J. Math. Anal. Appl. ••• (••••) ••••••

Contents lists available at ScienceDirect

Journal of Mathematical Analysis and Applications

www.elsevier.com/locate/jmaa

Regular Articles

Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I

Tuan Anh Phan [a], Jianjun Paul Tian [b]

[a] *Institute for Modeling Collaboration and Innovation, The University of Idaho, Moscow, ID 83844, USA*
[b] *Department of Mathematical Sciences, New Mexico State University, Las Cruces, NM 88001, USA*

ARTICLE INFO

Article history:
Received 7 January 2022
Available online xxxx
Submitted by E. Braverman

Keywords:
Equilibrium manifold
Hopf bifurcation without parameters
Virotherapy
Innate and adaptive immune responses

ABSTRACT

In this research, we propose deterministic and stochastic models to explain the complexity of interactions in cancer virotherapy and outcomes of current preclinical and clinical trials of oncolytic viral treatments. In Part I, we analyze the deterministic model. The model incorporates both innate and adaptive immune responses which have opposite effects on the outcome of the therapy. According to relative immune clearance rates, the model can be reduced to two subsystems, one with only innate immunity and one with only adaptive immunity, which provide detailed dynamical properties for the full model. The full system shows many different asymptotic behaviors which correspond to outcomes of the therapy. It undergoes classical Hopf bifurcation when the infectivity constant passes through a particular value and, interestingly, it also undergoes Hopf bifurcation without parameters when the tumor cell number passes through some particular value. We conduct numerical simulations to demonstrate our analytical results and provide detailed medical interpretations.

1. Introduction

Tumor virotherapy is a promising strategy to fight against cancers [9], which makes use of oncolytic viruses that are specific to cancer cells [14]. Upon entering the tumor, oncolytic viruses infect tumor cells and replicate inside them while they do not attack normal cells. Through lysis of infected cancer cells, new viruses come out and infect other cancer cells [34,22]. Oncolytic viruses can be genetically manipulated to incorporate additional features for improving safety and efficacy [9,42]. After US Food and Drug Administration (FDA) approved oncolytic viruses for clinic trials in 2015 [37], the virotherapy has shown some auspicious outcomes in preclinical tests and clinical trials for a number of viruses in variant of solid tumors [3,8,25,11]. However, the virotherapy does not live up to it full potential due to the complexity of interactions in the oncolytic virotherapy [21,16,24,43]. One major problem is the interaction of oncolytic viruses

E-mail addresses: tphan@uidaho.edu (T.A. Phan), jtian@nmsu.edu (J.P. Tian).

https://doi.org/10.1016/j.jmaa.2022.126278
0022-247X/

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

and immune systems which causes both antitumor and antivirus effects. The infected tumor cells induce the adaptive immune response which is against tumor cells while the infected tumor cells also induce the innate immune response which tends to limit viruses and infections [20,6,15,12]. This requires a deep study about how to strategically manipulate the balance between antivirus and antitumor immune responses in clinical and experiments [27,17].

Mathematical modeling is a useful tool to decipher complexities of biological and medical processes. There are several mathematical models which have been proposed to understand the virus spreading dynamics of oncolytic viral therapy. The early model was proposed in study [38,39], and was generalized in [10] later on. These models were formulated with three variables: uninfected tumor cells, free viruses, and infected tumor cells. The uninfected tumor cells were assumed to undergo logistic growth, and infected by virus particles, which replicate rapidly with infected tumor cells. Infected tumor cells were removed from the system due to natural or virus-inflicted death, resulting in new virus particles bursting to the free virus population. Motivated by experimental evidence, the study [5] suggested that the forming of syncytia by fusing of uninfected and infected tumor cells rather than the free virus particles was the physical mechanism which drives intratumor virus spreading. The study [19] proposed and analyzed several general mathematical formulations for oncolytic virus infection which categorized two types of virus spread, slow and fast spread. Our work [35] proposed a simple system to describe the interactions among uninfected tumor cells, infected tumor cells, and oncolytic viruses. Our results concluded that the oncolytic viral dynamics is mainly determined by the viral burst size. It is known that the immune responses are one major factor which determines the outcome of oncolytic viral treatment. There are several models which include immune responses. For example, early models [40,13] incorporate immune responses. We proposed and studied a model with only the innate immune response [29]. However, these models do not distinguish innate and adaptive responses which have opposite effects on the outcomes of the therapy. To understand antivirus and antitumor immune responses in one dynamical system, we proposed a model [36].

Our model [36] has six physical variables consisting of tumor cells, infected tumor cells, innate immune cells, adaptive immune cells, free viruses, and necrotic cells. It is a free boundary problem of parabolic partial differential equation system. We did numerical analysis with some chosen parameter values. However, a deep understanding about how the two immune systems work together to influence the outcome of the therapy still is needed. In this research, based on interactions among the physical variables proposed in our PDE model, we propose a basic ODE model for cancer virotherapy that incorporates both innate and adaptive immune responses. Let $x(t)$ denote the uninfected tumor cell population, $y(t)$ the infected tumor cell population, $z_1(t)$ the innate immune cell population, and $z_2(t)$ the adaptive immune cell population. Our model is as follows.

$$\begin{aligned}
\frac{dx}{dt} &= \lambda x\left(1-\frac{x+y}{C}\right)-\beta xy-k_2xz_2,\\
\frac{dy}{dt} &= \beta xy-k_1yz_1-\delta y,\\
\frac{dz_1}{dt} &= s_1yz_1-c_1z_1,\\
\frac{dz_2}{dt} &= s_2yz_2-c_2z_2.
\end{aligned} \tag{1.1}$$

A common logistic growth with the per capita growth rate λ and the carrying capacity C are used to model the tumor growth. The term βxy represents the infection process, with β being the infectivity rate. Our model does not include the free virus population explicitly. Infection by free viruses and the release of new viruses by infected tumor cells are only indirectly modeled by the mass interaction law and the rate β that captures virus production. The term δy represents the death rate of infected tumor cells as a consequence of virus infection, and $\frac{1}{\delta}$ represents the lytic cycle of virus reproduction. The antitumor adaptive immune

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

response kills the uninfected tumor cells at a rate k_2, while the antivirus innate immune response works against the virotherapy and kills the infected tumor cells at a rate k_1. Both innate and adaptive immune cells are stimulated through their interaction with the infected tumor cells at rates of s_1 and s_2, and are cleared at rates of c_1 and c_2, respectively.

We conduct a detailed analysis about this deterministic model. We find the dynamics or outcome of the therapy is largely determined by the relative clearance rates of the immune responses. If the relative clearance rate of the innate immune response is smaller than that of the adaptive immune response, the system (1.1) is reduced to a system without the adaptive immunity; if the relative clearance rate of the innate immune response is greater than that of the adaptive immune response, the system (1.1) is reduced to a system without the innate immunity; if the relative clearance rate of the innate immune response is equal to that of the adaptive immune response, there occurs Poincare-Andronov-Hopf bifurcation without parameters [23]. However, because the relative clearance rates may change due to immune cell number density and other tumor-immune environmental factors [1,7,28] and, particularly, the case of bifurcation without parameters, the outcome of the viral therapy seems to have a high uncertainty. To gain deep insights into viral oncolytic processes, we would like to further study how the environmental noises influence on the outcome of the therapy.

In recent years, several attempts have been made to characterize microenvironmental fluctuations and noises in viral dynamics for oncolytic viral therapy using stochastic differential equations (SDEs). To understand the stochastic effects in tumor growth rate, infection process, and virus spreading, we proposed a stochastic model [30]. In study [41], a stochastic differential equation model was derived based on a basic deterministic viral dynamic model which was applied to HIV dynamics. The work [18] derived a SDE system only included adaptive immune response and conducted numerical simulations. Based on infected cell fusion model [10], stochastic models were developed and numerical simulations were carried out [32,33]. Except our model [30], most of these stochastic models were formulated by transforming ODE systems using the method proposed in [2]. These transformed SDE models may have some computational advantages.

There are several ways to incorporate the microenvironmental noises and uncertainties into mathematical modeling. We briefly recall our methods to derive SDE models [30,31]. Consider P is a population and its change is modeled as $\frac{dP}{dt} = f(t,P)$. To count for environmental noise, we assume each individual make almost same contribution to the stochastic effects and receive the same environmental noise. Then, the environmental noises and stochastic effects can be represented by $\tau P\xi$, where ξ is a unit noise and τ is an average variation of each individual. If we take the noise to be white noise $\xi = \frac{dW(t)}{dt}$, where $W(t)$ is the standard Wiener process, we obtain an Ito stochastic differential equation $dP = f(t,P)dt + \tau P dW$. Now, we consider the innate and adaptive immune responses in our model (1.1). The innate and adaptive immune cell population are supposed to have environmental noises and stochastic effects $\tau_1 z_1 \frac{dW_1}{dt}$ and $\tau_2 z_2 \frac{dW_2}{dt}$, respectively, where $W_1(t)$ and $W_2(t)$ are independent Wiener processes. Therefore, we have the following stochastic model based on (1.1):

$$\begin{aligned} dx &= \left[\lambda x\left(1-\frac{x+y}{C}\right) - \beta xy - k_2 x z_2\right] dt, \\ dy &= (\beta xy - k_1 y z_1 - \delta y)\, dt, \\ dz_1 &= (s_1 y z_1 - c_1 z_1)\, dt + \tau_1 z_1 dW_1, \\ dz_2 &= (s_2 y z_2 - c_2 z_2)\, dt + \tau_2 z_2 dW_2. \end{aligned} \tag{1.2}$$

We carry out a thorough analysis about this SDE system. We find the sum of the relative immune clearance rate and relative noise variance plays an important role in determining the dynamics of the system. We also discover there is Poincare-Andronov-Hopf bifurcation without parameters, which is a new phenomenon in stochastic dynamical systems.

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

We will present our work as two parts. Part I is about the deterministic system and Part II is about the stochastic system. The rest of this article is organized as follows. In Section 2, we list notations and results, and give some medical interpretations about our results. In Section 3, we provide detailed analysis and proof of the results. In Section 4, we provide numerical analysis and simulations to demonstrate our analysis results and medical implications, and we also discuss some aspects of our results.

2. Results and interpretations

We non-dimensionalize the system (1.1) by setting $x = C\overline{x}$, $y = C\overline{y}$, $z_1 = C\overline{z}_1$, $z_2 = C\overline{z}_2$, $r = \frac{\lambda}{\delta}$, $a = \frac{\beta C}{\delta}$, $l_i = \frac{k_i C}{\delta}$, $e_i = \frac{s_i C}{\delta}$, $d_i = \frac{c_i}{\delta}$, and $T = \delta t$. After dropping all bars over the variables and writing T as t, the system (1.1) becomes

$$\begin{aligned}
\frac{dx}{dt} &= rx(1-x-y) - axy - l_2 x z_2,\\
\frac{dy}{dt} &= axy - l_1 y z_1 - y,\\
\frac{dz_1}{dt} &= e_1 y z_1 - d_1 z_1,\\
\frac{dz_2}{dt} &= e_2 y z_2 - d_2 z_2.
\end{aligned} \tag{2.1}$$

All parameters are positive. It is straightforward to verify that the non-compact region

$$D = \{(x, y, z_1, z_2) : x \geq 0,\ y \geq 0,\ z_1 \geq 0,\ z_2 \geq 0,\ x + y \leq 1\}$$

is the positive invariant domain for the ODE system (2.1) (see [35] and [29]). Then we refer it to be a global domain. The dynamics of the non-dimensionalized system (2.1) is determined by the non-unit parameter a and two ratios $\frac{d_1}{e_1}$ and $\frac{d_2}{e_2}$. The parameter a still represents infection possibility, call it the infectivity constant. The ratio $\frac{d_1}{e_1}$ represents a relative clearance rate which is relative to the stimulation of the innate response by the infected tumor cells, so we call it the relative clearance rate of the innate immune cells. Similarly, we call the ratio $\frac{d_2}{e_2}$ the relative clearance rate of the adaptive immune cells. We may look at $\frac{e_1}{d_1}$, this ratio measures the ability of recruiting innate immune cells into the tumor by the infection of viruses. Similar, we may interpret $\frac{e_2}{d_2}$. Under certain conditions, the system (2.1) has the following possible equilibrium points: $E_0 = (0,0,0,0)^T$, $E_1 = (1,0,0,0)^T$, $E_2 = \left(\frac{1}{a}, \frac{r(a-1)}{a(a+r)}, 0, 0\right)^T$, $E_3 = \left(1 - \frac{d_1}{e_1} - \frac{ad_1}{re_1}, \frac{d_1}{e_1}, \frac{a}{l_1}\left(1 - \frac{d_1}{e_1} - \frac{ad_1}{re_1} - \frac{1}{a}\right), 0\right)^T$, $E_4 = \left(\frac{1}{a}, \frac{d_2}{e_2}, 0, \frac{r}{l_2}\left(1 - \frac{d_2}{e_2} - \frac{ad_2}{re_2} - \frac{1}{a}\right)\right)^T$. In order to state our theorems, we introduce the following notations: $a_{2i} = \frac{e_i}{e_i - d_i}$, $a_{3i} = \frac{r(e_i - d_i)}{d_i}$, $a_{4i,5i} = \frac{1}{2}a_{3i} \mp \frac{1}{2}\sqrt{a_{3i}(a_{3i} - 4a_{2i})}$, $\delta_i = r^2\left(\frac{e_i}{d_i} - \frac{1}{d_i} - 1\right)^2 - 4\left(\frac{re_i}{d_i} + \frac{r^2}{d_i}\right)$, $a_{6i,7i} = \frac{1}{2}r\left(\frac{e_i}{d_i} - \frac{1}{d_i} - 1\right) \mp \frac{1}{2}\sqrt{\delta_i}$, $i = 1, 2$; when $\frac{d_1}{e_1} = \frac{d_2}{e_2} = \frac{d}{e}$, this notation has no second subscript.

When $\frac{d_1}{e_1} < \frac{d_2}{e_2}$, adaptive immune cells get stimulated less by infected tumor cells and get cleared more than innate immune cells. In this case, the adaptive immune cell population decays to 0 very quickly and the 4-dimensional ODE system (2.1) is reduced to the 3-dimensional ODE system

$$\begin{aligned}
\frac{dx}{dt} &= rx(1-x-y) - axy,\\
\frac{dy}{dt} &= axy - l_1 y z_1 - y,\\
\frac{dz_1}{dt} &= e_1 y z_1 - d_1 z_1,
\end{aligned} \tag{2.2}$$

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

where $D_1 = \{(x, y, z_1) : x \geq 0, y \geq 0, z_1 \geq 0, x + y \leq 1\}$ is its positive invariant domain. Under some condition, this system has four equilibria: $\overline{E}_0 = (0,0,0)^T$, $\overline{E}_1 = (1,0,0)^T$, $\overline{E}_2 = \left(\frac{1}{a}, \frac{r(a-1)}{a(a+r)}, 0\right)^T$, $\overline{E}_3 = \left(1 - \frac{d_1}{e_1} - \frac{ad_1}{re_1}, \frac{d_1}{e_1}, \frac{a}{l_1}\left(1 - \frac{d_1}{e_1} - \frac{ad_1}{re_1} - \frac{1}{a}\right)\right)^T$. The dynamics of the system (2.2) on D_1 is summarized in the following theorem.

Theorem 2.1. *Assume that $\frac{d_1}{e_1} < \frac{d_2}{e_2}$. Then the long-term behavior of the system (2.1) on the invariant domain D is governed by the long-term behavior of the system (2.2) on the invariant domain D_1. The system (2.2) has 3 equilibria $\overline{E}_0$, $\overline{E}_1$, and $\overline{E}_2$ on ∂D_1 and a unique positive equilibrium $\overline{E}_3$ in D_1°. $\overline{E}_0$ is always unstable for all positive values of a. $\overline{E}_1$ is globally asymptotically stable when $0 < a < 1$, and unstable when $a > 1$. At $a = 1$, $\overline{E}_1$ is locally asymptotically stable and $\overline{E}_2$ moves into the domain D_1. A similar type of transcritical bifurcation occurs with $\overline{E}_1$ and $\overline{E}_2$. When $a > 1$, assume that $\frac{d_1}{e_1} < 1$, there are cases as follows.*

(i) *If $(a_{31} \leq 4a_{21}) \vee (a_{31} > 4a_{21}, a \in (1, a_{41}) \cup (a_{51}, \infty))$ then $\overline{E}_2$ is globally asymptotically stable.*
(ii) *If $a_{31} > 4a_{21}$ and $a \in (a_{41}, a_{51})$ then $\overline{E}_2$ becomes unstable, $\overline{E}_3$ enters the domain D_1, and $\overline{E}_3$ is globally asymptotically stable.*

When $\frac{d_1}{e_1} > \frac{d_2}{e_2}$, adaptive immune cells become more dominated because innate immune cells get stimulated less and get cleared more. Then innate immune cell population decays to 0 exponentially fast and hence the system (2.1) can be reduced to the 3-dimensional ODE system

$$\begin{aligned} \frac{dx}{dt} &= rx(1 - x - y) - axy - l_2 xz_2, \\ \frac{dy}{dt} &= axy - y, \\ \frac{dz_2}{dt} &= e_2 yz_2 - d_2 z_2, \end{aligned} \tag{2.3}$$

on the positive invariant domain $D_2 = \{(x, y, z_2) : x \geq 0, y \geq 0, z_2 \geq 0, x + y \leq 1\}$. Under some conditions, this system has four equilibrium solutions: $\widetilde{E}_0 = (0,0,0)^T$, $\widetilde{E}_1 = (1,0,0)^T$, $\widetilde{E}_2 = \left(\frac{1}{a}, \frac{r(a-1)}{a(a+r)}, 0\right)^T$, $\widetilde{E}_4 = \left(\frac{1}{a}, \frac{d_2}{e_2}, \frac{1}{l_2}\left(r - \frac{r}{a} - \frac{rd_2}{e_2} - \frac{ad_2}{e_2}\right)\right)^T$. We summarize the dynamics of this reduced system in the following theorem.

Theorem 2.2. *Assume that $\frac{d_2}{e_2} < \frac{d_1}{e_1}$. Then the long-term behavior of the system (2.1) on the invariant domain D can be reduced to that of the system (2.3) on the invariant domain D_2. The system (2.3) has 3 equilibria $\widetilde{E}_0$, $\widetilde{E}_1$, and $\widetilde{E}_2$ on ∂D_2 and a unique positive equilibrium $\widetilde{E}_4$ in D_2°. $\widetilde{E}_0$ is always unstable for all positive values of a. $\widetilde{E}_1$ is globally asymptotically stable when $0 < a < 1$, and unstable when $a > 1$. At $a = 1$, $\widetilde{E}_1$ is locally asymptotically stable and $\widetilde{E}_2$ moves into the domain D_1. A similar type of transcritical bifurcation occurs with $\widetilde{E}_1$ and $\widetilde{E}_2$. When $a > 1$, assume that $\frac{d_2}{e_2} < 1$. There are the following cases.*

(i) *If $(a \in (1, a_{22})) \vee (a_{32} < 4a_{22}) \vee (a_{32} = 4a_{22}, a \in (1, \frac{2e_2}{e_2 - d_2}) \cup (\frac{2e_2}{e_2 - d_2}, \infty)) \vee (a_{32} > 4a_{22}, a \in [a_{22}, a_{42}) \cup (a_{52}, \infty))$ then $\widetilde{E}_2$ is globally asymptotically stable.*
(ii) *If $a_{32} > 4a_{22}$ and $a \in (a_{42}, a_{52})$ then $\widetilde{E}_2$ becomes unstable, $\widetilde{E}_4$ enters the domain D_2. Hopf bifurcation occurs from $\widetilde{E}_4$ at $a = a_{62}$ and $a = a_{72}$.*

An interesting phenomenon occurs when $\frac{d_1}{e_1} = \frac{d_2}{e_2}$. In this case, two types of immune responses, innate and adaptive, are cleared with the same relative clearance rate. Under certain conditions, there exists a

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

closed manifold of equilibria M which connects two equilibrium point E_3 and E_4 in the positive invariant domain D,

$$M = \left\{ E_5(\xi) : \xi \in \left[\frac{1}{a}, 1 - \frac{d}{e} - \frac{ad}{re} \right] \right\},$$

where $E_5(\xi) = \left(\xi, \frac{d}{e}, \frac{a\xi - 1}{l_1}, \frac{r}{l_2}\left(1 - \frac{d}{e} - \frac{ad}{re} - \xi\right) \right)^T$. The system (2.1) undergoes the Poincare-Andronov-Hopf bifurcation without parameters. The results of this case are summarized in the following theorem.

Theorem 2.3. *Under the assumption* $\frac{d_1}{e_1} = \frac{d_2}{e_2} =: \frac{d}{e} < 1$, *the system* (2.1) *has three equilibrium points* E_0, E_1, E_2, *and the manifold of equilibria* M. E_0 *is always unstable for all positive values of* a. E_1 *is globally asymptotically stable when* $0 < a < 1$, *and unstable when* $a > 1$. *At* $a = 1$, E_1 *is locally asymptotically stable and the equilibrium point* E_2 *enters into the positive invariant domain* D, *a similar type of transcritical bifurcation occurs with* E_1 *and* E_2. *When* $a > 1$, *there are the following cases.*

(i) *If* $(a_3 < 4a_2) \vee (a_3 = 4a_2, a \in (1, \frac{2e}{e-d}) \cup (\frac{2e}{e-d}, \infty)) \vee (a_3 > 4a_2, a \in (1, a_4) \cup (a_5, \infty))$ *then* E_2 *is globally asymptotically stable.*

(ii) *If* $a_3 > 4a_2$ *and* $a \in (a_4, a_5)$ *then* E_2 *becomes unstable and a manifold of equilibria* M *moves into the domain* D. *There are two cases.*
- *if* $(\frac{e}{d} \le \frac{1}{\rho d_1} + 1) \vee (\frac{e}{d} > \frac{1}{\rho d_1} + 1, \delta \le 0) \vee (\frac{e}{d} > \frac{1}{\rho d_1} + 1, \delta > 0, a \in (a_4, a_6) \cup (a_7, a_5))$ *then* M° *is locally stable.*
- *if* $\frac{e}{d} > \frac{1}{\rho d_1} + 1$, $\delta > 0$, *and* $a \in (a_6, a_7)$, *then the system* (2.1) *undergoes the Poincare-Andronov-Hopf bifurcation without parameters.*

Medical interpretations 2.1. *The equilibrium points* E_0, $\overline{E}_0$, $\widetilde{E}_0$ *are unstable for any positive parameter values in their systems. This is reasonable since the tumor always grows when it starts.*

For the infectivity constant $a = \frac{\beta C}{\delta}$, *the tumor carrying capacity* C *is a fixed quantity for a specific tumor, while the infection rate* β *and the lytic cycle of the virus* $\frac{1}{\delta}$ *depend on a specific type of virus. When this constant is smaller than 1, that is,* $\frac{\beta}{\delta} < \frac{1}{C}$, *this inequality biologically means that, within a period of virus reproduction or one run of an infected tumor cell, the possibility that each infected tumor cell infects one uninfected tumor cell is smaller than one cell as a portion in the full tumor. Under this condition, it is obvious that viral therapy completely fails because it is necessary to infect each tumor cell in order to destroy the tumor. This is biological interpretation of the statement that the equilibrium points* E_1, $\overline{E}_1$, $\widetilde{E}_1$ *are globally asymptotically stable when* $0 < a < 1$ *in their systems. Similarly, it is easy to interpret that* E_1, $\overline{E}_1$, $\widetilde{E}_1$ *are unstable when* $a > 1$. *It should be noticed that "unstable" just means the therapy does not completely fail, and it might be partially successful.*

When the infectivity constant a *is above 1, one partial success of the therapy is represented by the equilibrium point* E_2 *in the full model. There are several intervals of the infectivity constant* a *in which the therapy can achieve such outcome. In the two subsystems, we have* $\overline{E}_2$ *and* $\widetilde{E}_2$, *which can be reached in each sub-model under the condition of the infectivity constant within some intervals. The total tumor burden in the equilibrium is* $\frac{1}{a} + \frac{r(a-1)}{a(a+r)} = \frac{1+r}{1+a}$.

In oncolytic viral therapy, the innate immune system and the adaptive immune system do not compete each other. We may regard immune cells as predators in which innate immune cells prey on infected tumor cells and adaptive immune cells prey on tumor cells; while infected tumor cells may also be considered as predators who prey on tumor cells. However, both the relative clearance rates $\frac{d_i}{e_i}$ *seem not directly related to prey-predator dynamics. If we look at the reciprocal of the relative clearance rates,* $\frac{e_i}{d_i} = \frac{1}{c_i} s_i C$, *where* $\frac{1}{c_i}$ *is the average life time of cells* z_i, C *is the cell number of the tumor carrying capacity, and* s_i *is the possibility that one infected tumor cell stimulates one* z_i *cell in unit time, this reciprocal may mean the possibility one*

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

infected tumor cell recruits C many z_i cells within the z_i cell average life time. These two ratios give some classifications of our model system (2.1).

When $\frac{d_1}{e_1} < \frac{d_2}{e_2}$, the system (2.1) is reduced to the subsystem (2.2). The condition means that the possibility one infected tumor cell recruits C many innate immune cells within the average life time of the innate immune cells is greater than the possibility one infected tumor cell recruit C many adaptive immune cells within the average life time of the adaptive immune cells. In this case, besides $\overline{E}_2$, there is an equilibrium point $\overline{E}_3$ which also represents partial success of the therapy but with the innate immune cells. This case might not be what we want if we cannot achieve complete success. This case has only one outcome $\overline{E}_3$ which are not shared with other cases, and the tumor burden may be still high if we have numerical numbers.

When $\frac{d_2}{e_2} < \frac{d_1}{e_1}$, the system (2.1) is reduced to the subsystem (2.3). As explained above, the adaptive immune cells are more likely recruited by infected tumor cells. Beside the equilibrium point $\widetilde{E}_2$, the subsystem has the equilibrium solution $\widetilde{E}_4$ which represents a partial success of the therapy and the occurrence of Hopf bifurcation arising from $\widetilde{E}_4$ may give more outcomes [35].

When $\frac{d_1}{e_1} = \frac{d_2}{e_2}$, the full system (2.1) has the equilibrium point E_2 which is stable in several intervals of the infectivity constant a. More importantly, when the infectivity constant a is in some interval, there occurs Poincare-Andronov-Hopf bifurcation without parameters. The manifold of equilibria M is actually parameterized by the first component, namely tumor cells x. When the tumor cells reach to some number, there occurs periodic solutions. However, depending on where these solutions start (initial values), these periodic solutions behave differently. Some solutions may set down to equilibrium, some solutions may increase indefinitely, while some solutions may increase and then decrease and vice versa. This complicates the outcomes of the therapy. If the tumor grows under the therapy, it reaches some equilibrium point in M or suddenly tumor cells increase or decrease indefinitely.

3. Analysis of the model

This section is devoted to proving three theorems in Section 2. We mainly use Routh-Hurwitz's criterion, LaSalle's Principle, Lyapunov functions, Center Manifold Theorem, Foliation of domains, etc. To be concise and clear, we will present them in five subsections.

3.1. Equilibrium solutions

First, we analyze all possible equilibrium solutions in this subsection.

Let $U = (x, y, z_1, z_2)^T$ and

$$f(U) = (rx(1-x-y) - axy - l_2xz_2,\ axy - l_1yz_1 - y,\ e_1yz_1 - d_1z_1,\ e_2yz_2 - d_2z_2)^T.$$

Then the system (2.1) can be written as $dU/dt = f(U)$ and we assume that $U \in D$. The equilibria are solutions to the equation $f(U) = 0$; that is

$$x[r(1-x-y) - ay - l_2z_2] = 0, \tag{3.1}$$

$$y(ax - l_1z_1 - 1) = 0, \tag{3.2}$$

$$z_1(e_1y - d_1) = 0, \tag{3.3}$$

$$z_2(e_2y - d_2) = 0. \tag{3.4}$$

If $x = 0$ then the equation (3.2) implies $y(-l_1z_1 - 1) = 0$. This follows that $y = 0$. So the last two equations (3.3) and (3.4) lead to $z_1 = z_2 = 0$. Hence $E_0 = (0, 0, 0, 0)^T$ is an equilibrium point. If $x \neq 0$ then the equation (3.1) implies

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

$$r(1-x-y) = ay + l_2 z_2. \tag{3.5}$$

If $y = 0$ then, from the equation (3.5), we get $r(1-x) = l_2 z_2$. By (3.3) and (3.4), $y = 0$ implies $z_1 = z_2 = 0$, which follows that $x = 1$. So $E_1 = (1,0,0,0)^T$ is an equilibrium point. Now we assume that $y \neq 0$. Then the equation (3.2) follows

$$ax = l_1 z_1 + 1. \tag{3.6}$$

We consider the following cases.

Case 1. $z_1 = z_2 = 0$. The equation (3.6) implies $x = \frac{1}{a}$. Plugging this into the equation (3.5) gives $r(1 - \frac{1}{a} - y) = ay$, which implies that $y = \frac{r(a-1)}{a(a+r)}$. Then we obtain the equilibrium point

$$E_2 = \left(\frac{1}{a}, \frac{r(a-1)}{a(a+r)}, 0, 0\right)^T.$$

This equilibrium E_2 moves into the domain D provided $0 \leq \frac{1}{a} + \frac{r(a-1)}{a(a+r)} \leq 1$, which is equivalent to $a \geq 1$. Notice that, when $a = 1$, both equilibria E_1 and E_2 coincide.

Case 2. $z_1 \neq 0$, $z_2 = 0$. From the equation (3.3) and $z_1 \neq 0$, we get $y = \frac{d_1}{e_1}$. Combining this with (3.5) we have $r(1 - x - \frac{d_1}{e_1}) = \frac{ad_1}{e_1}$, which implies that $x = 1 - \frac{d_1}{e_1} - \frac{ad_1}{re_1}$. Then the equation (3.6) implies $z_1 = \frac{a}{l_1}(1 - \frac{d_1}{e_1} - \frac{ad_1}{re_1} - \frac{1}{a})$. So we obtain an equilibrium point

$$E_3 = \left(1 - \frac{d_1}{e_1} - \frac{ad_1}{re_1}, \frac{d_1}{e_1}, \frac{a}{l_1}\left(1 - \frac{d_1}{e_1} - \frac{ad_1}{re_1} - \frac{1}{a}\right), 0\right)^T.$$

The equilibrium E_3 will enter the domain D if $1 - \frac{d_1}{e_1} - \frac{ad_1}{re_1} > 0$ and $1 - \frac{d_1}{e_1} - \frac{ad_1}{re_1} - \frac{1}{a} > 0$. Note that the inequality $1 - \frac{d_1}{e_1} - \frac{ad_1}{re_1} > 0$ is equivalent to $a < a_{31}$ and $\frac{d_1}{e_1} < 1$, where $a_{31} := \frac{r(e_1 - d_1)}{d_1}$. If either $\frac{d_1}{e_1} \geq 1$ or $\frac{d_1}{e_1} < 1$, $a \geq a_{31}$ then E_3 is not in D. So we assume that $\frac{d_1}{e_1} < 1$ and $a < a_{31}$. The inequality $1 - \frac{d_1}{e_1} - \frac{ad_1}{re_1} - \frac{1}{a} > 0$ is the same as $g_1(a) := a^2 - \frac{r(e_1-d_1)}{d_1}a + \frac{re_1}{d_1} < 0$. Let $a_{21} := \frac{e_1}{e_1 - d_1}$, then it is easy to compute the discriminant $\Delta_1 = a_{31}(a_{31} - 4a_{21})$ of the quadratic $g_1(a)$. If $a_{31} \leq 4a_{21}$ then $\Delta_1 \leq 0$, which follows that $g_1(a) \geq 0$ for all a. This means that the condition $1 - \frac{d_1}{e_1} - \frac{ad_1}{re_1} - \frac{1}{a} > 0$ does not hold and hence E_3 goes beyond the domain D. If $a_{31} > 4a_{21}$ then $\Delta_1 > 0$ and we can compute two positive zeros of the above quadratic function

$$a_{41} := \frac{1}{2}a_{31} - \frac{1}{2}\sqrt{a_{31}(a_{31} - 4a_{21})}, \quad a_{51} := \frac{1}{2}a_{31} + \frac{1}{2}\sqrt{a_{31}(a_{31} - 4a_{21})}.$$

So the condition $1 - \frac{d_1}{e_1} - \frac{ad_1}{re_1} - \frac{1}{a} > 0$ is equivalent to $a_{41} < a < a_{51}$. Since $1 < a_{21} < a_{41} < a_{51} < a_{31}$, E_3 moves into D provided $\frac{d_1}{e_1} < 1$, $a_{31} > 4a_{21}$, and $a_{41} < a < a_{51}$.

Case 3. $z_1 = 0$, $z_2 \neq 0$. By (3.6), $z_1 = 0$ implies $x = \frac{1}{a}$. Combining this with (3.5), we have $r(1 - \frac{1}{a} - y) = ay + l_2 z_2$. From the equation (3.4) and $z_2 \neq 0$, we get $y = \frac{d_2}{e_2}$. This implies that $z_2 = \frac{r}{l_2}(1 - \frac{d_2}{e_2} - \frac{ad_2}{re_2} - \frac{1}{a})$. Hence

$$E_4 = \left(\frac{1}{a}, \frac{d_2}{e_2}, 0, \frac{r}{l_2}\left(1 - \frac{d_2}{e_2} - \frac{ad_2}{re_2} - \frac{1}{a}\right)\right)^T$$

is an equilibrium point. E_4 will enter the domain D if $\frac{1}{a} + \frac{d_2}{e_2} \leq 1$ and $r - \frac{r}{a} - \frac{rd_2}{e_2} - \frac{ad_2}{e_2} > 0$. Note that the inequality $\frac{1}{a} + \frac{d_2}{e_2} \leq 1$ is equivalent to $a \geq a_{22}$ and $\frac{d_2}{e_2} < 1$ where $a_{22} := \frac{e_2}{e_2 - d_2}$. If either $\frac{d_2}{e_2} \geq 1$ or $\frac{d_2}{e_2} < 1$, $a < a_{22}$ then E_4 is not in D. So we assume that $\frac{d_2}{e_2} < 1$ and $a \geq a_{22}$. The inequality $r - \frac{r}{a} - \frac{rd_2}{e_2} - \frac{ad_2}{e_2} > 0$

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

is the same as $g_2(a) := a^2 - \frac{r(e_2-d_2)}{d_2}a + \frac{re_2}{d_2} < 0$. Let $a_{32} := \frac{r(e_2-d_2)}{d_2}$, then it is easy to compute the discriminant $\Delta_2 = a_{32}(a_{32} - 4a_{22})$ of the quadratic $g_2(a)$. By the same argument as in Case 2, E_4 moves into D provided $\frac{d_2}{e_2} < 1$, $a_{32} > 4a_{22}$, and $a_{42} < a < a_{52}$ where

$$a_{42} := \frac{1}{2}a_{32} - \frac{1}{2}\sqrt{a_{32}(a_{32} - 4a_{22})},\ a_{52} := \frac{1}{2}a_{32} + \frac{1}{2}\sqrt{a_{32}(a_{32} - 4a_{22})}.$$

Case 4. $z_1 \neq 0$, $z_2 \neq 0$. If $\frac{d_1}{e_1} \neq \frac{d_2}{e_2}$ then there is no positive value y that satisfies both (3.3) and (3.4). Hence, in this case, the system (2.1) does not have any positive equilibrium in the interior of the domain D. Now we consider three cases. First assume that $\frac{d_1}{e_1} < \frac{d_2}{e_2}$. The last two equations of the system (2.1) imply

$$\frac{dz_1}{z_1} = \frac{e_1}{e_2}\frac{dz_2}{z_2} + Kdt,$$

where $K = e_1(\frac{d_2}{e_2} - \frac{d_1}{e_1}) > 0$. It follows that

$$z_2(t)^{e_1/e_2} = Cz_1(t)e^{-Kt}, \tag{3.7}$$

where $C = z_1(0)z_2(0)^{-e_1/e_2}$. From the third equation of (2.1),

$$z_1(t) = z_1(0)\exp\{e_1\int_0^t y(s)ds - d_1t\},$$

so $\lim_{t\to\infty} z_1(t)$ exists. By way of contradiction, we suppose that $\lim_{t\to\infty} z_1(t) = \infty$. Then $\lim_{t\to\infty} \frac{1}{t}\int_0^t z_1(s)ds = \infty$. By the second equation of (2.1), we get

$$\frac{\ln y(t) - \ln y(0)}{t} = \frac{1}{t}\int_0^t ax(s)ds - \frac{1}{t}\int_0^t l_1z_1(s)ds - 1,$$

which implies that $\lim_{t\to\infty} \frac{\ln y(t)}{t} = -\infty$. Hence $\lim_{t\to\infty} y(t) = 0$. But then, from the third equation of (2.1), we can easily show that $\lim_{t\to\infty} z_1(t) = 0$. This is a contradiction. Thus $\lim_{t\to\infty} z_1(t) < \infty$. By (3.7), we obtain $\lim_{t\to\infty} z_2(t) = 0$ exponentially fast. So the system (2.1) can be reduced to the system (2.2) on the boundary $\{z_2 = 0\} \subseteq \partial D$. It is easy to see that

$$\overline{E}_3 = \left(1 - \frac{d_1}{e_1} - \frac{ad_1}{re_1}, \frac{d_1}{e_1}, \frac{a}{l_1}\left(1 - \frac{d_1}{e_1} - \frac{ad_1}{re_1} - \frac{1}{a}\right)\right)^T$$

is the unique positive equilibrium of (2.2) on the invariant domain

$$D_1 = \{(x, y, z_1) : x \geq 0, y \geq 0, z_1 \geq 0, x + y \leq 1\}.$$

Clearly, $\overline{E}_3$ corresponds to the equilibrium E_3 of the system (2.1). Also, on ∂D_1, the system (2.2) has 3 equilibria $\overline{E}_0 = (0, 0, 0)^T$, $\overline{E}_1 = (1, 0, 0)^T$, and $\overline{E}_2 = (\frac{1}{a}, \frac{r(a-1)}{a(a+r)}, 0)^T$. These 3 equilibria correspond to the equilibria E_0, E_1, and E_2 of the system (2.1), respectively. By the same reasoning as in Case 3, $\overline{E}_3$ enters D_1 iff $\frac{d_1}{e_1} < 1$, $a_{31} > 4a_{21}$, and $a \in (a_{41}, a_{51})$.

Second, we assume that $\frac{d_2}{e_2} < \frac{d_1}{e_1}$. By the completely similar argument as above, $\lim_{t\to\infty} z_1(t) = 0$ exponentially fast. Then we reduce the system (2.1) to the system (2.3) on the boundary $\{z_1 = 0\} \subseteq \partial D$. The invariant domain of (2.3) is

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

$$D_2 = \{(x, y, z_2) : x \geq 0, y \geq 0, z_2 \geq 0, x + y \leq 1\}.$$

The system (2.3) also has 3 equilibria $\widetilde{E}_0 = (0,0,0)^T$, $\widetilde{E}_1 = (1,0,0)^T$, and $\widetilde{E}_2 = (\frac{1}{a}, \frac{r(a-1)}{a(a+r)}, 0)^T$ on ∂D_2. These equilibria correspond to the equilibria E_0, E_1, and E_2 of the system (2.1), respectively. The unique positive equilibrium of (2.3) on D_2 is

$$\widetilde{E}_4 = \left(\frac{1}{a}, \frac{d_2}{e_2}, \frac{1}{l_2}\left(r - \frac{r}{a} - \frac{rd_2}{e_2} - \frac{ad_2}{e_2}\right)\right)^T,$$

which enters D_2 iff $\frac{d_2}{e_2} < 1$, $a_{32} > 4a_{22}$, and $a \in (a_{42}, a_{52})$.

Lastly, we assume that $\frac{d_1}{e_1} = \frac{d_2}{e_2} =: \frac{d}{e}$. Clearly, the equations (3.3) and (3.4) follow $y = \frac{d}{e}$. Plugging this into equations (3.5) and (3.6) yields $rx + l_2 z_2 = r\left(1 - \frac{d}{e}\right) - \frac{ad}{e}$ and $ax - l_1 z_1 = 1$. Solving these equations for z_1 and z_2 in terms of x, $z_1 = \frac{ax-1}{l_1}$ and $z_2 = \frac{r}{l_2}(1 - \frac{d}{e} - \frac{ad}{re} - x)$. Let $x = \xi$, then we obtain a line of equilibria (depending on ξ)

$$E_5(\xi) = \left(\xi, \frac{d}{e}, \frac{a\xi - 1}{l_1}, \frac{r}{l_2}\left(1 - \frac{d}{e} - \frac{ad}{re} - \xi\right)\right)^T.$$

Since $\frac{d_1}{e_1} = \frac{d_2}{e_2}$, we get $a_2 := a_{2i}$, $a_3 := a_{3i}$, $a_4 := a_{4i}$, and $a_5 := a_{5i}$ for $i = 1, 2$. The same reasoning as in Case 2 shows that $E_5(\xi)$ moves into D provided $\frac{d}{e} < 1$, $a_3 > 4a_2$, $a_4 < a < a_5$, and $\frac{1}{a} < \xi < 1 - \frac{d}{e} - \frac{ad}{re}$. Notice that, when $\xi = \frac{1}{a}$, E_5 coalesces into E_4 and, when $\xi = 1 - \frac{d}{e} - \frac{ad}{re}$, E_5 merges into E_3. Thus we can incorporate two equilibria E_3 and E_4 into the line segment of equilibria $E_5(\xi)$ with $\xi \in [\frac{1}{a}, 1 - \frac{d}{e} - \frac{ad}{re}]$.

Our equilibrium analysis above can be summarized as follows.

1. If $\frac{d_1}{e_1} < \frac{d_2}{e_2}$ then $\lim_{t\to\infty} z_2(t) = 0$ and so the long-term behavior of the system (2.1) on the invariant domain D is governed by the long-term behavior of the system (2.2) on the invariant domain D_1. When $a \leq 1$, the system (2.2) has only two equilibria $\overline{E}_0$ and $\overline{E}_1$. When $a > 1$, $\overline{E}_2$ enters the domain D_1. Assume that $\frac{d_1}{e_1} < 1$ and then we have 2 cases.

(a1) If $(a_{31} \leq 4a_{21}) \vee (a_{31} > 4a_{21}, a \in (1, a_{41}) \cup (a_{51}, \infty))$ then there are only 3 equilibria for the system (2.2) which are $\overline{E}_0$, $\overline{E}_1$, and $\overline{E}_2$.
(b1) If $a_{31} > 4a_{21}$ and $a \in (a_{41}, a_{51})$ then the positive equilibrium $\overline{E}_3$ moves into D_1 besides $\overline{E}_0$, $\overline{E}_1$, and $\overline{E}_2$.

2. If $\frac{d_2}{e_2} < \frac{d_1}{e_1}$ then $\lim_{t\to\infty} z_1(t) = 0$ and so the long-term behavior of the system (2.1) on the invariant domain D is governed by the long-term behavior of the system (2.3) on the invariant domain D_2. When $a \leq 1$, the system (2.3) has only two equilibria $\widetilde{E}_0$ and $\widetilde{E}_1$. When $a > 1$, $\widetilde{E}_2$ enters the domain D_2. Assume that $\frac{d_2}{e_2} < 1$ and then we have 2 cases.

(a2) If $(a \in (1, a_{22})) \vee (a_{32} \leq 4a_{22}) \vee (a_{32} > 4a_{22}, a \in [a_{22}, a_{42}) \cup (a_{52}, \infty))$ then there are only 3 equilibria for the system (2.2) which are $\widetilde{E}_0$, $\widetilde{E}_1$, and $\widetilde{E}_2$.
(b2) If $a_{32} > 4a_{22}$ and $a \in (a_{42}, a_{52})$ then the positive equilibrium $\widetilde{E}_4$ moves into D_2 besides $\widetilde{E}_0$, $\widetilde{E}_1$, and $\widetilde{E}_2$.

3. Assume that $\frac{d_1}{e_1} = \frac{d_2}{e_2} =: \frac{d}{e}$. When $a \leq 1$, the system (2.1) has only two equilibria E_0 and E_1. When $a > 1$, the equilibrium E_2 enters the positive domain D. Suppose that $\frac{d}{e} < 1$. We have the following cases.

(a3) If $(a_3 \leq 4a_2) \vee (a_3 > 4a_2, a \in (1, a_4) \cup (a_5, \infty))$ then there are only three equilibria for the system (2.1) which are E_0, E_1, and E_2.

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

(b3) If $a_3 > 4a_2$ and $a \in (a_4, a_5)$ then a line segment of equilibria

$$E_5(\xi) = \left(\xi, \frac{d}{e}, \frac{a\xi - 1}{l_1}, \frac{r}{l_2}\left(1 - \frac{d}{e} - \frac{ad}{re} - \xi\right)\right)^T,$$

with $\frac{1}{a} \le \xi \le 1 - \frac{d}{e} - \frac{ad}{re}$, moves into the domain D besides E_0, E_1, and E_2.

3.2. Stability of E_0 and E_1

In this subsection, we study the stability of the equilibrium solutions E_0 and E_1, which automatically includes $\overline{E}_0$, $\overline{E}_1$, $\widetilde{E}_0$, and $\widetilde{E}_1$.

The variational matrix of the system (2.1) is given by

$$Df(U) = \begin{bmatrix} r - 2rx - ry - ay - l_2z_2 & -rx - ax & 0 & -l_2x \\ ay & ax - l_1z_1 - 1 & -l_1y & 0 \\ 0 & e_1z_1 & e_1y - d_1 & 0 \\ 0 & e_2z_2 & 0 & e_2y - d_2 \end{bmatrix}.$$

At the equilibrium E_0, the variational matrix is $Df(E_0) = \mathrm{diag}(r, -1, -d_1, -d_2)$. Then the eigenvalues are r, -1, $-d_1$ and $-d_2$. So E_0 is always unstable.

At the equilibrium E_1, the variational matrix is

$$Df(E_1) = \begin{bmatrix} -r & -r - a & 0 & -l_2 \\ 0 & a - 1 & 0 & 0 \\ 0 & 0 & -d_1 & 0 \\ 0 & 0 & 0 & -d_2 \end{bmatrix}.$$

Then the eigenvalues are $\lambda_1 = -r$, $\lambda_2 = a - 1$, $\lambda_3 = -d_1$ and $\lambda_4 = -d_2$. Hence E_1 is locally asymptotically stable if $a < 1$ and unstable if $a > 1$. In fact, we can show E_1 is globally asymptotically stable if $a < 1$. By changing of variables $\overline{x} = 1 - x$, $\overline{y} = y$, $\overline{z}_1 = z_1$, and $\overline{z}_2 = z_2$, we get the following system after dropping all the bars over variables

$$\begin{aligned} \frac{dx}{dt} &= (1 - x)(ry + ay + l_2z_2 - rx), \\ \frac{dy}{dt} &= a(1 - x)y - l_1yz_1 - y, \\ \frac{dz_1}{dt} &= e_1yz_1 - d_1z_1, \\ \frac{dz_2}{dt} &= e_2yz_2 - d_2z_2. \end{aligned} \tag{3.8}$$

The domain D is translated into

$$\overline{D} = \{(x, y, z_1, z_2) : 0 \le x \le 1, 0 \le x - y \le 1, z_1 \ge 0, z_2 \ge 0\}.$$

The equilibrium E_1 becomes $E_1' = (0, 0, 0, 0)$. The second equation of (3.8) implies

$$\frac{dy}{dt} = y(a - ax - l_1z_1 - 1) \le (a - 1)y,$$

which follows that $0 \le y(t) \le y(0)\exp\{(a - 1)t\} \to 0$ as $t \to \infty$ since $a < 1$. Therefore $y(t) \to 0$ as $t \to \infty$. Choose $\epsilon > 0$ such that $\epsilon < \min\{\frac{d_1}{e_1}, \frac{d_2}{e_2}\}$, then there exists $T > 0$ so that $t \ge T$ implies $y(t) < \epsilon$. For $t > T$ and $i = 1, 2$ we get

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

$$e_i \int_0^t y(s)ds - d_i t \le e_i \int_0^T y(s)ds + (\epsilon e_i - d_i)t.$$

From the last two equations of (3.8), for $i = 1, 2$

$$0 \le z_i(t) = z_i(0) \exp\left\{ e_i \int_0^t y(s)ds - d_i t \right\} \le z_i(0) \exp\left\{ e_i \int_0^T y(s)ds \right\} \exp\{(\epsilon e_i - d_i)t\}.$$

Letting $t \to \infty$ yields $z_i(t) \to 0$. Lastly, since $1 - x \le 1$, the first equation of (3.8) implies $\frac{dx}{dt} \le ry + ay + l_2 z_2 - rx$. Hence

$$0 \le x(t) \le x(0)e^{-rt} + e^{-rt} \int_0^t [ry(s) + ay(s) + l_2 z_2(s)]e^{rs} ds.$$

By L'Hospital Rule,

$$\lim_{t\to\infty} e^{-rt} \int_0^t [ry(s) + ay(s) + l_2 z_2(s)]e^{rs} ds = \lim_{t\to\infty} \frac{[ry(t) + ay(t) + l_2 z_2(t)]e^{rt}}{re^{rt}} = 0.$$

Thus $x(t) \to 0$ as $t \to \infty$. In other words, E_1' is globally asymptotically stable and so is E_1.

When $a = 1$, the linearized system at E_1' has one zero eigenvalue and three negative eigenvalues. To determine its stability, we will use the center manifold theorem to reduce the system (3.8) into a center manifold and examine the stability of E_1' based on the reduced system. First, we start with the matrix corresponding to the linear part of the system (3.8), which is

$$L = \begin{bmatrix} -r & r+1 & 0 & l_2 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & -d_1 & 0 \\ 0 & 0 & 0 & -d_2 \end{bmatrix}.$$

Without loss of generality, we can assume that $r \ne d_2$ since for $r = d_2$ the argument is completely the same. Then L has eigenvalues $-r$, 0, $-d_1$, and $-d_2$. The eigenvalue $-r$ has an associated eigenvector $U_1 = (1, 0, 0, 0)^T$, the zero eigenvalue has an associated eigenvector $U_2 = (r+1, r, 0, 0)^T$, and the eigenvalues $-d_1$ and $-d_2$ has $U_3 = (0, 0, 1, 0)^T$ and $U_4 = (l_2, 0, 0, r - d_2)^T$ as the respective eigenvectors. Set the transformation matrix to be $T = (U_1, U_2, U_3, U_4)$. The system (3.8) can be written as $\frac{dU}{dt} = LU + F$, where

$$F = (rx^2 - (1 + r)xy - l_2 xz_2, -xy - l_1 yz_1, eyz_1, eyz_2)^T.$$

Denote $U = TY$, then we get $\frac{dY}{dt} = T^{-1}LTY + T^{-1}F$, where $T^{-1}LT = \mathrm{diag}(-r, 0, -d_1, -d_2)$ and $Y = (y_1, y_2, y_3, y_4)^T$. Notice that $x = y_1 + (1 + r)y_2 + l_2 y_4$, $y = ry_2$, $z_1 = y_3$, and $z_2 = (r - d_2)y_4$. Denote $T^{-1}F = (f_1, f_2, f_3, f_4)^T$, then by computation we have

$$f_1 = A_{11}y_1^2 + A_{22}y_2^2 + A_{44}y_4^2 + A_{12}y_1y_2 + A_{14}y_1y_4 + A_{23}y_2y_3 + A_{24}y_2y_4,$$
$$A_{11} = r,\ A_{22} = A_{12} = (r + 1)^2,\ A_{44} = d_2 l_2^2,\ A_{14} = l_2(r + d_2),$$
$$A_{23} = l_1(r + 1),\ A_{24} = l_2(1 + d_2 + r + d_2 r - e_2 r),$$
$$f_2 = B_{22}y_2^2 + B_{12}y_1y_2 + B_{23}y_2y_3 + B_{24}y_2y_4,$$

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

$$B_{22} = -r - 1,\ B_{12} = -1,\ B_{23} = -l_1,\ B_{24} = -l_2,$$
$$f_3 = C_{23} y_2 y_3,\ C_{23} = e_1 r,$$
$$f_4 = D_{24} y_2 y_4,\ D_{24} = e_2 r.$$

Then the transformed system can be rewritten as

$$\frac{dZ}{dt} = BZ + (f_1, f_3, f_4)^T,$$
$$\frac{dy_2}{dt} = Ay_2 + f_2,$$

where $B = \operatorname{diag}(-r, -d_1, -d_2)$, $A = (0)$, and $Z = (y_1, y_3, y_4)^T$. It is clear that A has zero eigenvalue, B has negative eigenvalues, and the functions f_k, $k = 1, 2, 3, 4$, are C^2 differentiable functions satisfying $f_k(0,0,0,0) = 0$ and $Df_k(0,0,0,0) = 0$ where Df_k is the first derivative of the function f_k. By the Center Manifold Theorem, there is a center manifold given by $Z = h(y_2) = (y_1, y_3, y_4)^T = (h_1(y_2), h_3(y_2), h_4(y_2))^T$ such that $h(0) = 0$, $Dh(0) = 0$, and it satisfies

$$Bh(y_2) + \begin{pmatrix} f_1(h(y_2), y_2) \\ f_3(h(y_2), y_2) \\ f_4(h(y_2), y_2) \end{pmatrix} = Dh(y_2)(Ay_2 + f_2(h(y_2), y_2)).$$

Since $h(0) = Dh(0) = 0$, we can assume that $h_1(u) = m_2u^2 + m_3u^3 + o(u^3)$, $h_3(u) = n_2u^2 + n_3u^3 + o(u^3)$, and $h_4(u) = p_2u^2 + p_3u^3 + o(u^3)$. Here we use variable u instead of y_2 for simplicity. Then the equation on the center manifold becomes

$$\begin{pmatrix} -r & 0 & 0 \\ 0 & -d_1 & 0 \\ 0 & 0 & -d_2 \end{pmatrix} \begin{pmatrix} m_2u^2 + m_3u^3 + o(u^3) \\ n_2u^2 + n_3u^3 + o(u^3) \\ p_2u^2 + p_3u^3 + o(u^3) \end{pmatrix} + \begin{pmatrix} f_1(h(u), u) \\ f_3(h(u), u) \\ f_4(h(u), u) \end{pmatrix}$$
$$= \begin{pmatrix} 2m_2u + 3m_3u^2 + o(u^2) \\ 2n_2u + 3n_3u^2 + o(u^2) \\ 2p_2u + 3p_3u^2 + o(u^2) \end{pmatrix} f_2(h(u), u).$$

Substitute f_k, $k = 1, 2, 3, 4$, into the above equation and compare the coefficients on the both sides of the equation, we get

$$-rm_2 + A_{22} = 0,\ -dn_2 = -dp_2 = 0,$$
$$-rm_3 + A_{12}m_2 + A_{23}n_2 + A_{24}p_2 = 2m_2B_{22},$$
$$-dn_3 + C_{23}n_2 = 2n_2B_{22},$$
$$-dp_3 + D_{24}p_2 = 2p_2B_{22}.$$

Solving these equations, we obtain $m_2 = \frac{(r+1)^2}{r}$, $n_2 = p_2 = 0$, $m_3 = \frac{(r+1)^3(r+3)}{r^2}$, $n_3 = p_3 = 0$. Now we reduce the system (3.8) to its center manifold, which is a single equation of y_2

$$\frac{dy_2}{dt} = f_2(h(y_2), y_2) = -(r+1)y_2^2 - \frac{(r+1)^2}{r}y_2^3 + o(y_2^3).$$

Hence the trivial solution $y_2 = 0$ of the above equation is locally asymptotically stable. This implies that E_1 is locally asymptotically stable.

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

3.3. Stability of $\overline{E}_2$ and $\overline{E}_3$

From now on, we assume that $a > 1$. Then the equilibrium E_2 moves into the domain D. To analyze the behavior of the system (2.1) when $a > 1$, we consider 3 cases. In this subsection, we analyze the stability of the equilibrium solution $\overline{E}_2$ and $\overline{E}_3$ in the subsystem (2.2).

First, we assume $\frac{d_1}{e_1} < \frac{d_2}{e_2}$, then z_2 decays to 0 exponentially fast. The system (2.1) is reduced to the system (2.2) and the behavior of E_2 is the same as that of $\overline{E}_2$. Denote $U_1 = (x, y, z_1)^T$ and $f^1(U_1) = (rx(1-x-y) - axy, axy - l_1yz_1 - y, e_1yz_1 - d_1z_1)^T$. The variational matrix of (2.2) at $\overline{E}_2$ is

$$Df^1(\overline{E}_2) = \begin{bmatrix} -\frac{r}{a} & -\frac{r}{a} - 1 & 0 \\ \frac{r(a-1)}{a+r} & 0 & -\frac{l_1r(a-1)}{a(a+r)} \\ 0 & 0 & \frac{e_1r(a-1)}{a(a+r)} - d_1 \end{bmatrix}.$$

Then the eigenvalues of $Df^1(\overline{E}_2)$ are $\lambda_1 = \frac{re_1(a-1)}{a(a+r)} - d_1$ and $\lambda_{2,3}$ where $\lambda_{2,3}$ are solutions to the equation $\lambda^2 + \frac{r}{a}\lambda + \frac{r}{a}(a-1) = 0$. By Routh-Hurwitz criterion, since $\frac{r}{a} > 0$ and $\frac{r}{a}(a-1) > 0$, the real parts of $\lambda_{2,3}$ are always negative. Notice that $\lambda_1 < 0$ iff $g_1(a) > 0$, $\lambda_1 = 0$ iff $g_1(a) = 0$, and $\lambda_1 > 0$ iff $g_1(a) < 0$. When $a_{31} - 4a_{21} < 0$, $g_1(a) > 0$ which implies that $\lambda_1 < 0$ and hence $\overline{E}_2$ is locally asymptotically stable. When $a_{31} - 4a_{21} = 0$, $g_1(a) = (a - \frac{1}{2}a_{31})^2$. In this case, $a_{41} = a_{51} = \frac{1}{2}a_{31}$. Since $a_{31} = 4a_{21}$, $r = \frac{4e_1d_1}{(e_1-d_1)^2}$ and so $\frac{1}{2}a_{31} = \frac{2e_1}{e_1-d_1}$. It implies that, when $a \in (1, \frac{2e_1}{e_1-d_1}) \cup (\frac{2e_1}{e_1-d_1}, \infty)$, $g_1(a) > 0$ and hence $\lambda_1 < 0$. Thus $\overline{E}_2$ is locally asymptotically stable when $a_{31} - 4a_{21} = 0$ and $\frac{2e_1}{e_1-d_1} \neq a > 1$. When $a_{31} - 4a_{21} > 0$ and $a \in (1, a_{41}) \cup (a_{51}, \infty)$, $g_1(a) > 0$ and hence $\overline{E}_2$ is locally asymptotically stable. When $a_{31} - 4a_{21} > 0$ and $a \in (a_{41}, a_{51})$, $\overline{E}_3$ comes into the domain D_1 and, since $g_1(a) < 0$, $\overline{E}_2$ is unstable.

In fact, we can show a stronger result that, when $g_1(a) \geq 0$, $\overline{E}_2$ is globally asymptotically stable. Consider the function

$$V_1(x, y, z_1) = x - x_1^* - x_1^* \ln \frac{x}{x_1^*} + \frac{r+a}{a}\left(y - y_1^* - y_1^* \ln \frac{y}{y_1^*}\right) + \frac{l_1(r+a)}{ae_1}z_1$$

where $x_1^* := \frac{1}{a}$, $y_1^* := \frac{r(a-1)}{a(a+r)}$. By computation,

$$\frac{dV_1}{dt}\Big|_{(2.2)} = -r(x - x_1^*)^2 + \frac{l_1r}{a}\left(1 - \frac{d_1}{e_1} - \frac{ad_1}{re_1} - \frac{1}{a}\right)z_1.$$

Since $g_1(a) \geq 0$, $1 - \frac{d_1}{e_1} - \frac{ad_1}{re_1} - \frac{1}{a} \leq 0$ and hence $\frac{dV_1}{dt} \leq 0$ along solutions to (2.2). If $g_1(a) < 0$, then $\frac{dV_1}{dt} = 0$ iff $x = x_1^*$ and $z_1 = 0$. It follows that the maximal compact invariant set in the set where $\frac{dV_1}{dt} = 0$ is the singleton $\{\overline{E}_2 = (x_1^*, y_1^*, 0)^T\}$. By LaSalle's principle, $\overline{E}_{21}$ is globally asymptotically stable. If $g_1(a) = 0$ then $\frac{dV_1}{dt} = 0$ iff $x = x_1^*$. Let $\mathcal{E}_1$ be the set of all points $(x, y, z_1)^T \in D_1$ such that $\frac{dV_1}{dt}\big|_{(2.2)}(x, y, z_1) = 0$. Then $\mathcal{E}_1$ is the set of points in D_1 having the form $(x_1^*, y, z_1)^T$. Let $\mathcal{M}_1$ be the set of all solutions $(x(t), y(t), z_1(t))^T$ to the system (2.2) that start in $\mathcal{E}_1$ and remain in $\mathcal{E}_1$ for all $t > 0$. Now let $(x(t), y(t), z_1(t))^T \in \mathcal{M}_1$ then $x(t) = x_1^*$ for all $t > 0$. The system (2.2) becomes

$$\begin{aligned} \frac{dx_1^*}{dt} &= [r(1 - x_1^* - y) - ay]x_1^* = 0, \\ \frac{dy}{dt} &= (ax_1^* - l_1z_1 - 1)y, \\ \frac{dz_1}{dt} &= (e_1y - d_1)z_1. \end{aligned}$$

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

The first equation implies that $r(1-x_1^*-y(t))-ay(t)=0$ for all $t>0$ and hence $y(t)=y_1^*$ for all $t>0$. By the second equation, $ax_1^*-l_1z_1(t)-1=0$ for all $t>0$ and so $z_1(t)=0$ for all $t>0$. Thus $\mathcal{M}_1=\{\overline{E}_2\}$. The LaSalle principle follows that $\overline{E}_2$ is globally asymptotically stable.

Next, we assume that $a_{31}-4a_{21}>0$ and $a\in(a_{41},a_{51})$. We claim that $\overline{E}_3$ is globally asymptotically stable. Indeed, the variational matrix of (2.2) at $\overline{E}_3$ is

$$Df^1(\overline{E}_3)=\begin{bmatrix} -r(1-\frac{d_1}{e_1}-\frac{ad_1}{re_1}) & -(r+a)(1-\frac{d_1}{e_1}-\frac{ad_1}{re_1}) & 0\\ \frac{ad_1}{e_1} & 0 & -\frac{l_1d_1}{e_1}\\ 0 & \frac{ae_1}{l_1}(1-\frac{d_1}{e_1}-\frac{ad_1}{re_1}-\frac{1}{a}) & 0\end{bmatrix}.$$

The characteristic polynomial of this matrix is given by $-p_1(\lambda)=-(\lambda^3+\overline{b}_1\lambda^2+\overline{b}_2\lambda+\overline{b}_3)$ where

$$\overline{b}_1:=r(1-\frac{d_1}{e_1}-\frac{ad_1}{re_1}),\ \overline{b}_2:=ad_1\left[\left(1+\frac{r}{e_1}+\frac{a}{e_1}\right)\left(1-\frac{d_1}{e_1}-\frac{ad_1}{re_1}\right)-\frac{1}{a}\right],\ \text{and}$$
$$\overline{b}_3:=ard_1\left(1-\frac{d_1}{e_1}-\frac{ad_1}{re_1}\right)\left(1-\frac{d_1}{e_1}-\frac{ad_1}{re_1}-\frac{1}{a}\right).$$

Since $a\in(a_{41},a_{51})$, $\overline{b}_1>0$, $\overline{b}_2>0$, and $\overline{b}_3>0$. Furthermore, by computation,

$$\overline{b}_1\overline{b}_2-\overline{b}_3=ard_1\left(1-\frac{d_1}{e_1}-\frac{ad_1}{re_1}\right)^2\left(\frac{r}{e_1}+\frac{a}{e_1}\right)>0.$$

All the roots of $p_1(\lambda)$ always have negative real parts. Hence $\overline{E}_3$ is locally asymptotically stable. Next, consider the function

$$V_2(x,y,z_1)=x-x_2^*-x_2^*\ln\frac{x}{x_2^*}+\frac{r+a}{a}\left(y-y_2^*-y_2^*\ln\frac{y}{y_2^*}\right)+\frac{l_1(r+a)}{ae_1}\left(z_1-z_1^*-z_1^*\ln\frac{z_1}{z_1^*}\right)$$

where $x_2^*:=1-\frac{d_1}{e_1}-\frac{ad_1}{re_1}$, $y_2^*:=\frac{d_1}{e_1}$, and $z_1^*:=\frac{a}{l_1}(1-\frac{d_1}{e_1}-\frac{ad_1}{re_1}-\frac{1}{a})$. By computation,

$$\frac{dV_2}{dt}\Big|_{(2.2)}=-r(x-x_2^*)^2\le 0.$$

Then $\frac{dV_2}{dt}\big|_{(2.2)}=0$ iff $x=x_2^*$. Let $\mathcal{E}_2$ be the set of all points $(x,y,z_1)^T\in D_1$ such that $\frac{dV_2}{dt}\big|_{(2.2)}(x,y,z_1)=0$. Then $\mathcal{E}_2$ is the set of points in D_1 having the form $(x_2^*,y,z_1)^T$. Let $\mathcal{M}_2$ be the set of all solutions $(x(t),y(t),z_1(t))^T$ to the system (2.2) that start in $\mathcal{E}_2$ and remain in $\mathcal{E}_2$ for all $t>0$. Now let $(x(t),y(t),z_1(t))^T\in\mathcal{M}$ then $x(t)=x_2^*$ for all $t>0$. The system (2.2) becomes

$$\frac{dx_2^*}{dt}=[r(1-x_2^*-y)-ay]x_2^*=0,$$
$$\frac{dy}{dt}=(ax_2^*-l_1z_1-1)y,$$
$$\frac{dz_1}{dt}=(e_1y-d_1)z_1.$$

The first equation implies that $r(1-x_2^*-y(t))-ay(t)=0$ for all $t>0$ and hence $y(t)=y_2^*$ for all $t>0$. By the second equation, $ax_2^*-l_1z_1(t)-1=0$ for all $t>0$ and so $z_1(t)=z_1^*$ for all $t>0$. Thus $\mathcal{M}_2=\{\overline{E}_3\}$. The LaSalle principle follows that $\overline{E}_3$ is globally asymptotically stable. Hence, combining Section 3.2, Theorem 2.1 is proved.

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

3.4. Stability of $\widetilde{E}_2$ and $\widetilde{E}_4$

In this subsection, we study the subsystem (2.3).

We assume that $\frac{d_2}{e_2} < \frac{d_1}{e_1}$. Then the solution component z_1 of the system (2.1) decays to 0 exponentially fast. Studying the behavior of the system (2.1) is equivalent to studying the behavior of the reduced system (2.3). Now fix all parameters except $a > 1$ and we will examine the behaviors of equilibria $\widetilde{E}_2$ and $\widetilde{E}_4$ as a is varied. Denote $U_2 = (x, y, z_2)^T$ and $f^2(U_2) = (rx(1-x-y) - axy - l_2xz_2, axy - y, e_2yz_2 - d_2z_2)^T$. Then the variational matrix of (2.3) at $\widetilde{E}_2$ is

$$Df^2(\widetilde{E}_2) = \begin{bmatrix} -\frac{r}{a} & -\frac{r}{a} - 1 & -\frac{l_2}{a} \\ \frac{r(a-1)}{a+r} & 0 & 0 \\ 0 & 0 & \frac{e_2 r(a-1)}{a(a+r)} - d_2 \end{bmatrix}.$$

By the same argument as in the case $\frac{d_1}{e_1} < \frac{d_2}{e_2}$, when $a_{32} < 4a_{22}$ or $a_{32} = 4a_{22}$, $a \in (1, \frac{2e_2}{e_2 - d_2}) \cup (\frac{2e_2}{e_2 - d_2}, \infty)$ or $a_{32} > 4a_{22}$, $a \in (1, a_{42}) \cup (a_{52}, \infty)$, $\widetilde{E}_2$ is locally asymptotically stable. In fact, we can claim that $\widetilde{E}_2$ is globally asymptotically stable under one of these assumptions, which is equivalent to $\frac{d_2}{e_2} - \frac{r(a-1)}{a(a+r)} > 0$. Indeed, by comparison theorem for ODEs, since $l_2xz_2 \geq 0$, the first equation of (2.3) implies $\frac{dx}{dt} \leq rx(1-x-y) - axy$. Let $(\tilde{x}(t), \tilde{y}(t), \tilde{z}_2(t))$ be the solution to

$$\begin{aligned} \frac{dx}{dt} &= rx(1-x-y) - axy, \\ \frac{dy}{dt} &= axy - y, \\ \frac{dz_2}{dt} &= e_2yz_2 - d_2z_2, \end{aligned} \tag{3.9}$$

with initial condition $\tilde{x}(0) = x(0) > 0$, $\tilde{y}(0) = y(0) > 0$, $\tilde{z}_2(0) = z_2(0)$, and $\tilde{x}(0) + \tilde{y}(0) < 1$. Then $x(t) \leq \tilde{x}(t)$ and so, by the second equation of (2.3), $y(t) \leq \tilde{y}(t)$. Using the Lyapunov function

$$V_3(\tilde{x}, \tilde{y}) = \tilde{x} - x_1^* - x_1^* \ln \frac{\tilde{x}}{x_1^*} + \frac{r+a}{a}\left(\tilde{y} - y_1^* - y_1^* \ln \frac{\tilde{y}}{y_1^*}\right)$$

and LaSalle's principle, we can easily show that $(\tilde{x}(t), \tilde{y}(t)) \to (x_1^*, y_1^*)$ as $t \to \infty$. Then, for all $0 < \epsilon < \frac{d_2}{e_2} - \frac{r(a-1)}{a(a+r)}$, there is a $T > 0$ such that $t \geq T$ implies $|\tilde{y}(t) - y_1^*| < \epsilon$. So the third equation of (3.9) implies

$$\begin{aligned} \frac{d\tilde{z}_2}{dt} &= \left[e_2(\tilde{y}(t) - y_1^*) + \frac{e_2 r(a-1)}{a(a+r)} - d_2\right]\tilde{z}_2 \\ &\leq \left[e_2\left(\frac{r(a-1)}{a(a+r)} + \epsilon\right) - d_2\right]\tilde{z}_2 \end{aligned}$$

which follows that

$$0 \leq \tilde{z}_2(t) \leq \tilde{z}_2(T) \exp\left\{\left[e_2\left(\frac{r(a-1)}{a(a+r)} + \epsilon\right) - d_2\right](t-T)\right\}.$$

Thus $\tilde{z}_2(t) \to 0$ as $t \to \infty$. By the third equation of (2.3), since $y(t) \leq \tilde{y}(t)$, $0 \leq z_2(t) \leq \tilde{z}_2(t)$ and, therefore, $z(t) \to 0$ as $t \to \infty$. Then, for any $\epsilon > 0$, there exists a $\overline{T} > 0$ such that $0 < z_2(t) < \epsilon$ for all $t \geq \overline{T}$. The first equation of (2.3) follows $\frac{dx}{dt} \geq rx(1-x-y) - axy - l_2\epsilon x$. Let $(\tilde{x}_\epsilon(t), \tilde{y}_\epsilon(t), \tilde{z}_{2\epsilon}(t))$ be the solution to

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

$$\begin{aligned}\frac{dx}{dt} &= rx(1-x-y) - axy - l_2\epsilon x,\\ \frac{dy}{dt} &= axy - y,\\ \frac{dz_2}{dt} &= e_2yz_2 - d_2z_2,\end{aligned} \tag{3.10}$$

with initial condition $\tilde{x}_\epsilon(0) = x(0) > 0$, $\tilde{y}_\epsilon(0) = y(0) > 0$, $\tilde{z}_{2\epsilon}(0) = z_2(0)$, and $\tilde{x}_\epsilon(0) + \tilde{y}_\epsilon(0) < 1$. Let $x^*_{1\epsilon} = \frac{1}{a}$ and $y^*_{1\epsilon} = \frac{r(a-1)}{a(a+r)} - l_2\epsilon$. Using the Lyapunov function

$$V_4(\tilde{x}_\epsilon, \tilde{y}_\epsilon) = \tilde{x}_\epsilon - x^*_{1\epsilon} - x^*_{1\epsilon}\ln\frac{\tilde{x}_\epsilon}{x^*_{1\epsilon}} + \frac{r+a}{a}\left(\tilde{y}_\epsilon - y^*_{1\epsilon} - y^*_{1\epsilon}\ln\frac{\tilde{y}_\epsilon}{y^*_{1\epsilon}}\right)$$

and LaSalle's principle, we can easily show that $(\tilde{x}_\epsilon(t), \tilde{y}_\epsilon(t)) \to (x^*_{1\epsilon}, y^*_{1\epsilon})$ as $t \to \infty$. It is straightforward that $\tilde{x}_\epsilon(t) \le x(t) \le \tilde{x}(t)$, $\tilde{y}_\epsilon(t) \le y(t) \le \tilde{y}(t)$, and $\tilde{z}_{2\epsilon}(t) \le z_2(t) \le \tilde{z}_2(t)$. Letting $t \to \infty$ and then $\epsilon \to 0$, we obtain $(x(t), y(t), z_2(t)) \to (x^*_1, y^*_1, 0)$ as $t \to \infty$ for any initial condition $(x(0), y(0), z_2(0)) \in D_2^\circ$.

When $a_{32} > 4a_{22}$ and $a \in (a_{42}, a_{52})$, $\widetilde{E}_2$ is unstable and $\widetilde{E}_4$ moves into the invariant domain D_2. The variational matrix of (2.3) at $\widetilde{E}_4$ is

$$Df^2(\widetilde{E}_4) = \begin{bmatrix} -\frac{r}{a} & -\frac{r}{a} - 1 & -\frac{l_2}{a} \\ \frac{ad_2}{e_2} & 0 & 0 \\ 0 & \frac{re_2}{l_2}(1 - \frac{d_2}{e_2} - \frac{ad_2}{re_2} - \frac{1}{a}) & 0 \end{bmatrix}.$$

The corresponding characteristic polynomial is given by $-p_2(\lambda) = -(\lambda^3 + \tilde{b}_1(a)\lambda^2 + \tilde{b}_2(a)\lambda + \tilde{b}_3(a))$ where

$$\tilde{b}_1 := \tilde{b}_1(a) = \frac{r}{a},\ \tilde{b}_2 := \tilde{b}_2(a) = \frac{ad_2}{e_2}\left(\frac{r}{a} + 1\right),\ \text{and } \tilde{b}_3 := \tilde{b}_3(a) = rd_2\left(1 - \frac{d_2}{e_2} - \frac{ad_2}{re_2} - \frac{1}{a}\right).$$

Since $a \in (a_{42}, a_{52})$, $\tilde{b}_1 > 0$, $\tilde{b}_2 > 0$, and $\tilde{b}_3 > 0$. Since $\tilde{b}_3 \gtrless 0$, $p_2(0) > 0$ and so $p_2(\lambda)$ has at least one negative real root, say $\tilde{\lambda}_0 < 0$. Let $\tilde{\lambda}(a) := \tilde{\alpha}(a) + i\tilde{\beta}(a)$ and $\overline{\tilde{\lambda}(a)}$ be the two remaining roots of $p_2(\lambda)$. Then the eigenvalues of the variational matrix $Df^2(\widetilde{E}_4)$ are $\tilde{\lambda}_0$, $\tilde{\lambda}(a)$, and $\overline{\tilde{\lambda}(a)}$. By computation,

$$\tilde{b}_1\tilde{b}_2 - \tilde{b}_3 = rd_2\left(1 + \frac{r}{e_2} + \frac{a}{e_2}\right)\left(\frac{1}{a} - x^*\right)$$

where $x^* := \frac{1 - \frac{d_2}{e_2} - \frac{ad_2}{re_2}}{1 + \frac{r}{e_2} + \frac{a}{e_2}}$. Clearly, $x^* < 1 - \frac{d_2}{e_2} - \frac{ad_2}{re_2}$ for all $a \in (a_{42}, a_{52})$. By Routh-Hurwitz's criterion, $\tilde{b}_1\tilde{b}_2 - \tilde{b}_3 < 0$ iff $x^* > \frac{1}{a}$ iff $\tilde{\alpha}(a) > 0$, $\tilde{b}_1\tilde{b}_2 - \tilde{b}_3 = 0$ iff $x^* = \frac{1}{a}$ iff $\tilde{\alpha}(a) = 0$, and $\tilde{b}_1\tilde{b}_2 - \tilde{b}_3 > 0$ iff $x^* < \frac{1}{a}$ iff $\tilde{\alpha}(a) < 0$. Let $h_2(a) := a^2 - r(\frac{e_2}{d_2} - \frac{1}{d_2} - 1)a + \frac{re_2}{d_2} + \frac{r^2}{d_2}$. It is easy to see that $h_2(a) < 0$ iff $x^* > \frac{1}{a}$, $h_2(a) = 0$ iff $x^* = \frac{1}{a}$, and $h_2(a) > 0$ iff $x^* < \frac{1}{a}$. Since a is varied between a_{42} and a_{52}, $\widetilde{E}_4$ depends on a. So in order to investigate the behavior of $\widetilde{E}_4$ we need to study how the sign of $\tilde{b}_1\tilde{b}_2 - \tilde{b}_3$ changes as a changes between a_{42} and a_{52}. Let $\delta_2 := r^2\left(\frac{e_2}{d_2} - \frac{1}{d_2} - 1\right)^2 - 4\left(\frac{re_2}{d_2} + \frac{r^2}{d_2}\right)$. Consider 2 cases. (i) If $e_2 \le d_2 + 1$ then $h_2(a) > 0$ for all $a \in (a_{42}, a_{52})$ which implies that $x^* < \frac{1}{a}$ and hence $\tilde{b}_1\tilde{b}_2 - \tilde{b}_3 > 0$. So $\widetilde{E}_4$ is locally asymptotically stable. (ii) If $e_2 > d_2 + 1$ then $\frac{e_2}{d_2} - \frac{1}{d_2} - 1 > 0$ and let's look at the discriminant δ_2 of $h_2(a)$. When $\delta_2 < 0$, $h_2(a) > 0$ for all $a \in (a_{42}, a_{52})$ which follows that $x^* < \frac{1}{a}$ and hence $\widetilde{E}_4$ is locally asymptotically stable. When $\delta_2 = 0$, then $r = \frac{4e_2d_2}{(e_2-d_2-1)^2-4d_2}$ and so $h_2(a) = (a - \overline{a})^2$ where $\overline{a} := \frac{2e_2(e_2-d_2-1)}{(e_2-d_2-1)^2-4d_2}$. It is clear to see that $\overline{a} \in (a_{42}, a_{52})$. Hence $h_2(a) > 0$ for all $a \in (a_{42}, \overline{a}) \cup (\overline{a}, a_{52})$. In this case, $\widetilde{E}_4$ is locally asymptotically stable for any $a \in (a_{42}, a_{52})$ except $a = \overline{a}$. When $\delta_2 > 0$, $h_2(a)$ has two distinct real roots

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

$$a_{62,72} := \frac{1}{2}r\left(\frac{e_2}{d_2} - \frac{1}{d_2} - 1\right) \mp \frac{1}{2}\sqrt{\delta_2}.$$

It is straightforward that $a_{42} < a_{62} < a_{72} < a_{52}$. If $a \in (a_{42}, a_{62}) \cup (a_{72}, a_{52})$ then $h_2(a) > 0$ which implies that $\tilde{\alpha}(a) < 0$, hence $\widetilde{E}_4$ is locally asymptotically stable. If $a \in (a_{62}, a_{72})$ then $h_2(a) < 0$ which follows that $\tilde{\alpha}(a) > 0$, thus $\widetilde{E}_4$ is unstable. When either $a = a_{62}$ or $a = a_{72}$, $h_2(a) = 0$ and so $\tilde{\alpha}(a) = 0$. We have shown that as a passes through a_{62}, $\tilde{\alpha}(a)$ changes its sign from negative to positive and, as a passes through a_{72}, $\tilde{\alpha}(a)$ changes its sign from positive to negative. Furthermore, using Lemma 3.11 and Theorem 3.12 in [35], we can show that $\tilde{\alpha}'(a_{62}) \neq 0$ and $\tilde{\alpha}'(a_{72}) \neq 0$. Hence, Hopf bifurcation arises from $\widetilde{E}_4$ at $a = a_{62}$ and $a = a_{72}$. Therefore, combining Section 3.2, the proof of Theorem 2.2 is completed.

3.5. Stability of E_2 and manifold of equilibria M

In this subsection, we study the full system, particularly, the stability of the equilibrium solution E_2 and the manifold of equilibria M, and show the system undergoes the Poincare-Andronov-Hopf bifurcation without parameters.

We assume that $\frac{d_1}{e_1} = \frac{d_2}{e_2} =: \frac{d}{e}$. We first look at the stability of the equilibrium E_2. Then the variational matrix of the system (2.1) at this equilibrium is

$$Df(E_2) = \begin{bmatrix} -\frac{r}{a} & -\frac{r}{a} - 1 & 0 & -\frac{l_2}{a} \\ \frac{r(a-1)}{a+r} & 0 & -\frac{l_1 r(a-1)}{a(a+r)} & 0 \\ 0 & 0 & \frac{e_1 r(a-1)}{a(a+r)} - d_1 & 0 \\ 0 & 0 & 0 & \frac{e_2 r(a-1)}{a(a+r)} - d_2 \end{bmatrix}.$$

The characteristic polynomial is given by

$$\left[\frac{re_1(a-1)}{a(a+r)} - d_1 - \lambda\right]\left[\frac{re_2(a-1)}{a(a+r)} - d_2 - \lambda\right]\left(\lambda^2 + \frac{r}{a}\lambda + \frac{r}{a}(a-1)\right).$$

Then the eigenvalues of $Df(E_2)$ are $\lambda_{1,2} = \frac{re_{1,2}(a-1)}{a(a+r)} - d_{1,2}$ and $\lambda_{3,4}$ where $\lambda_{3,4}$ are solutions to the equation $\lambda^2 + \frac{r}{a}\lambda + \frac{r}{a}(a-1) = 0$. By Routh-Hurwitz criterion, since $\frac{r}{a} > 0$ and $\frac{r}{a}(a-1) > 0$, the real parts of $\lambda_{3,4}$ are always negative. Notice that the sign of $\lambda_{1,2}$ is the opposite to that of the quadratic function $g(a) := a^2 - r(\frac{e}{d} - 1)a + \frac{re}{d}$. There are four cases.

Case 1. $a_3 - 4a_2 < 0$. Then $g(a) > 0$, which is equivalent to $\lambda_{1,2} < 0$. Hence E_2 is locally asymptotically stable.

Case 2. $a_3 - 4a_2 = 0$. Then $g(a) = (a - \frac{1}{2}a_3)^2$. Notice that, in this case, $a_4 = a_5 = \frac{1}{2}a_3$. Since $a_3 = 4a_2$, $r = \frac{4ed}{(e-d)^2}$ and so $\frac{1}{2}a_3 = \frac{2e}{e-d}$. It implies that, when $a \in (1, \frac{2e}{e-d}) \cup (\frac{2e}{e-d}, \infty)$, $g(a) > 0$ and hence $\lambda_{1,2} < 0$. Thus E_2 is locally asymptotically stable when $\frac{2e}{e-d} \neq a > 1$.

Case 3. $a_3 - 4a_2 > 0$ and $a \in (1, a_4) \cup (a_5, \infty)$. There is no new equilibrium point that moves into the domain D and $g(a) > 0$. Hence E_2 is locally asymptotically stable.

By the same arguments as in proving the global stability of $\tilde{E}_2$, in three cases above, we can show that E_2 is globally asymptotically stable.

Case 4. $a_3 - 4a_2 > 0$ and $a \in (a_4, a_5)$. A line segment of equilibria $E_5(\xi)$, $\xi \in [\frac{1}{a}, 1 - \frac{d}{e} - \frac{ad}{re}]$, moves into the domain D and $g(a) < 0$, which implies that E_2 is unstable.

Finally, we study the stability of the line segment of equilibria $E_5(\xi)$ under the assumptions that $a_3 - 4a_2 > 0$ and $a \in (a_4, a_5)$. Consider the manifold of equilibria

$$M := \left\{E_5(\xi) : \xi \in \left[\frac{1}{a}, 1 - \frac{d}{e} - \frac{ad}{re}\right]\right\}.$$

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

From the last two equations of (2.1), since $\frac{d_1}{e_1} = \frac{d_2}{e_2}$, we get $\frac{dz_2}{z_2} = \rho\frac{dz_1}{z_1}$ where $\rho := \frac{e_2}{e_1}$, which implies that $z_2 = kz_1^\rho$ for some constant $k \geq 0$. These equations $z_2 = kz_1^\rho$ represent invariant hypersurfaces (3 dimensional manifolds) of the system (2.1) for arbitrary nonnegative constant k. Clearly, these hypersurfaces foliate completely the positive invariant domain D, that is, through each point in D there passes one and only one hypersurface of the family $z_2 = kz_1^\rho$. For each value of k, consider the restriction of the system (2.1) to the invariant hypersurface parameterized by x, y, z_1.

$$\begin{aligned}
\frac{dx}{dt} &= rx(1-x-y) - axy - kl_2xz_1^\rho,\\
\frac{dy}{dt} &= axy - l_1yz_1 - y,\\
\frac{dz_1}{dt} &= e_1yz_1 - d_1z_1.
\end{aligned} \tag{3.11}$$

The positive invariant domain of the reduced system (3.11) is also denoted by

$$D = \{(x, y, z_1) : x \geq 0, y \geq 0, z_1 \geq 0, x + y \leq 1\}.$$

Let $\xi \in \left[\frac{1}{a}, 1 - \frac{d}{e} - \frac{ad}{re}\right]$ such that $E_5(\xi) = M \cap \{z_2 = kz_1^\rho\}$. Then ξ is a unique solution to

$$\frac{r}{l_2}\left(1 - \frac{d}{e} - \frac{ad}{re} - \xi\right) = k\left(\frac{a\xi - 1}{l_1}\right)^\rho. \tag{3.12}$$

It is straightforward to see that ξ depends continuously on k. If there is no danger of confusion, the short notation $\xi := \xi(k)$ will be used. Notice that $\xi(k) \in [\frac{1}{a}, 1 - \frac{d}{e} - \frac{ad}{re}]$ for any value of $k \geq 0$. Furthermore, $\lim_{k\to 0}\xi(k) = 1 - \frac{d}{e} - \frac{ad}{re}$ and $\lim_{k\to\infty}\xi(k) = \frac{1}{a}$. It can be shown from (3.12) that the value of $\xi = \xi(k)$ decreases from $1 - \frac{d}{e} - \frac{ad}{re}$ to $\frac{1}{a}$ as k increases from 0 to ∞.

The unique positive equilibrium of the reduced system (3.11) is also denoted by

$$E_5(\xi) = \left(\xi, \frac{d}{e}, \frac{a\xi - 1}{l_1}\right)^T,$$

where $\xi \in (\frac{1}{a}, 1 - \frac{d}{e} - \frac{ad}{re})$. In order to study the behavior of $E_5(\xi)$, we fix all parameters with $a \in (a_4, a_5)$ and allow the constant $k \in (0, \infty)$ to vary. We also denote $U = (x, y, z_1)^T$ and $f(U) = (rx(1-x-y) - axy - kl_2xz_1^\rho, axy - l_1yz_1 - y, e_1yz_1 - d_1z_1)^T$. Then the variational matrix of the system (3.11) at $E_5(\xi)$ is

$$Df(E_5(\xi)) = \begin{bmatrix} -r\xi & -r\xi - a\xi & -kl_2\rho\xi(\frac{a\xi-1}{l_1})^{\rho-1} \\ \frac{ad}{e} & 0 & -\frac{l_1d}{e} \\ 0 & \frac{e_1}{l_1}(a\xi - 1) & 0 \end{bmatrix}.$$

The characteristic equation of this matrix is equivalent to $p(\lambda) := \lambda^3 + b_1(\xi)\lambda^2 + b_2(\xi)\lambda + b_3(\xi) = 0$ where

$$\begin{aligned}
b_1 := b_1(\xi) &= r\xi,\ b_2 := b_2(\xi) = d_1(a\xi - 1) + \frac{ad}{e}(r + a)\xi,\\
b_3 := b_3(\xi) &= rd_1\xi(a\xi - 1) + ad_1\rho\xi kl_2\left(\frac{a\xi - 1}{l_1}\right)^\rho.
\end{aligned}$$

Since $\xi \in (\frac{1}{a}, 1 - \frac{d}{e} - \frac{ad}{re})$, we get $b_1(\xi) > 0$, $b_2(\xi) > 0$, and $b_3(\xi) > 0$. By computation, we obtain

$$b_1b_2 - b_3 = ard_1\xi\left[\left(\frac{r}{e_1} + \frac{a}{e_1}\right)\xi - \rho\frac{kl_2}{r}\left(\frac{a\xi - 1}{l_1}\right)^\rho\right]$$

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

Using (3.12), we get

$$\frac{kl_2}{r}\left(\frac{a\xi-1}{l_1}\right)^{\rho} = 1-\frac{d}{e}-\frac{ad}{re}-\xi.$$

Thus

$$b_1b_2-b_3 = ard_1\xi\rho\left[\left(1+\frac{r}{\rho e_1}+\frac{a}{\rho e_1}\right)\xi-\left(1-\frac{d}{e}-\frac{ad}{re}\right)\right].$$

Let $\xi^* := \dfrac{1-\frac{d}{e}-\frac{ad}{re}}{1+\frac{r}{\rho e_1}+\frac{a}{\rho e_1}}$. Notice that $\xi^* < 1-\frac{d}{e}-\frac{ad}{re}$ for any $a \in (a_4, a_5)$ and

$$b_1b_2-b_3 = ard_1\xi\rho\left(1+\frac{r}{\rho e_1}+\frac{a}{\rho e_1}\right)(\xi-\xi^*).$$

Thus $b_1b_2-b_3 < 0$ iff $\xi < \xi^*$, $b_1b_2-b_3 = 0$ iff $\xi = \xi^*$, and $b_1b_2-b_3 > 0$ iff $\xi > \xi^*$. Since $b_3 > 0$, $p(0) > 0$ and hence $p(\lambda)$ has at least one negative real root, say λ_0. Let $\lambda(\xi) = \alpha(\xi) + i\beta(\xi)$ and $\overline{\lambda(\xi)}$ be the two remaining roots of $p(\lambda)$. Then eigenvalues of the variational matrix $Df(E_5(\xi))$ are $\lambda_0 < 0$, $\lambda(\xi)$, and $\overline{\lambda(\xi)}$. Let $h(a) = a^2 - r(\frac{e}{d} - \frac{1}{\rho d_1} - 1)a + \frac{re}{d} + \frac{r^2}{\rho d_1}$, then it is straightforward to see that $h(a) < 0$ iff $\xi^* > \frac{1}{a}$, $h(a) = 0$ iff $\xi^* = \frac{1}{a}$, and $h(a) > 0$ iff $\xi^* < \frac{1}{a}$. In order to investigate the behavior of the equilibrium $E_5(\xi)$, we need to study how the sign of $b_1b_2-b_3$ changes as ξ decreases from $1-\frac{d}{e}-\frac{ad}{re}$ to $\frac{1}{a}$. This requires us to look into the sign of the quadratic function $h(a)$. We consider the following cases.

Case 1. $\frac{e}{d} \le \frac{1}{\rho d_1} + 1$. Then $\frac{e}{d} - \frac{1}{\rho d_1} - 1 \le 0$ and it implies that $h(a) > 0$ for all $a \in (a_4, a_5)$, which is equivalent to $\xi^* < \frac{1}{a}$. Since $\xi \in (\frac{1}{a}, 1-\frac{d}{e}-\frac{ad}{re})$, $\xi > \xi^*$. This follows that $b_1b_2-b_3 > 0$. By Routh-Hurwitz's criterion and Lemma 3.10 in [35], $\alpha(\xi) < 0$. So $E_5(\xi)$ is locally asymptotically stable. Because this is true for each value of $k \in (0, \infty)$, thus $M^\circ := \{E_5(\xi) : \xi \in (\frac{1}{a}, 1-\frac{d}{e}-\frac{ad}{re})\}$ is locally stable in the sense that any solution of the system (2.1) starting sufficiently close to any point $E_5(\xi)$ on M° will approach a point near $E_5(\xi)$ on M° (see [4] or [26]).

Case 2. $\frac{e}{d} > \frac{1}{\rho d_1} + 1$. This follows that $\frac{e}{d} - \frac{1}{\rho d_1} - 1 > 0$. Let us look at the discriminant of the quadratic $h(a)$, which is

$$\delta := r^2\left(\frac{e}{d}-\frac{1}{\rho d_1}-1\right)^2 - 4\left(\frac{re}{d}+\frac{r^2}{\rho d_1}\right).$$

There are two cases.

- If $\delta \le 0$ then $h(a) \ge 0$ for all $a \in (a_4, a_5)$, which is equivalent to $\xi^* \le \frac{1}{a}$. The same argument as in Case 1 shows that M° is locally stable.
- If $\delta > 0$ then $h(a)$ has two positive roots $a_{6,7} = \frac{1}{2}r(\frac{e}{d} - \frac{1}{\rho d_1} - 1) \mp \frac{1}{2}\sqrt{\delta}$. Notice that $a_4 < a_6 < a_7 < a_5$. When $a \in (a_4, a_6) \cup (a_7, a_5)$, $h(a) > 0$ which follows that $\xi^* < \frac{1}{a}$. By the same argument as in Case 1, $E_5(\xi)$ is locally asymptotically stable and hence M° is locally stable. When $a \in (a_6, a_7)$, $h(a) < 0$ which implies that $\xi^* > \frac{1}{a}$. So $\xi^* \in (\frac{1}{a}, 1-\frac{d}{e}-\frac{ad}{re})$. By Routh-Hurwitz's criterion and Lemma 3.10 in [35], $b_1b_2-b_3 < 0$ if $\frac{1}{a} < \xi < \xi^*$, $b_1b_2-b_3 = 0$ if $\xi = \xi^*$, and $b_1b_2-b_3 > 0$ if $\xi^* < \xi < 1-\frac{d}{e}-\frac{ad}{re}$. Thus the real part $\alpha(\xi)$ of the complex roots of the polynomial $f(\lambda)$ changes sign when ξ passes through ξ^*. On the other hand, use the standard argument as Lemma 3.11 and Theorem 3.12 in [35], we can easily show that $\alpha'(\xi^*) \ne 0$. Therefore the system (2.1) undergoes the Poincare-Andronov-Hopf bifurcation without parameters (see Theorem 5.1 in [23]). Combining Section 3.2, we complete the proof of Theorem 2.3.

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

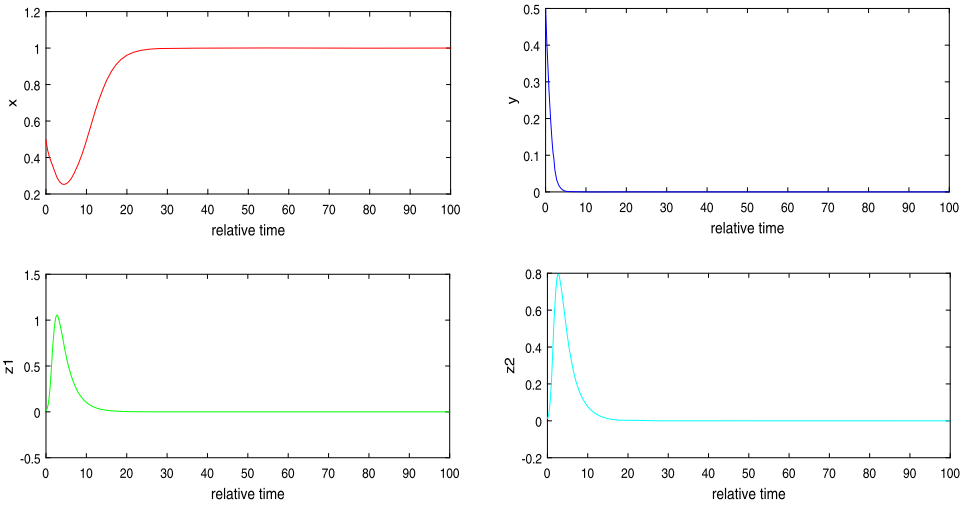

Fig. 1. Dynamics of the system (2.1) when $a = 0.75$ and initial values are $x = 0.5$, $y = 0.5$, $z_1 = 0.01$, and $z_2 = 0.01$.

4. Numerical simulation and discussion

4.1. Numerical simulation and medical interpretations

In this section, we conduct numerical simulations based on the non-dimensionalized system (2.1) to demonstrate the complete picture of the dynamics of the proposed model. The data of parameter values are taken from our previous research (see Table 1 in [36] and in [29]). After non-dimensionalization, we fix parameter values of the system (2.1) are $r = 0.36$, $l_1 = 0.48$, and $l_2 = 0.48$. The parameter a and two ratios $\frac{d_1}{e_1}$ and $\frac{d_2}{e_2}$ are adjusted to demonstrate the analytical results in Theorem 2.1, Theorem 2.2, and Theorem 2.3. Notice that the unit of uninfected tumor cells, infected tumor cells, innate and adaptive immune cells are not absolute numbers but relative numbers. The quantities such that x, y, z_1, and z_2 are, respectively, the portion of uninfected tumor cells, infected tumor cells, innate and adaptive immune cells over the tumor carrying capacity. We indicate them as relative uninfected tumor cells and so on in all the figures. For the time, it can be regarded as relative time since $T = \delta t$. Now we consider 3 cases.

Case 1. We demonstrate the situation when adaptive immunity gets stimulated less by infected tumor cells and gets cleared more than innate immunity. We take $d_1 = 0.36$, $e_1 = 10$, $d_2 = 0.36$, and $e_2 = 9.5$. Then $\frac{d_1}{e_1} < \frac{d_2}{e_2}$ and adaptive immune cells decay to 0 very quickly. By computation, we found $a_{21} = 1.0373$ and $a_{31} = 9.64$ which verify the condition $a_{31} - 4a_{21} > 0$. Then we can compute $a_{41} = 1.1824$ and $a_{51} = 8.4576$. In this case, we simulate the trajectories of the system (2.1) with the same initial value $(0.5, 0.5, 0.01, 0.01)$ and different values of the parameter a. When $a = 0.75$, that is, $0 < a < 1$, Fig. 1 shows the equilibrium $E_1 = (1, 0, 0, 0)$ is globally asymptotically stable. When a is increased to 1.1, which is $1 < a < a_{41}$, Fig. 2 shows the equilibrium $E_2 = (0.9091, 0.0224, 0, 0)$ is globally asymptotically stable. When $a = 5$, which is $a_{41} < a < a_{51}$, Fig. 3 shows globally asymptotical stability of the equilibrium $E_3 = (0.464, 0.036, 2.75, 0)$. With $a = 9$, Fig. 4 shows the equilibrium $E_2 = (0.1111, 0.0342, 0, 0)$ is globally asymptotically stable. The pattern is quite clear: as infectivity rate a decreases, the tumor grows fast; as infectivity rate a increases, the tumor grows slower. In particular, with a large value $a = 9$, the tumor load decreases in size for a long period of time.

Case 2. We demonstrate the situation when innate immune response gets stimulated less by infected tumor cells and gets cleared more than adaptive immune response, that is, $\frac{d_2}{e_2} < \frac{d_1}{e_1}$. Then innate immune cell population approaches 0 as time goes by. We take $d_1 = 0.36$, $e_1 = 9$, $d_2 = 0.36$, and $e_2 = 9.5$. By computation, we found $a_{22} = 1.0394$, $a_{32} = 9.14$, $a_{42} = 1.1958$, and $a_{52} = 7.9442$. Since $\delta_2 > 0$, we can compute $a_{62} = 1.4806$ and $a_{72} = 6.6594$. In this case, we simulate the trajectories of the system (2.1) with

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

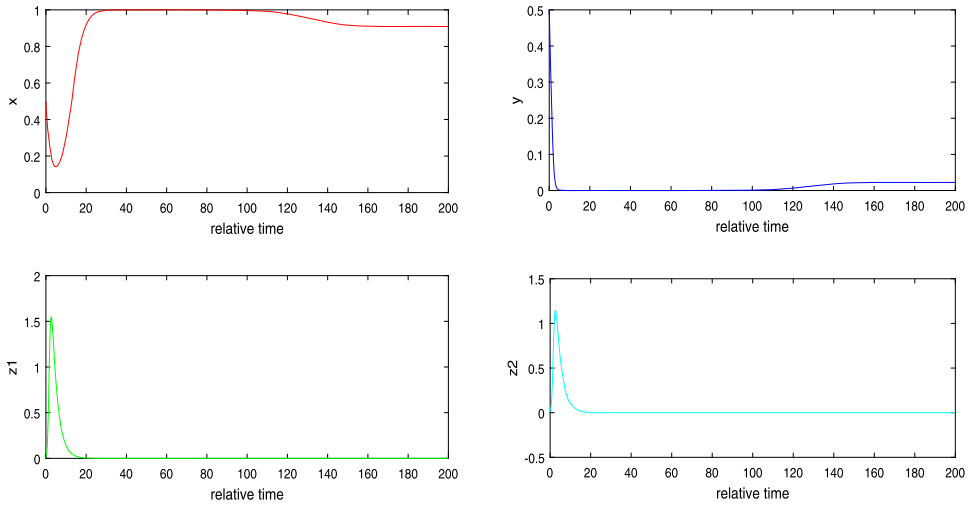

Fig. 2. Dynamics of the system (2.1) when $a = 1.1$ and initial values are $x = 0.5$, $y = 0.5$, $z_1 = 0.01$, and $z_2 = 0.01$.

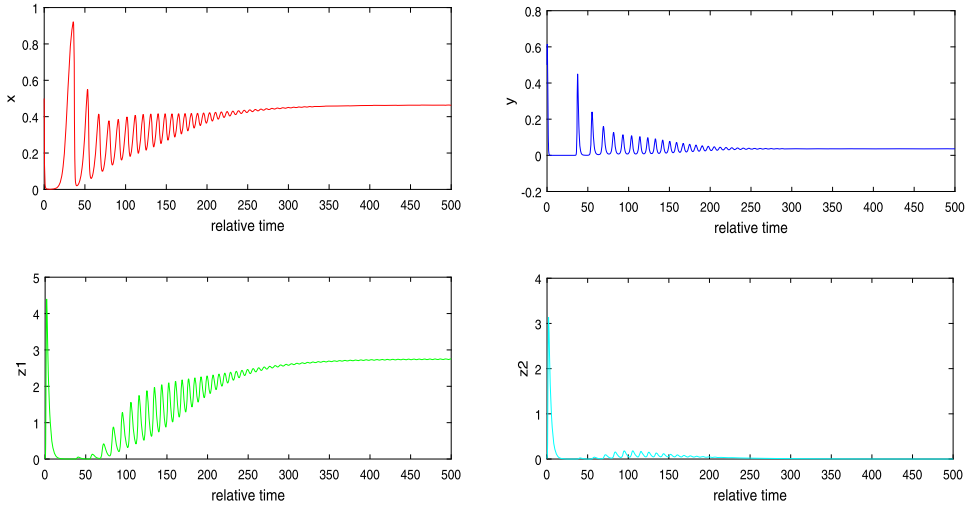

Fig. 3. Dynamics of the system (2.1) when $a = 5$ and initial values are $x = 0.5$, $y = 0.5$, $z_1 = 0.01$, and $z_2 = 0.01$.

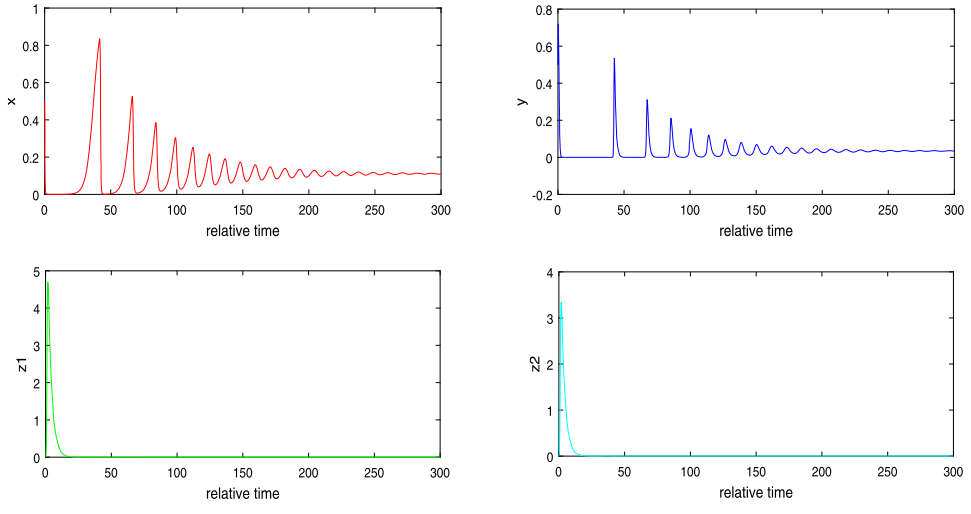

Fig. 4. Dynamics of the system (2.1) when $a = 9$ and initial values are $x = 0.5$, $y = 0.5$, $z_1 = 0.01$, and $z_2 = 0.01$.

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

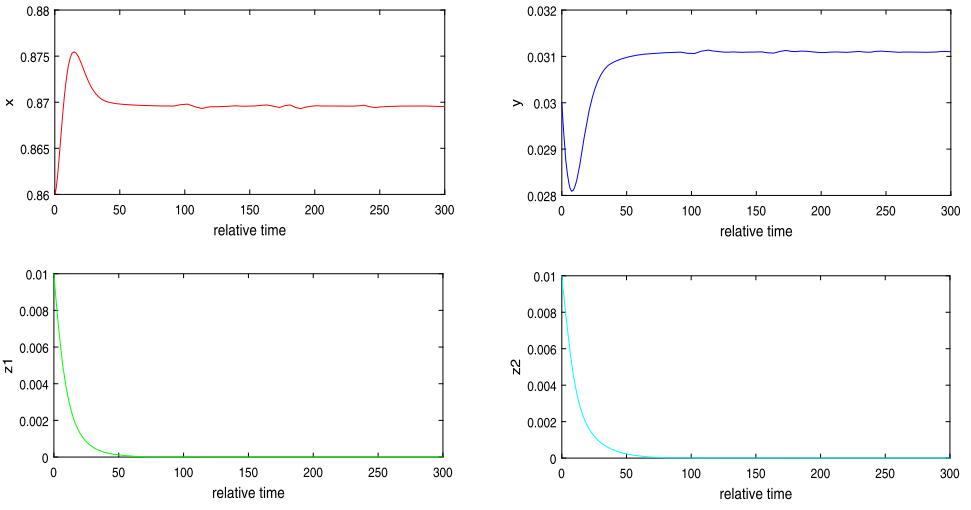

Fig. 5. Dynamics of the system (2.1) when $a = 1.15$ and initial values are $x = 0.8$, $y = 0.03$, $z_1 = 0.01$, and $z_2 = 0.01$.

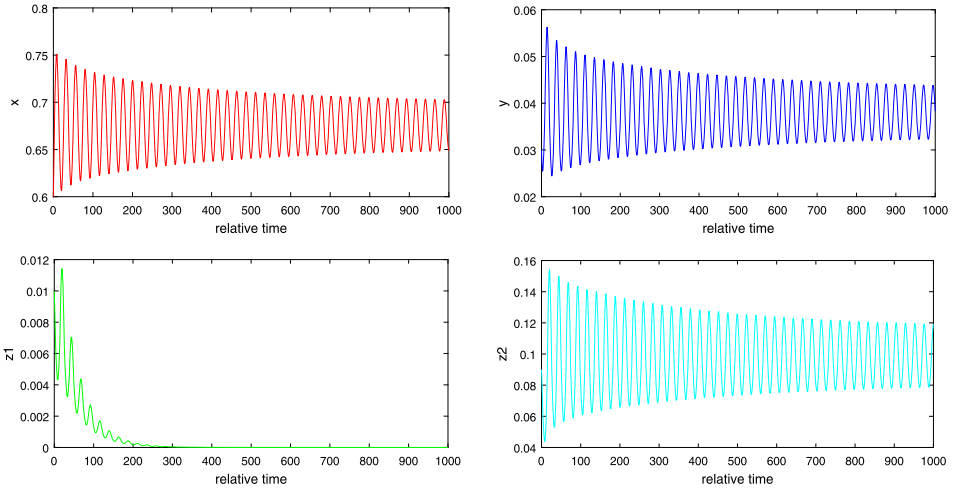

Fig. 6. Dynamics of the system (2.1) when $a = 1.48$ and initial values are $x = 0.6$, $y = 0.03$, $z_1 = 0.01$, and $z_2 = 0.09$.

different initial values and different values of the parameter a. When $a = 1.15$, that is, $a_{22} < a < a_{42}$, Fig. 5 shows the equilibrium $E_2 = (0.8696, 0.0311, 0, 0)$ is locally asymptotically stable. When $a = 1.48$, that is, $a_{42} < a < a_{52}$, Fig. 6 shows periodic solutions, arising from Hopf bifurcation as a is very close to a_{62}, fluctuate around the equilibrium $E_4 = (0.6757, 0.0379, 0, 0.098)$. When $a = 6.65$, Fig. 7 shows periodic solutions oscillate around the equilibrium $E_4 = (0.1504, 0.0379, 0, 0.0838)$ as a is very close of a_{72}. With the presence of adaptive immunity, the dynamics of the interaction between tumor cells and adaptive immune cells becomes more complicated but the tumor load reduces in size compared to Case 1. This demonstrates that the only presence of adaptive immunity has a positive effect on the success of virotherapy.

Case 3. We assume that both types of immune responses, innate and adaptive, would be stimulated simultaneously with the same ratio of clearance rate to stimulate rate, that is, $\frac{d_1}{e_1} = \frac{d_2}{e_2}$. We take $d = d_1 = d_2 = 0.4$ and $e = e_1 = e_2 = 10$. By computation, we found $a_2 = 1.0417$ and $a_3 = 8.64$, which verify the condition $a_3 - 4a_2 > 0$, and hence we can compute $a_4 = 1.2116$ and $a_5 = 7.4284$. Since $\delta = 22.6116 > 0$, $a_6 = 1.4924$ and $a_7 = 6.2476$. In this case, we simulate the trajectories of the system (2.1) with different initial values and different values of a to verify the stability of the manifold of equilibria M and demonstrate the occurrence of Poincare-Andronov-Hopf bifurcation without parameters for this system. When $a = 1.4$ $(a_4 < a < a_6)$ or $a = 6.5$ $(a_7 < a < a_5)$, Fig. 8 and 9 show the interior of the manifold of equilibria

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

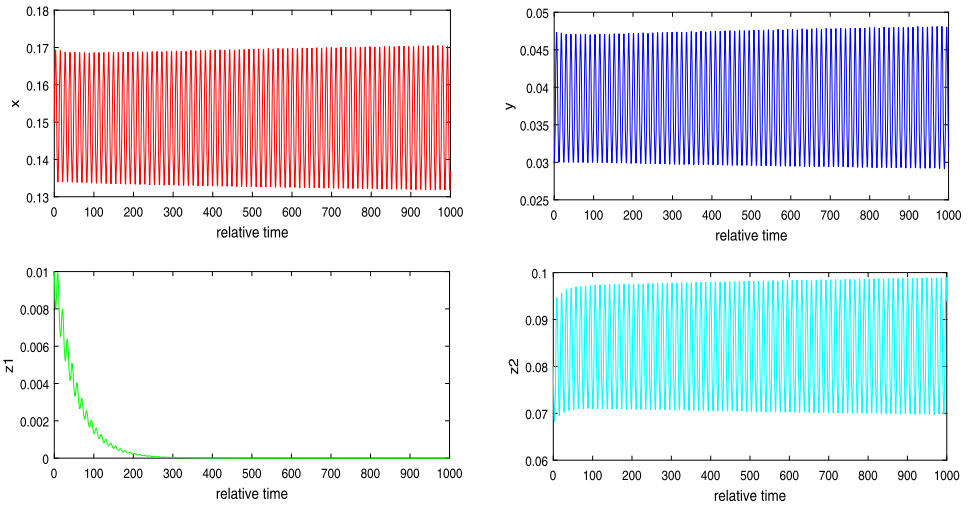

Fig. 7. Dynamics of the system (2.1) when $a = 6.65$ and initial values are $x = 0.15$, $y = 0.03$, $z_1 = 0.01$, and $z_2 = 0.08$.

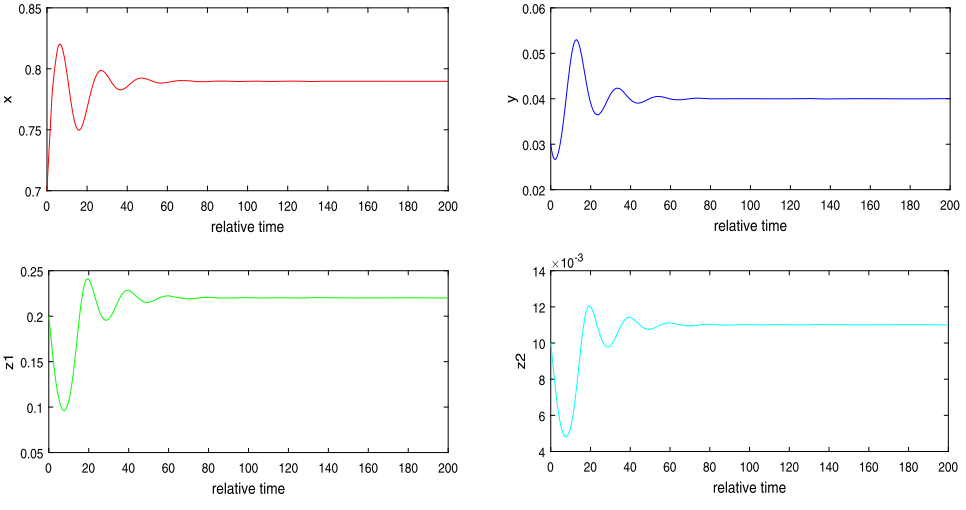

Fig. 8. Dynamics of the system (2.1) when $a = 1.4$ and initial values are $x = 0.7$, $y = 0.03$, $z_1 = 0.2$, and $z_2 = 0.01$.

$M^\circ = \{E_5(\zeta) : \frac{1}{a} < \zeta < 1 - \frac{d}{e} - \frac{ad}{re}\}$ is locally stable. When $a = 6$, that is, $a_6 < a < a_7$, Fig. 10 and 11 show 3-dim xyz_1 and xyz_2 phase portraits, respectively, together with three different periodic solutions that oscillate around the manifold of equilibria M in each one. With the presence of both immune responses, although the dynamics of the interaction between tumor cells and immune cells is quite complicated, the pattern is still clear: the higher the infectivity rate of infected tumor cells, the more successful the virotherapy treatment is.

As we know, the parameter a represents the relative infectivity rate of infected tumor cells, which is a key parameter for determining the dynamics of our model. Also a partially captures the strength of viruses and the replicability of the viruses. A large value of a implies the burst size of the viruses is large and vice versa. To further understanding of the effect of adaptive immune response on the efficacy of virotherapy treatment for different burst size of viruses, we perform simulations of uninfected tumor cell population for different values of two immune killing rates, l_1 for the innate immunity and l_2 for the adaptive immunity, with two different settings of other parameters. Fig. 12 displays the growth of uninfected tumor cells with respect to several different values of l_1 and l_2 when other parameter values are $r = 0.36$, $e = 10$, $d = 0.4$, and $a = 1.4$. As the immune killing rate l_2 for the adaptive immunity increases, the number density of uninfected tumor

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

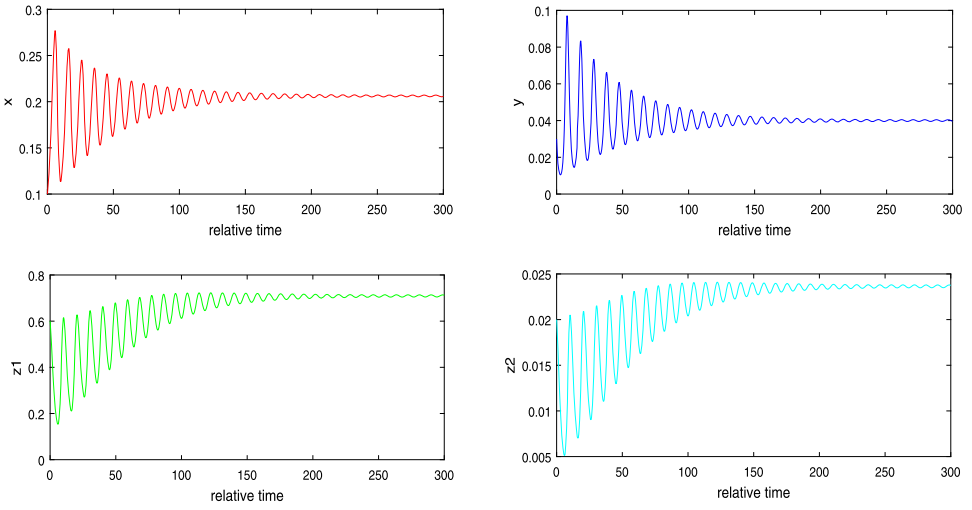

Fig. 9. Dynamics of the system (2.1) when $a = 6.5$ and initial values are $x = 0.1$, $y = 0.03$, $z_1 = 0.6$, and $z_2 = 0.02$.

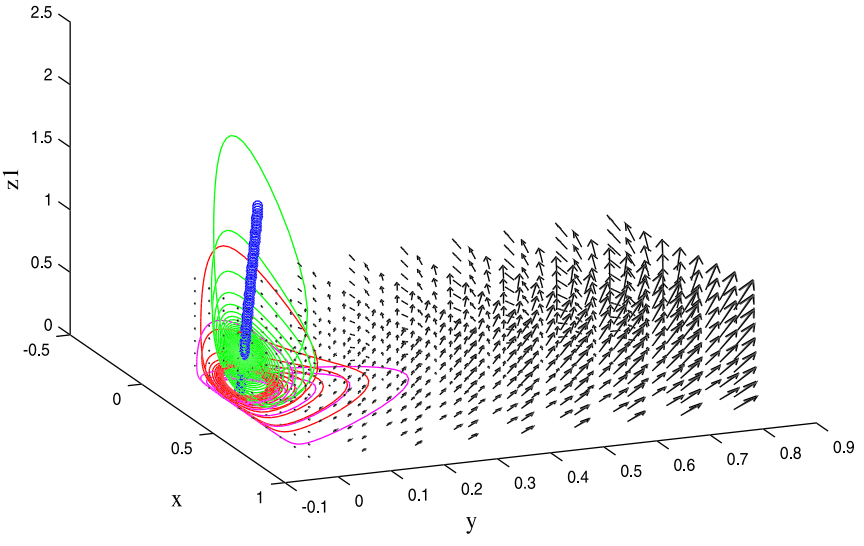

Fig. 10. Phase portrait view xyz_1 for the system (2.1) with three different periodic solutions when $a = 6$.

cells decreases. So the tumor grows slower and eventually reduces in size for a long period of time. This shows that adaptive immune response positively impacts the efficacy of virotherapy as the tumor is treated with viruses of small burst size. However, as viruses of large burst size are used, the treatment results are different. Fig. 13 displays the growth of uninfected tumor cell population with respect to several different values of l_1 and l_2 when other parameters are $r = 0.36$, $e = 10$, $d = 0.4$, and $a = 2.5$. When infectivity rate is increased to a large value, 2.5, and the killing rate l_2 for the adaptive immunity is large, 4.8, the number density of uninfected tumor cells fluctuates wildly. This may mean that the tumor becomes aggressive. In this case, the both immune response may not show effects on the success of virotherapy. This may be attributed to Hopf bifurcation without parameters.

4.2. Discussion

From experiments, preclinical, and clinical trials on oncolytic viral therapy, the innate immune response is not favorable to good outcomes of the treatment although the adaptive immune response helps to eradicate

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

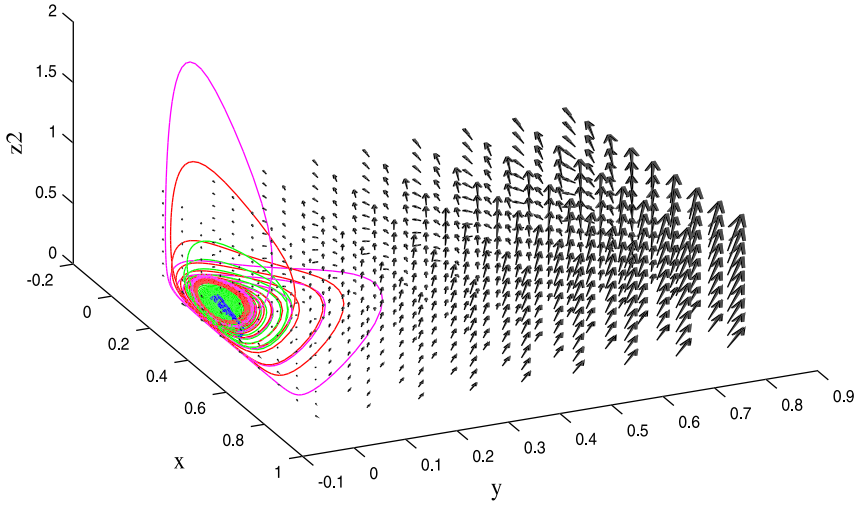

Fig. 11. Phase portrait view xyz_2 for the system (2.1) with three different periodic solutions when $a = 6$.

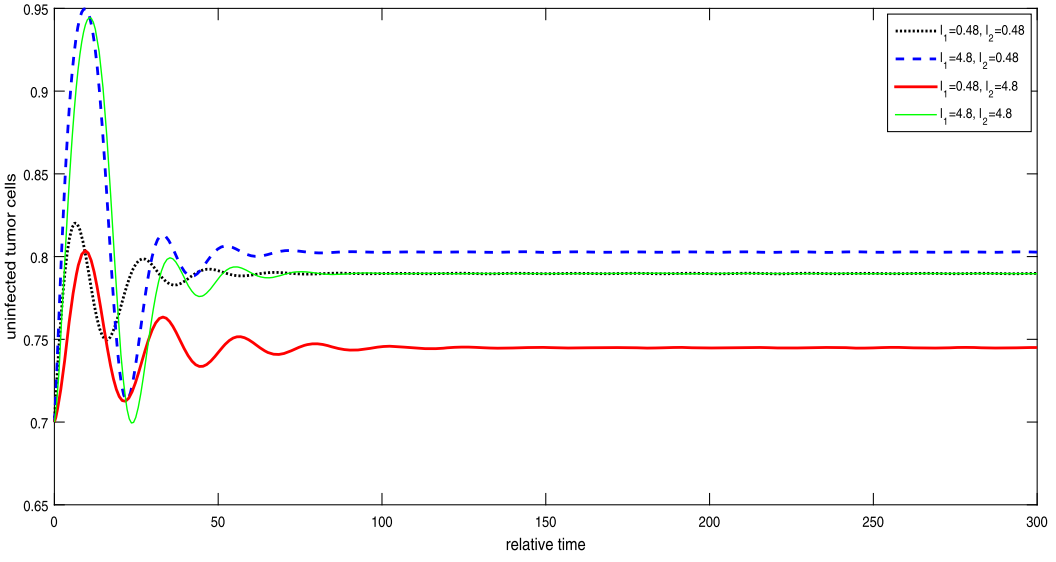

Fig. 12. Dynamics of uninfected tumor cell population with different values of l_1 and l_2 when $r = 0.36$, $a = 1.4$, $e = 10$, $d = 0.4$ and initial values are $x = 0.7$, $y = 0.03$, $z_1 = 0.2$, and $z_2 = 0.01$.

the tumor. The complexity of outcomes of virotherapy highly depends on the subtle interactions among many physical variables. In this virotherapy model, we utilize several essential physical variables which are tumor cells, infected tumor cells, innate immune cells, and adaptive immune cells. The dynamical behaviors of our model can be roughly classified according to relative immune clearance rates and infectivity constant. When the adaptive immune response is reduced from our model, the outcomes simply include four equilibria. When the innate immune response is diminished from our system, besides four equilibria, periodic solutions arising from classical Hopf bifurcation are additional outcomes. It is difficult to tell which of these two systems has a better outcome although the system with adaptive immunity has more possible outcomes. Using data from our previous studies, we demonstrate that only presence of adaptive immunity in the therapy has a better outcome. When both innate and adaptive immunities are present in the therapy, there are more possible outcomes. There are infinitely many equilibria and periodic solutions arising from Hopf bifurcation without parameters in the full model system. For some cases in the full system, we obtain better outcomes while we get worse outcomes in other cases. As we mentioned in Introduction, the immune

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

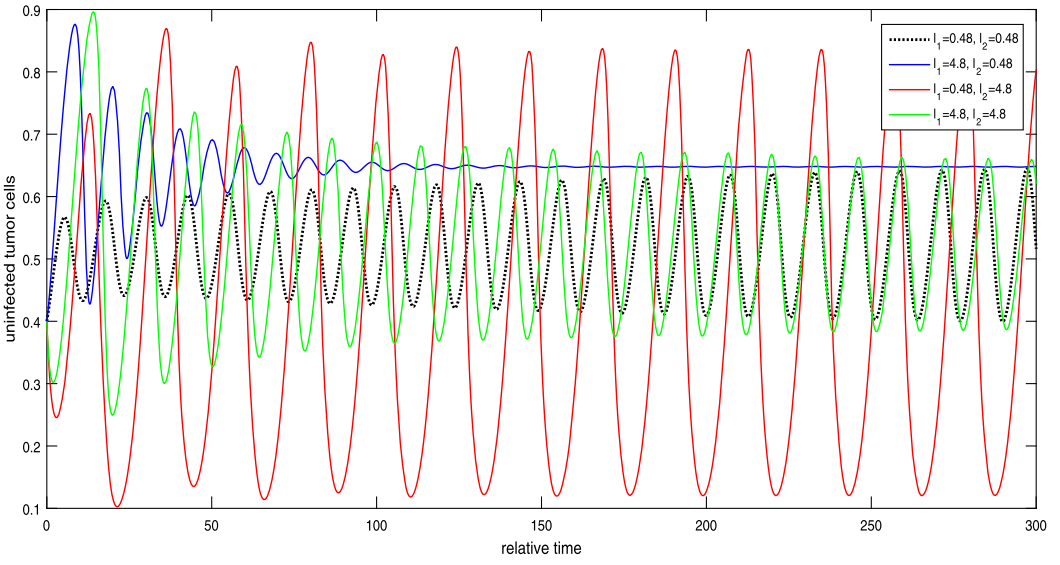

Fig. 13. Dynamics of uninfected tumor cell population with different values of l_1 and l_2 when $r = 0.36$, $a = 2.5$, $e = 10$, $d = 0.4$ and initial values are $x = 0.4$, $y = 0.03$, $z_1 = 0.5$, and $z_2 = 0.1$. (For interpretation of the colors in the figure, the reader is referred to the web version of this article.)

clearance rates are not fixed and change with densities of immune cells in the tumor. This means that all possible dynamical behaviors could appear in the viral treatment as we demonstrate numerically above. We may conclude that all possible outcomes of our model might represent the current situations in clinical tests.

Mathematically, our model demonstrates some new features. Our model has both classical Hopf bifurcation and Hopf bifurcation without parameters. Hopf bifurcation without parameters appears at some point in a line or curve of equilibria. The stable and unstable manifolds of this point divide the state space into three pieces. It should be noticed that manifolds here are open without boundaries in general. In each piece of the state space, periodic solutions have similar properties and similar asymptotic behaviors. In different pieces, periodic solutions have completely different properties and asymptotic behaviors. One major difference between classical Hopf bifurcation and Hopf bifurcation without parameters is as its name suggested. Classical Hopf bifurcation appears when a parameter passes through a particular value while Hopf bifurcation without parameters appears when a variable or coordinate of state space passes through a particular value, and, of course, Hopf bifurcation without parameters may be involved in many parameters. There is no common physical mechanism for Hopf bifurcation without parameters. From our model, it seems to be easier to explain why virotherapy has many outcomes. One reason is periodic solutions easily appear when tumor cells change together with the changing of immune clearance rates.

An interesting question is how stable or robust our results obtained from our model are when we take account of microenvironmental noises or parameter errors. This will be involved in stochastic modeling. Our research will continue on this direction in Part II.

Acknowledgments

This research started when TAP was a graduate student. JPT would like to acknowledge grant supports from National Science Foundation (DMS-1446139) and National Institutes of Health (U54CA132383), which also supported TAP in some semesters and summers during the grant periods.

References

[1] A.K. Abbas, A.H. Lichtman, Cellular and Molecularimmunology, Saunders, Philadelphia, 2003.

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

[2] L.J. Allen, Modeling with Ito Stochastic Differential Equations, Springer, Dordrecht, The Netherlands, 2007.
[3] R.H.I. Andtbacka, F. Collichio, K.J. Harrington, M.R. Middleton, G. Downey, K. Ohrling, et al., Final analyses of OPTiM: a randomized phase III trial of talimogene laherparepvec versus granulocyte-macrophage colonystimulating factor in unresectable stage III-IV melanoma, J. ImmunoTher. Cancer 7 (1) (2019) 145.
[4] B. Aulbach, Approach to hyperbolic manifolds of stationary solutions, in: H.W. Knobloch, K. Schmitt (Eds.), Equadiff 82, in: Lecture Notes in Mathematics, vol. 1017, Springer, Berlin, Heidelberg, 1983.
[5] Z. Bajzer, T. Carr, K. Josic, S.J. Russell, D. Dingli, Modeling of cancer virotherapy with recombinant measles viruses, J. Theor. Biol. 252 (2008) 109–122.
[6] V. Cerullo, C. Capasso, M. Vaha-Koskela, O. Hemminki, A. Hemminki, Cancer-targeted oncolytic adenoviruses for modulation of the immune system, Curr. Cancer Drug Targets 18 (2) (2018) 124–138.
[7] M. Chaplain, V. Kuznetsov, Z. James, A. Stepanova, Spatio-temporal dynamics of the immune system response to cancer, in: M.A. Horn, G. Simonett, G.F. Webb (Eds.), Mathematical Models in Medical and Health Sciences, Vanderbilt University Press, Nashville, 1998, pp. 79–97.
[8] J. Chesney, I. Puzanov, F. Collichio, P. Singh, M.M. Milhem, J. Glaspy, et al., Randomized, open-label phase II study evaluating the efficacy and safety of talimogene laherparepvec in combination with ipilimumab versus ipilimumab alone in patients with advanced, unresectable melanoma, J. Clin. Oncol. 36 (17) (2018) 1658–1667.
[9] E.A. Chiocca, Oncolytic viruses, Nat. Rev. Cancer 2 (2002) 938–950.
[10] D. Dingli, M.D. Cascino, K. Josic, S.J. Russell, Z. Bajzer, Mathematical modeling of cancer radiovirotherapy, Math. Biosci. 199 (2006) 55–78.
[11] A. Dispenzieri, C. Tong, B. LaPlant, M.Q. Lacy, K. Laumann, D. Dingli, et al., Phase I trial of systemic administration of Edmonston strain of measles virus genetically engineered to express the sodium iodide symporter in patients with recurrent or refractory multiple myeloma, Leukemia 31 (12) (2017) 2791–2798.
[12] J.D. Freedman, J. Hagel, E.M. Scott, I. Psallidas, A. Gupta, L. Spiers, et al., Oncolytic adenovirus expressing bispecific antibody targets T-cell cytotoxicity in cancer biopsies, EMBO Mol. Med. 9 (8) (2017) 1067–1087.
[13] A. Friedman, J.P. Tian, G. Fulci, E.A. Chiocca, J. Wang, Glioma virotherapy: effects of innate immune suppression and increased viral replication capacity, Cancer Res. 66 (2005) 2314–2319.
[14] O. Hemminki, A. Hemminki, A century of oncolysis evolves into oncolytic immunotherapy, OncoImmunology 5 (2) (2016) e1074377.
[15] O. Hemminki, M. Oksanen, K. Taipale, I. Liikanen, A. Koski, T. Joensuu, et al., Oncograms visualize factors influencing long-term survival of cancer patients treated with adenoviral oncolytic immunotherapy, Mol. Ther. Oncolytics 9 (2018) 41–50.
[16] O. Hemminki, J.M.D. Santos, A. Hemminki, Oncolytic viruses for cancer immunotherapy, J. Hematol. Oncol. 13 (2020) 84.
[17] H. Jiang, D.H. Shin, T.T. Nguyen, J. Fueyo, X. Fan, V. Henry, et al., Localized treatment with oncolytic adenovirus Delta-24-RGDOX induces systemic immunity against disseminated subcutaneous and intracranial melanomas, Clin. Cancer Res. 25 (22) (2019) 6801–6814.
[18] K.S. Kim, S. Kim, I.H. Jung, Dynamics of tumor virotherapy: a deterministic and stochastic model approach, Stoch. Anal. Appl. 34 (2016) 483–495.
[19] N.L. Komarova, D. Wodarz, ODE models for oncolytic virus dynamics, J. Theor. Biol. 263 (2010) 530–543.
[20] S.E. Lawler, E.A. Chiocca, Oncolytic virus-mediated immunotherapy: a combinatorial approach for cancer treatment, J. Clin. Oncol. 33 (2015) 2812–2814.
[21] S.E. Lawler, M.C. Speranza, C.F. Cho, E.A. Chiocca, Oncolytic viruses in cancer treatment: a review, JAMA Oncol. 3 (6) (2017) 841–850.
[22] E.Y.L. Leung, D.P. Ennis, P.R. Kennedy, C. Hansell, S. Dowson, M. Farquharson, et al., NK cells augment oncolytic adenovirus cytotoxicity in ovarian cancer, Mol. Ther. Oncolytics 16 (2020) 289–301.
[23] S. Liebscher, Bifurcation Without Parameters, Lecture Notes in Mathematics Series, vol. 2117, Springer International Publishing, 2015.
[24] N. Macedo, D.M. Miller, R. Haq, H.L. Kaufman, Clinical landscape of oncolytic virus research in 2020, J. ImmunoTher. Cancer 8 (2020) e001486.
[25] J.P. Machiels, R. Salazar, S. Rottey, I. Duran, L. Dirix, K. Geboes, et al., A phase 1 dose escalation study of the oncolytic adenovirus enadenotucirev, administered intravenously to patients with epithelial solid tumors (EVOLVE), J. ImmunoTher. Cancer 7 (1) (2019) 20.
[26] I.G. Malkin, Theory of stability of motion, Moscow, 1952 (in Russian).
[27] J. Niemann, N. Woller, J. Brooks, B. Fleischmann-Mundt, N.T. Martin, A. Kloos, et al., Molecular retargeting of antibodies converts immune defense against oncolytic viruses into cancer immunotherapy, Nat. Commun. 10 (1) (2019) 3236.
[28] J. O'Connell, M. Bennett, G. O'Sullivan, J. Collins, F. Shanahan, The Fas counterattack: cancer as a site of immune privilege, Immunol. Today 20 (1999) 46–52.
[29] T.A. Phan, J.P. Tian, The role of the innate immune system in oncolytic virotherapy, Comput. Math. Methods Med. 2017 (2017) 6587258.
[30] T.A. Phan, J.P. Tian, Basic stochastic model for tumor virotherapy, Math. Biosci. Eng. 17 (4) (2020) 4271–4294.
[31] T.A. Phan, J.P. Tian, B. Wang, Dynamics of cholera epidemic models in fluctuating environments, Stoch. Dyn. 21 (2) (2021) 2150011.
[32] M. Rajalakshmi, M. Ghosh, Modeling treatment of cancer using virotherapy with generalized logistic growth of tumor cells, Stoch. Anal. Appl. 36 (2018) 1068–1086.
[33] M. Rajalakshmi, M. Ghosh, Modeling treatment of cancer using oncolytic virotherapy with saturated incidence, Stoch. Anal. Appl. 38 (2020) 565–579.
[34] A.C. Shah, D. Benos, G.Y. Gillespie, J.M. Markert, Oncolytic viruses: clinical applications as vectors for the treatment of malignant gliomas, J. Neurooncol. 65 (2003) 203–226.

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

[35] J.P. Tian, The replicability of oncolytic virus: defining conditions on tumor virotherapy, Math. Biosci. Eng. 8 (2011) 841–860.
[36] A. Timalsina, J.P. Tian, J. Wang, Mathematical and computational modeling for tumor virotherapy with mediated immunity, Bull. Math. Biol. 79 (8) (2017) 1736–1758.
[37] US Food and Drug Administration, FDA approves first-of-its-kind product for the treatment of melanoma, published October 27, 2015, accessed December 6, 2015.
[38] D. Wodarz, Viruses as antitumor weapons: defining conditions for tumor remission, Cancer Res. 61 (2001) 3501–3507.
[39] D. Wodarz, Gene therapy for killing p53-negative cancer cells: use of replicating versus nonreplicating agents, Hum. Gene Ther. 159 (2003) 153–159.
[40] J.T. Wu, H.M. Byrne, D.H. Kirn, L.M. Wein, Modeling and analysis of a virus that replicates selectively in tumor cells, Bull. Math. Biol. 63 (2001) 731–768.
[41] Y. Yuan, L.J. Allen, Stochastic models for virus and immune system dynamics, Math. Biosci. 234 (2011) 84–94.
[42] S. Zafar, S. Sorsa, M. Siurala, O. Hemminki, R. Havunen, V. Cervera-Carrascon, et al., CD40L coding oncolytic adenovirus allows long-term survival of humanized mice receiving dendritic cell therapy, OncoImmunology 7 (10) (2018) e1490856.
[43] M. Zheng, J. Huang, A. Tong, H. Yang, Oncolytic viruses for cancer therapy: barriers and recent advances, Mol. Ther. Oncolytics 15 (2019) 234–247.

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278

Sponsor names

Do not correct this page. Please mark corrections to sponsor names and grant numbers in the main text.

National Science Foundation, *country*=United States, *grants*=DMS-1446139

National Institutes of Health, *country*=United States, *grants*=U54CA132383

Highlights

- Innate and adaptive immune responses have opposite effects in virotherapy.
- Outcome is determined by innate immune if it is cleared less than adaptive immune.
- Outcome is determined by adaptive immune if it is cleared less than innate immune.
- Hopf bifurcation without parameters occurs when two immunes are cleared equally.

Please cite this article in press as: T.A. Phan, J.P. Tian, Hopf bifurcation without parameters in deterministic and stochastic modeling of cancer virotherapy, part I, J. Math. Anal. Appl. (2022), https://doi.org/10.1016/j.jmaa.2022.126278