GLOBAL STABILITY OF A TUMOR-IMMUNE INTERACTION MODEL

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Abstract: Global stability analysis of Kuznetsov-Taylor model [9], representing the tumor immune interaction has been investigated in this paper. The model, representing by a decoupled continuous time dynamical system is non-dimensionalized. Positivity and boundedness property for the existence and uniqueness of the mathematical model have been investigated with the help of fundamental theorems and propositions. The global stability of the model by means of Lyapunov function has been proved.

Keywords: Boundedness, Global Stability, Lyapunov Function.

Introduction: Cancer is one of the highly fatal disease throughout the world. Every year 29% of male death and 25% of female death occur due to cancer [7]. A lot of experiments and research has been done over the last few decades but, its growth, progression and control is still an enigma. Various types of mathematical models have been proposed [1,2,3,4,6,8,9] and each of them has a different way to understand the dynamics of the growth and control of tumor cells. The issue of eradicating tumor from a patient is an important one which is mathematically addressed by performing stability analysis (namely, global stability) about equilibrium solutions. Our aim is to construct a suitable Lyapunov function to prove the global stability of tumor immune interaction model. The organization of the paper is as follows: In section 2, we describe the Kuznetsov-Taylor model in non-dimensional form. Section 3 gives the qualitative analysis of the model, including positivity, boundedness, equilibrium solution and linear stability analysis. Global stability of the interior equilibrium point by constructing suitable Lyapunov function is proved in section 4. The paper ends with a brief conclusion.

Mathematical Model: Kuznetsov et al. [9] considered the interaction between which tumor cells (TCs) and the effector cells (ECs), which consists of B cells, T cells, Macrophages, NK cells etc. The interaction between TCs and ECs is given by (in non-dimensional form)

$$\frac{dx}{dt} = \sigma + \frac{\rho x y}{\eta + y} - \mu x y - \delta x,$$

$$\frac{dy}{dt} = \alpha y(1-\beta y) - x y \qquad (2.1)$$

with initial conditions are given by $x(0) = x_0 > 0$ and $y(0) = y_0 > 0$.

Qualitative Analysis Of The Model

Positivity and Boundedness:

The right hand side of (2.1) is a continuous function of dependent variables. Integrating we get,

$$x(t) = x(0)\exp\left(\int_0^t \left[\frac{\sigma}{x(s)} + \frac{\rho y(s)}{\eta + y(s)} - \mu y(s) - \delta\right] ds\right)$$

Similarly,

$$y(t) = y(0)\exp\left(\int_0^t [\alpha\,(1-\beta\, y(s)) - x(s)]\, ds\right)$$

From the above expression it is obvious that $x(t), y(t)$ remain positive for all future time if they start from an interior point of $\Re_+^2 = \{(x, y) |\, x > 0,\, y > 0\}$. Therefore, $\Re_+^2$ is positively invariant for the above system (2.1) under some consideration. Using the non-negativity of the variables we obtain from (2.1),

$$\frac{dx}{dt} \le \sigma + \frac{\rho x y}{\eta + y} - \delta x; \quad \frac{dy}{dt} \le \alpha y(1-\beta y)$$

Now from the second equation, we get $y(t) \le \dfrac{C}{\beta\left(e^{-\alpha t} + C\right)}$, which implies $\limsup_{t\to\infty} y(t) \le \dfrac{1}{\beta}$ for all $t \ge 0$.

Now, from the first equation, $\dfrac{dx}{dt} \le \sigma + \dfrac{\rho x y}{\eta + y} - \delta x$, which implies

$$\frac{dx}{dt} \le \sigma + (A - \delta)x$$

where $A = \dfrac{\rho}{1 + \eta\beta}$.

Integration we get,

$$x(t) \le e^{(A-\delta)t}\left(x_0 + \frac{A\sigma}{A-\delta}\right) - \frac{\sigma}{A-\delta}$$

which implies $\limsup_{t\to\infty} x(t) \le \dfrac{\sigma}{\delta - A}$, provided $A < \delta$.

Equilibria and Linear Stability Analysis:
Biologically meaningful existing equilibrium points are obtained by the intersections of

$$\sigma + \frac{\rho x y}{\eta + y} - \mu x y - \delta x = 0$$ and

$\alpha y(1-\beta y) - x y = 0$ in the region $\Re_+^2 = \{(x,y) \in \Re^2 \mid x>0, y>0\}$. The system possesses two equilibrium points, namely, $E_1(\frac{\sigma}{\delta},0)$ and $E^*(x^*, y^*)$.

To investigate the stability of (2.1) about the equilibrium points, we compute the following Jacobian matrix:

$$J = \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix}$$

Where,

$$a_{11} = \frac{\rho y}{\eta + y} - \mu y - \delta; \quad a_{12} = \frac{\eta \rho x}{(\eta + y)^2} - \mu x;$$

$$a_{21} = -y; \qquad a_{22} = -\alpha \beta y$$

At, $E_1(\frac{\sigma}{\delta},0)$, the Eigen values of the Jacobian matrix J_{E_1} are given by, $\lambda_1 = -\delta$ and $\lambda_2 = \alpha - \frac{\sigma}{\delta}$. The tumor free equilibrium E_1 is stable if $\alpha < \frac{\sigma}{\delta}$, otherwise unstable.

For the co-existing equilibrium E^* and the corresponding characteristic equation is given by,

$$\lambda^2 - (a_{11} + a_{22})\lambda + a_{11} a_{22} - a_{12} a_{21} = 0$$

Then the interior equilibrium $E^*(x^*, y^*)$ is Locally Asymptotically Stable (LAS) (using Routh-Hurwitz criteria), if $a_{11} + a_{22} < 0$ and $a_{11} a_{22} - a_{12} a_{21} > 0$.

Global Stability Analysis:

To prove the global stability we define the Lyapunov function [5],

$$V(x,y) = (\eta + y^*)\left[\frac{(x-x^*)^2}{2}\right] + (y - y^* - y^* \ln(\frac{y}{y^*})) \tag{4.1}$$

The function V(x, y) is defined and continuous in $\text{Int}(\Re_+^2)$. From the construction of Lyapunov function it is clear that the defined function V(x, y) is zero at the interior equilibrium point (x^*, y^*) and is positive for all $x>0,\ y>0$ i.e. in the first quadrant. Therefore, $E^*(x^*, y^*)$ is the global minimum of V(x, y). The time derivative of V(x, y) along with the solution of the system of equation (4.1) is

$$\frac{dV}{dt} = (\eta + y^*)(x - x^*)\dot{x} + (\frac{y - y^*}{y})\dot{y}$$

$$= (\eta + y^*)(x - x^*)\left[\sigma + \frac{\rho x y}{\eta + y} - \mu x y - \delta x\right] + (y - y^*)\left[\alpha - \alpha \beta y - x\right]$$

$$= (\eta + y^*)(x - x^*)\left[-\delta(x - x^*) + \mu x^* y^* - \mu x y + \frac{\rho x y}{\eta + y} - \frac{\rho x^* y^*}{\eta + y^*}\right] + (y - y^*)\left[-(x - x^*) - \alpha\beta(y - y^*)\right]$$

$$= (\eta + y^*)(x - x^*)\left[-\delta(x - x^*) + \mu x^* y^* - \mu xy + \frac{\rho xy(\eta + y^*) - \rho x^* y^*(\eta + y)}{(\eta + y)(\eta + y^*)}\right] + (y - y^*)\left[-(x - x^*) - \alpha\beta(y - y^*)\right]$$

$$= (\eta + y^*)(x - x^*)\left[-\delta(x - x^*) - \mu x^*(y - y^*) - \mu y(x - x^*) + \frac{\eta\rho x^*(y - y^*) + \rho y^*(\eta + y)(x - x^*)}{(\eta + y)(\eta + y^*)}\right] + (y - y^*)\left[-(x - x^*) - \alpha\beta(y - y^*)\right]$$

$$= \left[-(\delta + \mu y)(\eta + y^*) + \rho y^*\right](x - x^*)^2 + \left[-1 - \mu x^*(\eta + y^*) + \frac{\eta \rho x}{\eta + y}\right](x - x^*)(y - y^*) - \alpha\beta(y - y^*)^2$$

The above expression can be represented in the matrix form as,

$$\frac{dV}{dt} = -\left(x - x^*, \quad y - y^*\right) C_{2\times 2} \begin{pmatrix} x - x^* \\ y - y^* \end{pmatrix} \tag{4.2}$$

Where $C_{2\times2} = \begin{bmatrix} -A(x,y) & -B(x,y) \\ -B(x,y) & \alpha\beta \end{bmatrix}$,

$$A(x,y) = -(\delta + \mu y)(\eta + y^*) + \rho y^*,$$

$$B(x,y) = \frac{1}{2}\left[-1 - \mu x^*(\eta + y^*) + \frac{\eta \rho x}{\eta + y}\right].$$

It is clear from the above equation (4.2) that $\frac{dV}{dt} < 0$, if the matrix $C_{2\times2}$ is positive definite. By Sylvester's criteria, the symmetric matrix is positive definite if and only if all the upper-left sub-matrices of $C_{2\times2}$ are positive, implying,

(i) $A(x,y) = -(\delta + \mu y)(\eta + y^*) + \rho y^* < 0$ and

(ii) $\Phi(x,y) = -\alpha\beta A(x,y) - B^2(x,y) > 0$

Now,

$$A(x,y) < 0 \Rightarrow -(\delta + \mu y)(\eta + y^*) + \rho y^* < 0$$

since, from the positively invariant set, all solutions satisfy $0 \le x \le \frac{\sigma}{\delta - A}$ and $0 \le y \le \frac{1}{\beta}$;

$$A(x,y) = -(\delta + \frac{\mu}{\beta})(\eta + \frac{1}{\beta}) + \frac{\rho}{\beta} < 0 \quad \Rightarrow$$

$$\rho < \frac{1}{\beta}(1 + \eta\beta)(\mu + \delta\beta)$$ as

$$0 < y^* \le \frac{1}{\beta} \quad \forall \ (x,y) \in \Re^2.$$

Again, $\Phi(x,y) = -\alpha\beta A(x,y) - B^2(x,y)$

$$= -\alpha\beta\left[-(\delta + \mu y)(\eta + y^*) + \rho y^*\right] - \frac{1}{4}\left[-1 - \mu x^*(\eta + y^*) + \frac{\eta\rho x}{\eta + y}\right]^2$$

Therefore,

$$\frac{\partial \Phi(x,y)}{\partial x} = \frac{1}{2}\left[1 + \mu x^*(\eta + y^*) - \frac{\eta\rho x}{\eta + y}\right]\left(\frac{\eta\rho}{\eta + y}\right)$$

for fixed y, implying

$$\frac{\partial^2 \Phi(x,y)}{\partial^2 x} = -\frac{1}{2}\left[\frac{\eta\rho}{\eta + y}\right]\left(\frac{\eta\rho}{\eta + y}\right) = -\frac{1}{2}\left(\frac{\eta\rho}{\eta + y}\right)^2 < 0$$

Hence, $\frac{\partial \Phi(x,y)}{\partial x}$ is strictly decreasing in $\Re^2_+$, with respect to x.

Now,

$$\frac{\partial \Phi(x,y)}{\partial x}\Big|_{x=0} = -\frac{1}{2}\left[-1 - \mu x^*(\eta + y^*)\right] = \frac{1}{2}\left[1 + \mu x^*(\eta + y^*)\right] > 0$$ in $\Re^2_+$

and so $\Phi(x,y)$ is increasing in $\Re^2_+$. This yields $\Phi(x,y) > \frac{\partial \Phi(x,y)}{\partial x}\Big|_{x=0}$ for $(x,y) \in \Re^2_+$; implying

$$\alpha\beta(\delta + \mu y)(\eta + y^*) > \alpha\beta\rho y^* + \frac{1}{4}\left[1 + \mu x^*(\eta + y^*)\right]^2$$

The result can be summarizing in the form of the following theorem.

Theorem: The interior equilibrium point $E^*(x^*, y^*)$ is globally asymptotically stable if

(i) $\rho < \frac{1}{\beta}(1 + \eta\beta)(\mu + \delta\beta)$ (ii) $(\delta + \mu y)(\eta + y^*) > \rho y^* + \frac{1}{4\alpha\beta}\left[1 + \mu x^*(\eta + y^*)\right]^2$

Conclusions

In this paper, we analyze Kuznetsov-Taylor model [9] for global stability by constructing suitable Lyapunov function. We obtain some conditions on the parameters, which need to be satisfied to obtain the global stability of the model. Numerically, we have shown that the system is globally asymptotically stable (see figure1). The global stability gives the condition under which the tumor cannot be eradicated. Hence, violating the condition implies the condition that the tumor cells may be eradicated, which is important from biological point of view.

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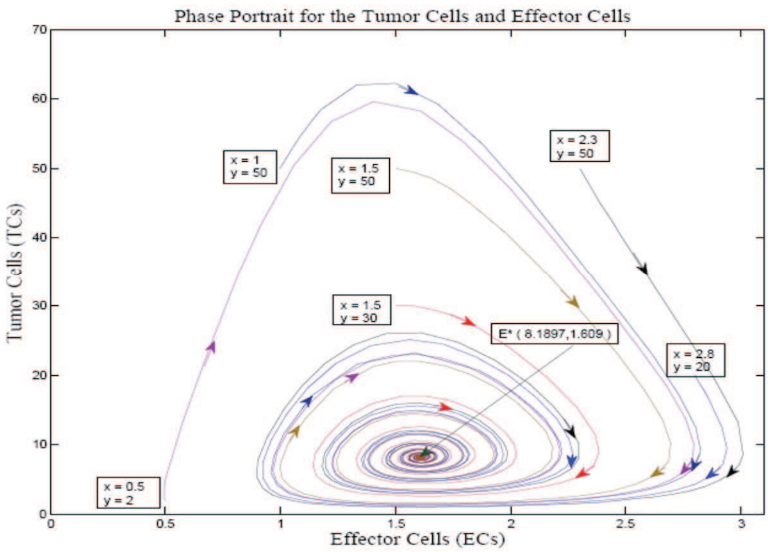

Figure 1: The phase portrait trajectories with reference to different initial values. The graph indicates that the interior equilibrium point $E^*(8.1897, 1.6092)$ is globally asymptotically stable. The parameter values are σ = 0.1181, ρ = 1.131, η = 20.19, μ = 0.00311, δ = 0.3743, α = 1.636, β = 0.002, obtained from [9].

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