - r\right) M_1 - \left(\frac{r_1}{k} + \beta_1\right) x^* M_2 \right] M_1 + \\
 & \psi_2 \left[-\left(\frac{r_2 y^*}{k} - \beta_1 y^*\right) M_1 - \left(\frac{r_2}{k}(x^* + 2y^*) - \beta_1 x^* + d - r\right) M_2 \right] M_2 + \psi_3 (-\gamma M_3) M_3 + \\
 & \frac{1}{2} \text{Tr} \left[g_1^T(M) \frac{\partial^2 \psi}{\partial M^2} g_1(M) \right]
 \end{aligned} \tag{16}$$

$$\text{With } \frac{1}{2} \text{Tr} \left[g_1^T(M) \frac{\partial^2 \psi}{\partial M^2} g_1(M) \right] = \frac{1}{2} [\psi_1 \sigma_1^2 M_1^2 + \psi_2 \sigma_2^2 M_2^2 + \psi_3 \sigma_3^2 M_3^2]$$

Set $\psi_1 \left(-\left(\frac{r_1 x^*}{k} + \beta_1 x^*\right)\right) = \psi_2 \left(-\left(\frac{r_1 y^*}{k} - \beta_1 y^*\right)\right)$ then (16) becomes

$$\begin{aligned}
 L(\psi(M)) = & -\left(\frac{r_1(2x^* + y^*)}{k} + \beta_1 y^* - r_1 - \frac{\sigma_1^2}{2}\right) \psi_1 M_1^2 - \left(\frac{r_2(x^* + 2y^*)}{k} - \beta_1 x^* + d - r_2 - \frac{\sigma_2^2}{2}\right) \psi_2 M_2^2 \\
 & - \gamma \psi_3 M_3^2 \\
 \psi_1 M_2 = & \psi_2 M_1
 \end{aligned}$$

Solution of (12) is trivial & globally asymptotically stable.

6. NUMERICALSIMULATIONS

Example.1 For the set of values $r_1=0.21$, $r_2=0.02$, $k=0.1$, $\beta=1.4$; $\alpha=0.000001$, $d=0.1$, $V=0.01$, $\gamma=0.09$ system (2) has interior equilibrium $E^*(0.0163, 0.0137, 0.0111)$, Figures1 –Figure3 shows that time delay $\tau_0 = 3.548$ when $0 \leq \tau < \tau_0$ E^* is asymptotically stable. When τ passes through τ_0 interior equilibrium loses its stability and periodic solutions bifurcate from E^* and $\tau > \tau_0$ system is unstable.

Example. 2 For the same set of values Figure.4 shows that dynamics of stochastic and deterministic model steady states around the interior equilibrium E^* with $\sigma_1=0.008$, $\sigma_2=0.008$, $\sigma_3=0.005$

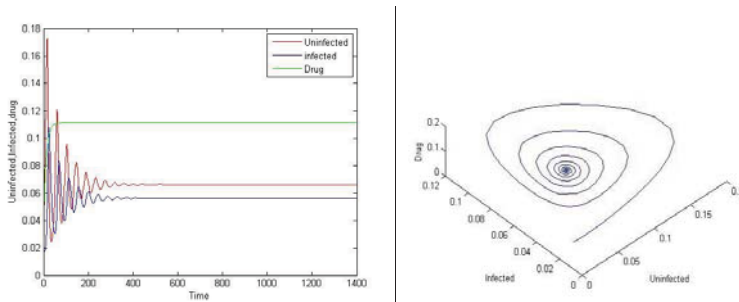
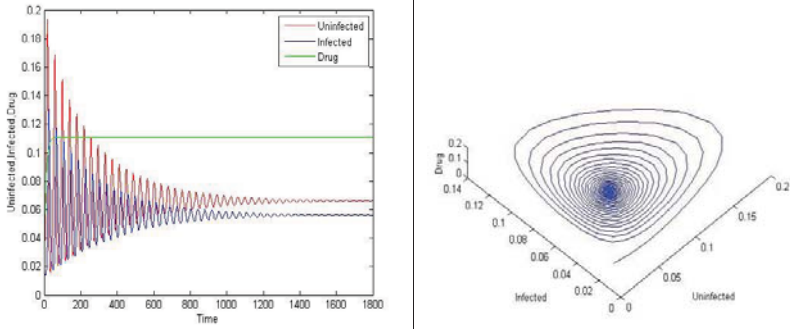
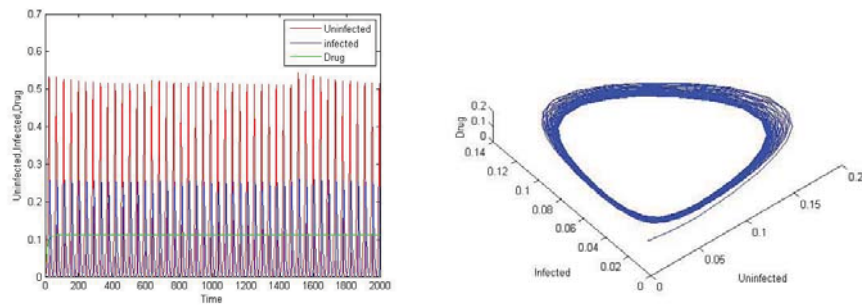
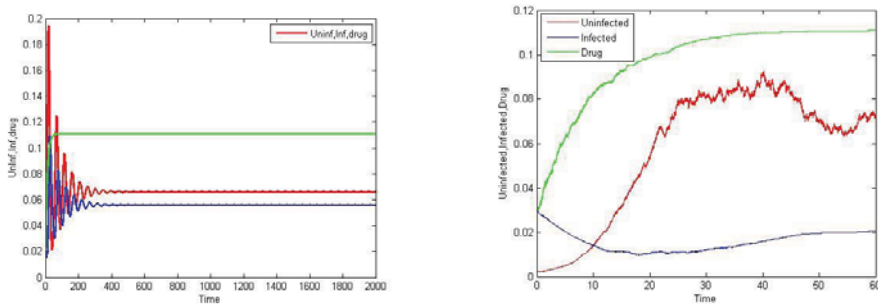


Figure1. Analysis of phase spaces (2) when $\tau = 2.958 < \tau_0 = 3.548$


 Figure2. Analysis of phase spaces (2) when $\tau = \tau_0 = 3.548$

 Figure3. Analysis of phase spaces (2) when $\tau = 3.948 > \tau_0 = 3.548$

 Figure4. Deterministic & Stochastic trajectories of system when $\sigma_1 = 0.008, \sigma_2 = 0.008, \sigma_3 = 0.005$

7. CONCLUSION

In this article we discussed a mathematical model of chemo therapy and oncolytic virotherapy with discrete time delay and random variations surrounding interior equilibrium point. From the stability analysis of (1), conditional stability of the equilibrium points $E_1(k, 0, 0)$ and $E_2(0, \bar{y}, \bar{z})$ are found, biologically stability of E^* is an important point since uninfected, infected tumor cells and drug concentration exists. Interior equilibrium point $E^*(x^*, y^*, z^*)$ is LAS by the Routh-Hurwitz criteria when

$0 \leq \tau < \tau_0$ and hopf bifurcation point τ_0 is found. In virotherapy progression, effect of delay in death rate also play crucial role. After virotherapy, particles of tumor killed by chemo therapy. Figure1 to figure 3 shown that stable to unstable variations around E^* and figure 4 shown that white noise disturbance from deterministic to stochastic model. The dynamical behaviour of the system is evident from the mean square stability perspective.

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