

Stability Analysis of Tumor treatment model using Virotherapy and Chemotherapy

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ABSTRACT

The present study proposed a mathematical model for the treatment of tumor using virotherapy and chemotherapy. In this model interaction among uninfected tumor cells, infected tumor cells, and chemotherapy are described by the nonlinear differential equations. Non-Negative equilibrium points of the system are derived and its stability analysis is carried out. Numerical simulations support the analytical results.

Keywords: Tumor cells with virus infected, Virus uninfected tumor cells, Stability Analysis, Virotherapy, chemotherapy.

Mathematical subject classification: 34D20, 93D05, 92B05

Journal of Economic Literature (JEL) Classification : C60, C62

1. INTRODUCTION

Cancer is still life-threatening disease in the worldwide .It is a series of disorder described by abnormal cell growth through which cells may attain the potential to scatter from the site of origin to other sites in the body. This process is called metastasis [1]. Metastasis is considered as the major causes of deaths due to cancer. Various treatment methods are utilized to cure cancer. Chemotherapy is a distinctive approach compare to surgical procedure and radiation therapy to treat cancer. It utilizes chemical agents (cytotoxic drugs) to interact with tumor cells to wipe out or control the growth of tumor. Different chemical agents not only kill the cancer cells but also damage the surrounding effector cells in different ways. Some of the common side effects in these treatments are hair loss, nausea, fatigue and drop in the blood

count cells [2]. If Chemotherapy is used alone then the lymphocyte damage may occur in the system, which could change the stability of the system at the tumor free equilibrium point. The advancement of science in the genetic engineering field has found an oncolytic virus to kill the tumor. Virotherapy treatment has been acknowledged as a less toxic treatment. In this treatment primary mechanism is oncolytic viruses contaminate multiply and directly lyse the cancer cells with no or less toxicity [3, 4]. The most important limitation of oncolytic viruses is the hasty progress of neutralizes the antibodies by the host, which limit the viral release to metastatic cancer sites and the therapeutic effect. To find the impact of a virus on tumor growth is extremely complex.

Combination of therapy strategies have shown significant effect on cancer and provides more therapeutic efficacy compare to single drug treatments. The combination of virotherapy and chemotherapy treatment determines the effect of drug response and virus infection rate. Researchers are convinced that mathematical theories should be useful to find the dynamical changes in virotherapy[5,6]. Recently several mathematical models are developed in virotherapy with the combination of chemotherapy or radiotherapy [7, 8, 9, 10, 11].

In this paper we modify the M.Agarwalmodel[12] by adding the chemotherapy treatment along with the virotherapy. Equilibrium points and its stability are analyzed theoretically and numerically.

2. MATHEMATICAL MODEL

Model equations are formulated by the system of differential equations.

$$\begin{aligned}\frac{dx}{dt} &= rx \left(1 - \frac{y+x}{k}\right) - \frac{\beta xy}{y+x+a} - d_1 xz \\ \frac{dy}{dt} &= \frac{\beta xy}{y+x+a} - \mu y - d_2 yz \\ \frac{dz}{dt} &= \nu - \psi z\end{aligned}\tag{1}$$

$y(t)$, $x(t)$ and $z(t)$ are the infected tumor cells ,uninfected tumor cells and chemotherapy respectively. k is carrying capacity, r is intrinsic growth rate, β is virus infection transmission rate, a is saturation constant, d_1 is death rate of uninfected cells by chemotherapy drug, Virus infected tumor cells death rate is μ , d_2 is the death rate of infected tumor cells by chemotherapy drug, ν drug injection, ψz is natural drug concentration decay.

3. EXISTENCE OF EQUILIBRIUM POINTS

Equilibrium points of the model are specified by $E_0\left(0, 0, \frac{\nu}{\psi}\right)$ which is equilibrium of tumor free, virus infection free equilibrium $E_1(\bar{x}, 0, \bar{z})$ and endemic equilibrium point $E_2(x^*, y^*, z^*)$. $\bar{x} = \frac{k}{r}(r - d_1\bar{z})$ where $r > d_1\bar{z}$ and $\bar{z} = \frac{\nu}{\psi}$

Equilibrium point E_1 is exists if $r > d_1\bar{z}$

The equilibrium point $x^* = (y^* + a)p$ where $p = \frac{\mu + d_2z^*}{\beta - (\mu + d_2z^*)}$ where $\beta > \mu + d_2z^*$

$z^* = \frac{\nu}{\psi}$ and y^* is determined by $ay^{*2} + by^* + c = 0$

$$y^* = \frac{-b + \sqrt{b^2 - 4ac}}{2a}$$

$$a = r(p+1)^2, \quad b = ar(p+1)^2 + \beta k - (k(r - d_1z^*) + rap)(1+p)$$

$$c = -ka \left[(r - d_1z^*)(1+p) - \frac{r}{k}ap(1+p) \right]$$

Equilibrium point E_2 exists if $b^2 - 4ac > 0$

4. STABILITY ANALYSIS

The local stability of a nonlinear system equilibrium points are investigated by linearizing the system around equilibrium points

4.1. Tumor free equilibrium and its stability

Jacobian matrix at E_0 is

$$J = \begin{bmatrix} -d_1 & 0 & 0 \\ 0 & -d_2 & 0 \\ 0 & 0 & -\psi \end{bmatrix}$$

Characteristic equation is $(-d_1 - \lambda)(-d_2 - \lambda)(-\psi - \lambda) = 0$

The eigen values are $\lambda_1 = -d_1, \lambda_2 = -d_2, \lambda_3 = -\psi$

Eigen values have negative real parts, by the Routh-Hurwitz criterion the system (1) has locally asymptotically stable (LAS) at E_0 .

4.2. Behavior of the virus infection free equilibrium point

Jacobian matrix at $E_1(\bar{x}, 0, \bar{z})$ is

$$J = \begin{bmatrix} r - \frac{2r\bar{x}}{k} - d_1\bar{z} & -\frac{r\bar{x}}{k} & -d_1\bar{x} \\ 0 & \frac{\beta\bar{x}(\bar{x}+a)}{(\bar{x}+a)^2} - \mu - d_2\bar{z} & 0 \\ 0 & 0 & -\psi \end{bmatrix}$$

Characteristic equation is

$$(-\psi - \lambda) \left(r - \frac{2r\bar{x}}{k} - d_1\bar{z} - \lambda \right) \left(\frac{\beta\bar{x}(\bar{x}+a)}{(\bar{x}+a)^2} - \mu - d_2\bar{z} - \lambda \right) = 0$$

$$\lambda_1 = -\psi, \lambda_2 = r - \frac{2r\bar{x}}{k} - d_1\bar{z}, \lambda_3 = \frac{\beta\bar{x}(\bar{x}+a)}{(\bar{x}+a)^2} - \mu - d_2\bar{z}$$

$$\lambda_2 \text{ is negative for } r < \frac{2r\bar{x}}{k} + d_1\bar{z} \text{ and } \lambda_3 \text{ is negative for } \frac{\beta\bar{x}(\bar{x}+a)}{(\bar{x}+a)^2} > \mu + d_2\bar{z}$$

If $r < \frac{2r\bar{x}}{k} + d_1\bar{z}$ and $\frac{\beta\bar{x}(\bar{x}+a)}{(\bar{x}+a)^2} > \mu + d_2\bar{z}$ then E_1 is locally asymptotically stable.

4.3. Endemic equilibrium and its stability

Jacobian matrix at endemic equilibrium $E_3(x^*, y^*, z^*)$ is

$$J(E_3) = \begin{bmatrix} r - \frac{r}{k}(2x+y) - \frac{\beta(y+a)y}{(y+x+a)^2} - d_1z & -\frac{rx}{k} & -d_1x \\ \frac{\beta(y+a)y}{(y+x+a)^2} & \frac{\beta x(x+a)}{(y+x+a)^2} - \mu - d_2z & -d_2y \\ 0 & 0 & -\psi \end{bmatrix}$$

Characteristic equation is

$$(-\psi - \lambda) \left(\left(r - \frac{r}{k}(2x+y) - \frac{(y+a)y\beta}{(y+x+a)^2} - d_1z - \lambda \right) \left(\frac{(x+a)\beta x}{(y+x+a)^2} - \mu - d_2z - \lambda \right) - \left(\frac{(y+a)y\beta}{(y+x+a)^2} - \frac{rx}{k} \right) \right) = 0$$

$$\lambda_1 = -\psi, \left(r - \frac{r}{k}(2x+y) - l_1 - d_1z - \lambda \right) (l_2 - \mu - d_2z - \lambda) + \frac{rx}{k} l_1 = 0$$

$$\text{where } l_1 = \frac{(y+a)y\beta}{(y+x+a)^2}, l_2 = \frac{(x+a)\beta x}{(y+x+a)^2}$$

$$\lambda^2 + \lambda \left((2x+y) \frac{r}{k} - r + l_1 + d_1z - l_2 + \mu + d_2z \right) + (\mu + d_2z) \left(\frac{r}{k}(2x+y) + l_1 + d_1z \right) +$$

$$l_2r + \frac{rx}{k} l_1 - l_2 \left(\frac{r}{k}(2x+y) + l_1 + d_1z \right) - r(\mu + d_2z) = 0$$

$$\lambda^2 + m_1\lambda + m_2 = 0 \text{ where } m_1 = \frac{r}{k}(2x+y) - r + l_1 + d_1z - l_2 + \mu + d_2z,$$

$$m_2 = \left((\mu + d_2z - l_2) \left(\frac{r}{k}(2x+y) + l_1 + d_1z \right) \right) + l_2r + \frac{rx}{k} l_1 - r(\mu + d_2z)$$

By Routh-Hurwitz criterion E_3 is locally asymptotically stable (LSA) if $m_1 > 0$ and $m_2 > 0$

4.4. Global Stability analysis

Consider a lyapunov function

$$V = (x - x^*) - x^* \ln\left(\frac{x}{x^*}\right) + (y - y^*) - y^* \ln\left(\frac{y}{y^*}\right) + (z - z^*) \ln\left(\frac{z}{z^*}\right)$$

$$\frac{dV}{dt} = \left(r - r \frac{(y+x)}{k} - \frac{\beta y}{y+x+a} - d_1 z\right)(x - x^*) + \left(\frac{\beta x}{y+x+a} - \mu - d_2 z\right)(y - y^*) - (z - z^*)^2 \psi$$

$$\frac{dV}{dt} = (x - x^*) \left[\frac{r}{k} \left(-(x+y) + (y^* + x^*) \right) - \left(\frac{y^*}{y^* + x^* + a} - \frac{y}{y+x+a} \right) \beta + d_1 (z^* - z) \right] + (y - y^*) \left[\left(\frac{x}{y+x+a} - \frac{x^*}{y^* + x^* + a} \right) \beta + d_2 (z^* - z) \right] - (z - z^*)^2 \psi$$

$$\frac{dV}{dt} = -\frac{r}{k}(x - x^*)^2 - \frac{r}{2k}((y - y^*)^2 + (x - x^*)^2) - \frac{d_1}{2}((z - z^*)^2 + (x - x^*)^2) - \frac{d_2}{2}((z - z^*)^2 + (y - y^*)^2) + \beta \left(\frac{y^*}{y^* + x^* + a} - \frac{y}{y+x+a} \right) (x - x^*) + \left[\beta \left(\frac{x}{y+x+a} - \frac{x^*}{y^* + x^* + a} \right) \right] (y - y^*) - \psi (z - z^*)^2$$

$$\begin{aligned} \frac{dW}{dt} = & -\frac{r}{k}(x - x^*)^2 - \frac{r}{2k}((y - y^*)^2 + (x - x^*)^2) - \frac{d_1}{2}((x - x^*)^2 + (z - z^*)^2) - \frac{d_2}{2}((z - z^*)^2 + (y - y^*)^2) \cdot \\ & \frac{\beta(x - x^*)^2 y^*}{(y^* + x^* + a)(y+x+a)} - \frac{\beta(y - y^*)^2 x^*}{(y^* + x^* + a)(y+x+a)} - \frac{\beta(x - x^*)(y - y^*)x^*}{(y^* + x^* + a)(y+x+a)} + \\ & \frac{\beta(x - x^*)(y - y^*)y^*}{(y^* + x^* + a)(y+x+a)} - \psi(z - z^*)^2 \end{aligned}$$

$$\frac{dV}{dt} = -\left[\frac{3r}{k} + \frac{d_1}{2} - \frac{\beta y^*}{(y^* + x^* + a)(y+x+a)} \right] (x - x^*)^2 - \left[\frac{r}{2k} + \frac{d_2}{2} + \frac{\beta x^*}{(y^* + x^* + a)(y+x+a)} \right] (y - y^*)^2 + \frac{\beta(y^* - x^*)}{(y^* + x^* + a)(y+x+a)} (x - x^*)(y - y^*) - (z - z^*)^2 \left(\psi + \frac{d_1}{2} + \frac{d_2}{2} \right)$$

we notice that $\frac{dV}{dt}$ is negative and definite if the following condition holds

$$\left(\frac{\beta(y^* - x^*)}{(y+x+a)(y^*+x^*+a)} \right)^2 < 4 \left[\left[\frac{3r}{k} + \frac{d_1}{2} - \frac{\beta y^*}{(y^*+x^*+a)(y+x+a)} \right] \left[\frac{r}{2k} + \frac{d_2}{2} + \frac{\beta x^*}{(y^*+x^*+a)(y+x+a)} \right] \right]$$

Therefore endemic equilibrium is globally asymptotically stable.

5. NUMERICAL SIMULATIONS

For the set of values

$r=20, k=80, \beta=20, d_1=0.001, \mu=0.01, d_2=0.01, V=5, \gamma=3.12, a=0.005$ equilibrium point $E_3(x^*, y^*, z^*)$ is (0.0021, 1.5377, 1.6033)

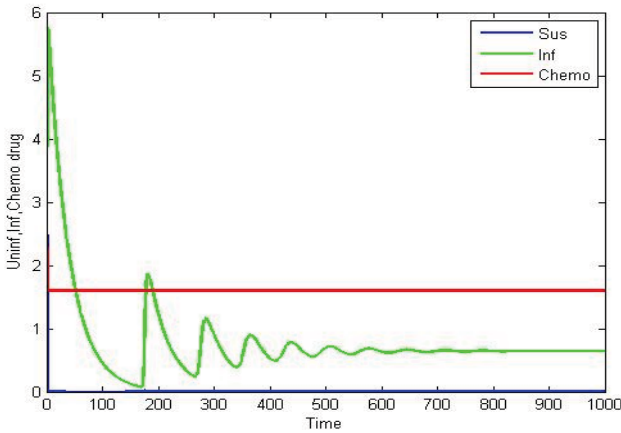


Figure1. Stability Analysis of the system at $E_3(x^*, y^*, z^*)$

For the set of values

$r=1.5, k=10, \beta=0.8, d_1=0.001, \mu=0.001, d_2=0.001, V=1.2, \gamma=0.9, a=0.001$ equilibrium point $E_3(x^*, y^*, z^*)$ is (0.0132, 4.5326, 1.3334)

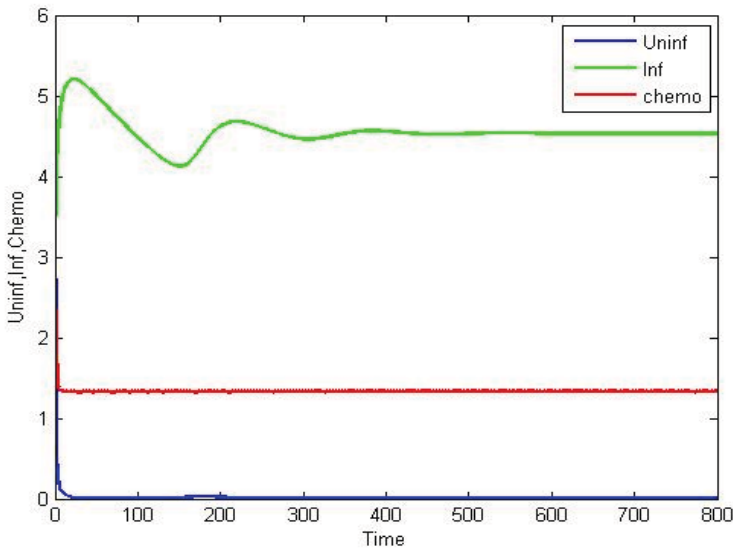


Figure2. Stability Analysis of the system at $E_3(x^*, y^*, z^*)$

From the numerical simulations we observed that endemic equilibrium point is locally asymptotically stable for different set of values. If virus infection of tumor is increasing then tumor load is reduced and by using combination of Chemo drug tumor cells may completely be eliminated.

6. CONCLUSION

In the present work we proposed a nonlinear ordinary differential equation model for the treatment of tumor by using the virotherapy and chemotherapy. Equilibrium points are analytically found and existence of the equilibrium points is discussed. Cancer free equilibrium point E_0 and the equilibrium point of virus

free E_1 is locally asymptotically stable if $r < \frac{2r\bar{x}}{k} + d_1\bar{z}$ and $\frac{\beta\bar{x}(\bar{x}+a)}{(\bar{x}+a)^2} > \mu + d_2\bar{z}$, endemic equilibrium

point E_2 is locally asymptotically stable by the Routh-Hurwitz criteria. Global stability of endemic equilibrium is found by using suitable lyapunov function. Numerical simulations support the analytical results.

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