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Hopf bifurcation analysis in a delayed system for cancer virotherapy

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Abstract

We consider a planar delay differential equation which is motivated biologically and simulates a cancer virotherapy. The singularities and their local stability are studied using the characteristic equation. Because of biological importance, we investigate a Hopf bifurcation around the interior singularity and determine the stability of corresponding Hopf cycles by computing the normal form of the model in the direction of the Hopf bifurcation.

Keywords: Delay differential equation; Hopf bifurcation; Stability

1. Introduction

Cancer is usually known as an unnatural growth in cell numbers which is called a tumor and sometimes causes death [2,24]. Thus, finding and developing methods that help us to control tumor growth have received a high importance in the medical sciences. Up to now many efforts have been carried out to promote therapeutic methods for cancer. For instance, surgery is the oldest one which involves collateral effects. Therefore, treating or controlling cancerous without surgery is potentially more beneficial.

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The idea of annihilating tumor by a virus infection was realized in the early twentieth century; although, experimental efforts did not begin until 1949 [14,17,11]. The first experiments were done using a virus found in nature, but it was not successful because the immune system response damaged the infection and prevented the virus from destroying cancer [14,9,18]. The next steps were carried out by genetic researchers. They produced a new generation of viruses which were capable of cancer therapy. Nowadays these viruses are known as *oncolytic viruses* [18,11,9]. These viruses infect tumor cells and kill them directly or annihilate them by increasing the immune system response.

Experimental observations show that the interaction between an oncolytic virus and tumor might be so complex that it is almost impossible to figure out a complete theory for finding all connections and analyzing them by biological observations alone. Researchers are now convinced that mathematical theories should be used to gain insight into the dynamics and effects of the virotherapy in cancer progression. Many useful mathematical models have been developed based on a system of differential equations (see [22,24,15] and references within). One of them has been introduced by D. Wodarz in 2001 [22,23] as below:

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

Here, $x(t)$ and $y(t)$ stand for the number of uninfected and infected cells respectively. The tumor grows in a logistic model at a rate r, and the growth rate of infected cells is shown by s. The maximum possible size which tumor can occupy (including both uninfected and infected cells), is limited by carrying capacity k. Uninfected cells are destroyed by the immune system at a rate d; moreover, viral infection spreads in tumor cells with a transmission rate β (this parameter can be viewed as summarizing of replication rate of the virus). Finally, infected cells die because of the viral infection at a rate a.

In this paper, based on experimental observations, we consider a delay for death of infected cells. Indeed, in 1997 Friberg and Mattson [2] studied tumor volume doubling time (TVDT) for human malignant tumors. They found that tumor volume may grow up to ten times within five months. This means that TVDT is about fifteen days. Thus, the tumor growth rate may exceed to 13.5%–60.3% for 2–9 days. Later, in 2000, Oyama et al. [16] studied on oncolytic virotherapy for human prostate cancer by conditionally replicating herpes simplex virus 1 vector G207. For the first 2 days after the injection of G207 no significant changes were observed in the diameter of tumor. In 2007, Määttä et al. [13] evaluated cancer virotherapy with attenuated replicative Semliki Forest virus (SFV) in different rodent tumor models. In their research, 9 days after of injecting SFV into the tumor, a few changes were observed. After that, same results confirmed the existence of a delay in virotherapy stages (see for example [8,3,25]). Therefore, we see that in cancer treatment, even one day delay is important depending on cancer type and oncolytic virus.

This reality about the time delay in death of infected cells is very pure and simple fact which should not be ignored. Thus, we propose the following model for tumor growth:

$$\begin{aligned} \dot{x} &= rx\left(1-\frac{x+y}{k}\right)-dx-\beta xy, \\ \dot{y} &= \beta xy+sy\left(1-\frac{x+y}{k}\right)-ay(t-\tau). \end{aligned} \tag{2}$$