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Application of Dynamical Systems in Cancer Therapy

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Abstract In this paper, we have proposed and analyzed a mathematical model for the study of interaction between tumor cells and oncolytic viruses. The model is analyzed using stability theory of differential equations.

Keywords Tumor · Stability · Virus therapy

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1 Introduction

Cancer is one of the dangerous illnesses which is responsible for the death of many people each year. Up to now, many efforts have been done for the treatment of cancer. It is important that tumor be treated or controlled without surgery. At the middle of the 20th century efforts to treat cancer with virus was discussed [6,3]. Poliovirus and Coxsackie virus were used for this method (see [6] and [3]).

The relation between the effect of virus and tumor growth is very complex. To better understand the relationship between the two, many mathematicians performed the modeling of their interactions with ordinary differential equations. This leads to better understanding and analysis of the treatment

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method. Several mathematical models that described these methods were recently developed [4]. Our analyzed model is based on the model of Novozhilov in [1] and simplify by help of model of Wodars in [7].

This paper is organized as follows: In Section 2, the model is outlined, In section 3, boundedness of solutions of the system is studied. section 4, deals with local stability analysis of equilibrium points and finally in section 5 we have determined conditions for global stability of internal equilibrium point.

2 Mathematical model

The model contains two types of tumor cells x and y that respectively is the size of uninfected tumor cells and infected tumor cells by the virus. In this model r is growth rate of tumor. The maximum size or space the tumor is allowed to occupy is given by its carrying capacity k. β is spread rate of virus in tumor cells. a is death rate of infected tumor cells by virus and s is growth rate.
With this assumption model is:

$$\begin{aligned} \dot{x} &= rx(1-\frac{x+y}{k}) - \beta xy \\ \dot{y} &= \beta xy + sy(1-\frac{x+y}{k}) - ay \end{aligned} \tag{1}$$

System (1) have 4 equilibrium points

$$\begin{aligned} E_0 &= (0,0), \\ E_1 &= (k,0), \\ E_2 &= (0,\frac{k(s-a)}{s}), \\ E_3 &= (\frac{\beta k(a-s)+ar}{\beta(\beta k+r-s)}, \frac{\beta kr-ar}{\beta(\beta k+r-s)}). \end{aligned}$$

Existence of E_0 and E_1 is trivial.
E_2 is biologically admissible if and only if $s > a$ and for existence of E_3 must numerator and denominator of fractions have equal signs.

3 Boundedness of solutions

Boundedness may be interpreted as a natural restriction to grow because of limited resources. To establish the biological validity of the model system, we have to show that the solutions of system (1) are bounded for this we find the region of attraction in the following lemma.

Lemma 1 *All the solutions of 1 starting in the positive orthant* $(R_0^+)^2$ *either approaches, enter or remain in the subset of* $(R_0^+)^2$ *defined by*

$$\Omega = \{(x,y) \in (R_0^+)^2 : 0 < x+y \leq k\}$$

where $(R_0^+)^2$ *denote the non-negative cone of* R^2 *including its lower dimensional faces.*

Proof From system 1 we get:

$$\dot{x} + \dot{y} = (rx + sy)(1 - \frac{x+y}{k}) - ay$$
$$\dot{x} + \dot{y} \leq \delta(x+y)(1 - \frac{x+y}{k})$$

where $\delta = max(r, s)$.
Then by usual comparison theorem, we get the following expression as $t \to \infty$,

$$\limsup_{t\to\infty} x(t) + y(t) \leq k$$

Thus, it suffices to consider solutions in the region Ω. Solutions of the initial value problem starting in Ω and defined by (1) exist and are unique on a maximal interval [2]. Since solutions remain bounded in the positively invariant region Ω , the maximal interval is well posed both mathematically and epidemiologically.

4 Local stability analysis of equilibrium points

To discuss the local stability of equilibrium points we compute the variational matrix of system 1. The signs of the real parts of the eigenvalues of the variational matrix evaluated at a given equilibrium points determine its stability[5]. The matrix is given by

$$V(E) = \begin{bmatrix} r(1 - \frac{x+y}{k}) - \frac{r}{k}x - \beta y & -\beta x - \frac{r}{k}x \\ \beta y - \frac{s}{k}y & s(1 - \frac{x+y}{k}) - \frac{s}{k}y + \beta x - a \end{bmatrix}$$

We denote the variational matrix corresponding to E_i by $V(E_i), \quad i = 0, 1, 2, 3$

4.1 Local stability analysis of E_0

The variational matrix of equilibrium point E_0 is given by

$$V(E_0) = \begin{bmatrix} r & 0 \\ 0 & s - a \end{bmatrix} \tag{2}$$

Eigenvalues of $V(E_0)$ are given by $\lambda_1 = r, \ \ \lambda_2 = s - a$.
E_0 is an unstable equilibrium point if and only if E_2 exists and is a saddle point if and only if E_2 does not exist.
Biological interpretation In this case this equilibrium point is unstable or saddle point then tumor don't destroyed.

4.2 Local stability analysis of E_1

The variational matrix $V(E_1)$ corresponding to E_1 as follows:

$$V(E_1) = \begin{bmatrix} -r & -(\beta k + r) \\ 0 & -a + \beta k \end{bmatrix} \tag{3}$$

From (3) we observe that eigenvalues of the matrix $V(E_1)$ are given by $\lambda_1 = -r$ and $\lambda_2 = -a + \beta k$.
Thus $V(E_1)$ has negative eigenvalues and $V(E_1)$ is stable equilibrium point if $a > \beta k$, consequently E_1 is a saddle point if $a < \beta k$.
Biological interpretation If this equilibrium point is stable it means that therapy is unsuccessful and finally all of cells are uninfected.

4.3 Local stability analysis of E_2

The variational matrix of equilibrium point E_2 is given by

$$V(E_2) = \begin{bmatrix} -\beta k + \frac{a(\beta k + r)}{s} & 0 \\ \frac{(a-s)(-\beta k + s)}{s} & a - s \end{bmatrix} \tag{4}$$

We observe that eigenvalues of the matrix $V(E_2)$ are given by $\lambda_1 = a - s$ and $\lambda_2 = -\beta k + (a(\beta k + r))/s$.
Thus $V(E_2)$ has negative eigenvalues and E_2 is stable equilibrium point if $a < (s\beta k)/(\beta k + r)$ consequently E_2 is a saddle point if $a > (s\beta k)/(\beta k + r)$.
Biological interpretation If this equilibrium point is stable it means that therapy is unsuccessful and finally all of cells are infected but they exist and don't die.

4.4 Local stability analysis of E_3

Variational matrix of E_3 is given by

$$V(E_3) = \begin{bmatrix} \frac{r(-a(\beta k + r) + \beta k s)}{\beta k(\beta k + r - s)} & \frac{(\beta k + r)(-a(\beta k + r) + \beta k s)}{\beta k(\beta k + r - s)} \\ \frac{(\beta k - s)(-ar + \beta k r)}{\beta k(\beta k + r - s)} & \frac{s(-\beta k r + ar)}{\beta k(\beta k + r - s)} \end{bmatrix} \tag{5}$$

From variational matrix $V(E_3)$, we find that eigenvalues are $\lambda_\pm$ where

$$\lambda_\pm = \frac{-ar}{2\beta k} \pm \sqrt{(\frac{-ar}{2\beta k})^2 + \frac{r(-\beta k + a)(\beta k(a - s) + ar)}{\beta k(\beta k + r - s)}} \tag{6}$$

If $\frac{(-\beta k + a)(\beta k(a-s) + ar)}{(\beta k + r - s)} > 0$ then E_3 is a saddle point and if $\frac{(-\beta k + a)(\beta k(a-s) + ar)}{(\beta k + r - s)} < 0$ then E_3 is a stable point.
Biological interpretation In this cases two infected and uninfected cells exist but if this equilibrium point is stable it means that size of tumor is constant and will not grow.

5 global stability of E_3

An equilibrium point is globally stable if system always approaches it regardless of its initial position. We construct Lyapunov functions that enable us to find biologically realistic conditions sufficient to ensure of a globally stable equilibrium state.
Global stability of the internal equilibrium point of system (1) is determined in the below theorem:

Theorem 1 *If $s > a + r$ and $a < \frac{\beta(rx+sy)}{r}$ then E_3 is globally stable.*

Proof We consider the following positive definite function about $E_3 = (x^*, y^*)$ (2)

$$V = x - x^* - x^* \ln \frac{x}{x^*} + y - y^* - y^* \ln \frac{y}{y^*}$$

Computing the derivative of V with respect to t, we get

$$\frac{dV}{dt} = -\Big(\frac{(s-a-r)(-ar+\beta(rx+sy))}{\beta(\beta k+r-s)} + \frac{(x+y)(-ar+\beta(rx+sy))}{\beta k}\Big)$$

We attend that if $s > a + r$ and $a < \frac{\beta(rx+sy)}{r}$ then $\frac{dV}{dt}$ is negative definite hence E_3 is globally stable.

Corollary 1 *If we provide conditions for parameters in theorem 1 it means that with this therapy we could control size of tumor, that is $x + y$, which not greater but tumor exists and not completely waste.*

6 Conclusion

In this paper we analyse globally stable for E_3 and the rest equilibrium points are unbounded because in terms of biology these are important. E_0 make sense that therapy is effective E_1 means that infection did not spread and virus therapy failed and finally tumor cells remain without infection. E_2 implies that all tumor cells were infected but virus coudn't destroyed cells and finally tumor cells remain with infection.

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