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Control exponential growth of tumor cells with slow spread of oncolytic virus ☆

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HIGHLIGHTS

- Investigate bifurcations of equilibria in the oncolytic virus dynamics model with exponential growth of tumor cells and slow virus-spread.
- Find conditions of parameters for saddle-node bifurcation, Hopf bifurcation and Bogdanov–Takens bifurcation.
- Give thresholds for slow virus-spread to control the population of tumor cells within an appropriate range.

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ABSTRACT

Great attention has been paid to cancer therapy by means of oncolytic viruses, but the fast virus-spread, which eliminates all tumor cells, cannot be applied to solid tumors. As slow virus-spread is applied, solid tumors are expected to be controlled but complicated dynamical behaviors appear. In this paper we investigate bifurcations of equilibria in the oncolytic virus dynamics model with exponential growth of tumor cells and slow virus-spread. We find conditions of parameters for saddle-node bifurcation, Hopf bifurcation and Bogdanov–Takens bifurcation. Those conditions give thresholds for slow virus-spread to control the population of tumor cells within an appropriate range.

1. Introduction

Cancer therapy by means of oncolytic viruses such as adenoviruses, vesicular stomatitis virus and Newcastle disease virus has attracted the attention of clinicians for a long time (see e.g. Aghi and Martuza, 2005; Bell, 2007; Davis and Fang, 2005; Lorence et al., 2003; McCormick, 2005). The idea behind this treatment is to infect a tumor with an engineered virus which specifically infects and kill tumor cells with potential to spread throughout the tumor. The aim is that the virus drives the tumor to extinct and then goes to extinct itself. In recent decade, the dynamics of oncolytic viruses was modeled by systems of differential equations (see e.g. Bajzer et al., 2008; Karev et al., 2006; Komarova and Wodarz, 2010; Pilisa, 2009; Wodarz, 2001), one of which is the following

$$\begin{cases} \dot{x} = xF(x,y) - byG(x,y), \\ \dot{y} = byG(x,y) - ay \end{cases} \tag{1.1}$$

in $\overline{\mathbb{R}^2_+}$, the closure of the first quadrant $\mathbb{R}^2_+ := \{(x,y) \in \mathbb{R}^2 : x > 0, y > 0\}$. This system was adopted from the general predator–prey type system by Komarova and Wodarz (2010) to describe the growth of tumor cells and infected tumor cells. In system (1.1), x and y represent the population of uninfected tumor cells and the population of infected tumor cells respectively, a is the death rate of infected tumor cells, and b the viral replication rate. Moreover, F reflects cancer growth and death processes, which was modeled in (Adam and Bellomo, 1997) in the forms $F_e(x,y) := 1$ for exponential growth, $F_\ell(x,y) := \eta/(\eta+x+y)$ for linear growth, $F_{lg}(x,y) := 1-(x+y)/W$ for logistic growth, and $F_{gm}(x,y) := \{\log\{(W+\eta)/\eta\}\}^{-1}\log\{(W+\eta)/(x+y+\eta)\}$ for gompertzian growth. The most important thing is G, the rate of infection of tumor cells by the virus, which can be chosen in either fast spread mode or slow spread mode (Komarova and Wodarz, 2010). As indicated in

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Komarova and Wodarz (2010, p.533), the fast mode and slow mode are distinguished by $G(x,\tilde{y}(x))$,where $\tilde{y}(x)$ is the explicit expression of the curve $\Gamma : xF(x,y)=ay$ in $\mathbb{R}^2_+$ on which all equilibria lie. More concretely the fast spread mode and the slow spread mode are defined by the limits $\lim_{x\to\infty}G(x,\tilde{y}(x))>0$ and $\lim_{x\to\infty}G(x,\tilde{y}(x))=0$ respectively. For example, $G_0(x,y):=x(1+\varepsilon_1)(1+\varepsilon_2)/(x+\varepsilon_1)(y+\varepsilon_2)$ presents a slow spread but $G_1(x,y):=x/(x+y+\varepsilon)$ presents a fast spread (see Komarova and Wodarz, 2010).

It is of special interest to consider the slow virus-spread treatment because the fast virus-spread is mainly effective to non-solid tumors such as leukemia and lymphoma, which are resulted from cancers of the blood. Most tumors such as breast cancer, prostate cancer, lung cancer, liver cancer, pancreatic cancer, and melanoma are solid ones. In addition, one pays attention to the form of an exponential growth because it appears in the early stage of tumor growth. Usually, it is more efficient to apply a slow virus-spread treatment in the early stage. As slow virus-spread is applied, one wants a pursuit of a control on the population of tumor cells, that is to find a treatment scheme making the tumor cells stable in a range of numbers. This requires to analyze the complicated dynamics of tumor cells. In 2010, Komarova and Wodarz (2010) investigated system (1.1) with $F=F_e(x,y)$ and $G=G_0(x,y)$ as chosen as above, i.e., the system

$$\begin{cases} \dfrac{dx}{dt}=x-by\dfrac{x(1+\varepsilon_1)(1+\varepsilon_2)}{(x+\varepsilon_1)(y+\varepsilon_2)}, \\ \dfrac{dy}{dt}=by\dfrac{x(1+\varepsilon_1)(1+\varepsilon_2)}{(x+\varepsilon_1)(y+\varepsilon_2)}-ay, \end{cases} \tag{1.2}$$

where ε_1 and ε_2 are arbitrary positive constants such that the virus spread term G satisfies the necessary biological requirements listed in (Komarova and Wodarz, 2010, p. 532). With rescaling $x\mapsto\varepsilon_1 x$, $y\mapsto\varepsilon_2 y$ and $t\mapsto(1+x)(y+1)t$, system (1.2) is simplified as

$$\begin{cases} \dfrac{dx}{dt}=x(x+1)(y+1)-\beta xy:=P(x,y), \\ \dfrac{dy}{dt}=\beta\gamma xy-\alpha y(x+1)(y+1):=Q(x,y), \end{cases} \tag{1.3}$$

where

$$\alpha=a, \quad \beta=b(1+\varepsilon_1)(1+\varepsilon_2)/\varepsilon_1 \quad \text{and} \quad \gamma=\varepsilon_1/\varepsilon_2. \tag{1.4}$$

Here $x(t)$, $y(t)$ are considered in the closure $\overline{\mathbb{R}^2_+}$ and α, β, γ are all positive coefficients. It is shown in Komarova and Wodarz (2010) that system (1.2) has exact one equilibrium $O:(0,0)$ as $0<b<b_c:=(\sqrt{a\varepsilon_2}+\sqrt{\varepsilon_1})^2/\{(1+\varepsilon_1)(1+\varepsilon_2)\}$, two equilibria $O:(0,0)$ and $B_0:(\sqrt{a\varepsilon_2/\varepsilon_1}, \sqrt{\varepsilon_1/(a\varepsilon_2)})$ as $b=b_c$, and three equilibria $O:(0,0)$, $B_-:(x_-,y_-)$ and $B_+:(x_+,y_+)$ as $b>b_c$, where $y_\pm=\varepsilon_1 x_\pm/(a\varepsilon_2)$ and

$$x_\pm=\frac{\varepsilon_2}{2\varepsilon_1}\left(-\left(a+\frac{\varepsilon_1-b(1+\varepsilon_1)(1+\varepsilon_2)}{\varepsilon_2}\right)\pm\sqrt{\left(a+\frac{\varepsilon_1-b(1+\varepsilon_1)(1+\varepsilon_2)}{\varepsilon_2}\right)^2-\frac{4a\varepsilon_1}{\varepsilon_2}}\right). \tag{1.5}$$

Correspondingly, system (1.3) has exact one equilibrium $O:(0,0)$ as $0<\beta<\beta_c:=(\sqrt{\alpha}+\sqrt{\gamma})^2/\gamma$, two equilibria $O:(0,0)$ and $E_0:(\sqrt{\alpha/\gamma}, \sqrt{\gamma/\alpha})$

Table 1
Properties of equilibrium B_-.

Possibility of a, b, ε_1 and ε_2			B_-
$a<1$	$\varepsilon_1\le\varepsilon_2$	$b>\frac{(\sqrt{a\varepsilon_2}+\sqrt{\varepsilon_1})^2}{(1+\varepsilon_1)(1+\varepsilon_2)}$	Unstable node or unstable focus
	$\varepsilon_2<\varepsilon_1<\frac{\varepsilon_2}{a}$	$\frac{(\sqrt{a\varepsilon_2}+\sqrt{\varepsilon_1})^2}{(1+\varepsilon_1)(1+\varepsilon_2)}<b<\frac{(a\varepsilon_2-\varepsilon_1)^2}{(a-1)(1+\varepsilon_1)(1+\varepsilon_2)(\varepsilon_2-\varepsilon_1)}$	Unstable node or unstable focus
		$b=\frac{(a\varepsilon_2-\varepsilon_1)^2}{(a-1)(1+\varepsilon_1)(1+\varepsilon_2)(\varepsilon_2-\varepsilon_1)}$	Center type
		$b>\frac{(a\varepsilon_2-\varepsilon_1)^2}{(a-1)(1+\varepsilon_1)(1+\varepsilon_2)(\varepsilon_2-\varepsilon_1)}$	Stable node or stable focus
	$\varepsilon_1\ge\frac{\varepsilon_2}{a}$	$b>\frac{(\sqrt{a\varepsilon_2}+\sqrt{\varepsilon_1})^2}{(1+\varepsilon_1)(1+\varepsilon_2)}$	Stable node or stable focus
$a=1$	$\varepsilon_1<\varepsilon_2$	$b>\frac{(\sqrt{\varepsilon_1}+\sqrt{\varepsilon_2})^2}{(1+\varepsilon_1)(1+\varepsilon_2)}$	Unstable node or unstable focus
	$\varepsilon_1=\varepsilon_2$	$b>\frac{4\varepsilon_2}{(1+\varepsilon_2)^2}$	Center type
	$\varepsilon_1>\varepsilon_2$	$b>\frac{(\sqrt{\varepsilon_1}+\sqrt{\varepsilon_2})^2}{(1+\varepsilon_1)(1+\varepsilon_2)}$	Stable node or stable focus
$a>1$	$\varepsilon_1\le\frac{\varepsilon_2}{a}$	$b>\frac{(\sqrt{a\varepsilon_2}+\sqrt{\varepsilon_1})^2}{(1+\varepsilon_1)(1+\varepsilon_2)}$	Unstable node or unstable focus
	$\frac{\varepsilon_2}{a}<\varepsilon_1<\varepsilon_2$	$\frac{(\sqrt{a\varepsilon_2}+\sqrt{\varepsilon_1})^2}{(1+\varepsilon_1)(1+\varepsilon_2)}<b<\frac{(a\varepsilon_2-\varepsilon_1)^2}{(a-1)(1+\varepsilon_1)(1+\varepsilon_2)(\varepsilon_2-\varepsilon_1)}$	Stable node or stable focus
		$b=\frac{(a\varepsilon_2-\varepsilon_1)^2}{(a-1)(1+\varepsilon_1)(1+\varepsilon_2)(\varepsilon_2-\varepsilon_1)}$	Center type
		$b>\frac{(a\varepsilon_2-\varepsilon_1)^2}{(a-1)(1+\varepsilon_1)(1+\varepsilon_2)(\varepsilon_2-\varepsilon_1)}$	Unstable node or unstable focus
	$\varepsilon_1\ge\varepsilon_2$	$b>\frac{(\sqrt{a\varepsilon_2}+\sqrt{\varepsilon_1})^2}{(1+\varepsilon_1)(1+\varepsilon_2)}$	Stable node or stable focus