PERIODIC SOLUTIONS OF A MODEL FOR
TUMOR VIROTHERAPY

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Abstract. In this article we study periodic solutions of a mathematical model for brain tumor virotherapy by finding Hopf bifurcations with respect to a biological significant parameter, the burst size of the oncolytic virus. The model is derived from a PDE free boundary problem. Our model is an ODE system with six variables, five of them represent different cell or virus populations, and one represents tumor radius. We prove the existence of Hopf bifurcations, and periodic solutions in a certain interval of the value of the burst size. The evolution of the tumor radius is much influenced by the value of the burst size. We also provide a numerical confirmation.

1. **Introduction.** Oncolytic viruses are genetically altered viruses which can infect and reproduce in cancer cells but leave healthy normal cells unharmed. Over the last decade, a great progress in understanding of the molecular mechanisms of viral cytotoxicity of oncolytic viruses has been providing a fascinating possible alternative of therapeutic approach to cancer patients. This alternative approach could be especially beneficial in the case of malignant brain tumor, glioma, since the standard therapy of surgery-radiation-chemotherapy does not typically destroy all the tumor cells; survival rate in high grade glioma is measured in months. Recent experiments in animals' brain tumors using genetically engineered viral strains, such as adenovirus, ONYX-15 and CV706, herpes simplex virus 1 and wild-type Newcastle disease virus show these viruses to be relatively non-toxic and tumor specific [1]. However, translation of the new cancer therapy into human brain cancers, for example, malignant glioma, has not yet lived up to its expectations. One reason is that once inside the cells the oncolytic virus, such as herpes simplex virus type 1 hrR3, replicate poorly; this difficulty may be overcome with advanced technology. Another more serious reason for the failure of efficacy of viral oncolytic therapy is the rapid host innate immune response to the viral infection. Preliminary experiments in animal models of brain tumors indicate that the process of viral oncolysis may be hampered in its very first hours by the innate immune system, regardless of

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the route of administration [2]. The experiments [2] also show that transient suppression of the innate immunity increases the efficacy of viral oncolysis in the brain. The drug that appears effective in suppressing the innate immune response and thereby in augmenting oncolysis is cyclophosphamide (CPA) [3]. Successful therapy requires an understanding of how oncolytic viruses, host cells, innate immune cells and immunosuppression drug influence tumor load. Mathematical modelings provide a good way to achieve a thorough understanding of the virotherapy treatment.

In [7], the authors formulate a mathematical model of spherical glioma that has been injected at its center with oncolytic viruses hrR3, which is a mutant of herpes simplex virus. The model includes uninfected and infected tumor cells, necrotic cells, free virus particles, innate immune cells, and cyclophosphamide. Their model is a five-component PDE free boundary problem. We would like to focus on the dynamics of interactions among five cell populations. Particularly, we study the periodic solutions and Hopf bifurcation on the biologically important parameter, namely, the burst size of virus. We therefore study an ODE version of the model in the present article. Although our model is an ODE system, our model still counts the spatial variable, tumor radius.

The article is organized as follows. In Section 2, we will introduce the ODE version of the model from the original model established in[7]. In section 3, we analyze Hopf bifurcation, and periodic solutions. One way of proving existence of periodic solutions is through finding a Hopf bifurcation with respect to a chosen control parameter. The control parameter here is chosen to be the burst size of the oncolytic virus. The finding of periodic solutions for the dynamical system in this case is important for proving existence of therapy success under a specific choice of parameters. In section 4, we present some numerical study.

2. **The nonlinear ODE model.** The Figure 1 shows the interactions among different cell populations during virotherapy of glioma.
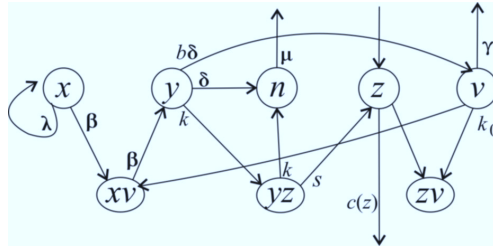

FIGURE 1. Dynamic diagram of virotherapy within a solid tumor

In the Figure 1, x, y, n, z, v represent uninfected tumor cells, infected tumor cells, necrotic cells, immune cells and free virus particles respectively. The parameter λ represents the proliferation rate of tumor cells, δ is the infected cells lysis rate, μ is the removal rate of necrotic cells, b is the burst size of the virus, β is the infection rate, k is the immune killing rate, k_0 is take-up rate of viruses, s is the stimulation rate by infected cells and γ is the clearance rate of viruses.

The proliferation and removal of cells cause a movement of cells within the tumor of radius $R(t)$, with a convection term, for tumor cells x, in the form $\frac{1}{r^2}\frac{\partial}{\partial r}(r^2 u(r,t) x(r,t))$, where $u(r,t)$ is the radial velocity. The other cells undergo

the same convection. The free virus particles undergo diffusion rather than convection. By mass conservation and convection of cells, the following equations are derived in [7]:

$$\begin{cases} \frac{\partial x(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}(r^2 u(r,t)x(r,t)) = \lambda x(r,t) - \beta x(r,t)v(r,t), \\ \frac{\partial y(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}(r^2 u(r,t)y(r,t)) = \beta x(r,t)v(r,t) - ky(r,t)z(r,t) - \delta y(r,t), \\ \frac{\partial n(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}(r^2 n(r,t)u(r,t)) = ky(r,t)z(r,t) + \delta y(r,t) - \mu n(r,t), \\ \frac{\partial z(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}(r^2 z(r,t)u(r,t)) = sy(r,t)z(r,t) - c(z(r,t))z(r,t) - P(r,t)z(r,t), \\ \frac{\partial v(r,t)}{\partial t} - D\frac{1}{r^2}\frac{\partial}{\partial r}(r^2 \frac{\partial v}{\partial r}) = b\delta y(r,t) - k_0 v(r,t)z(r,t) - \gamma v(r,t), \end{cases} \tag{1}$$

and the equation for velocity is

$$\frac{\theta}{r^2}\frac{\partial}{\partial r}(r^2 u(r,t)) = \lambda x(r,t) - \mu n(r,t) + sy(r,t)z(r,t) - c(z(r,t))z(r,t) - P(r,t)z(r,t).$$

The free boundary is subject to the kinematic condition

$$\frac{dR(t)}{dt} = u(R(t),t).$$

Here, $P(t)$ is the concentration of cyclophosphamide, an immuno-suppressing drug, and $\theta = x + y + z + n$ is the number density of cells within the tumor, which is a constant. Thus, one equation is redundant.

Let's take a domain transformation $\bar{r} = \frac{r(t)}{R(t)}$, and then integrate the equation for the velocity,

$$u(r,t) = \frac{R}{r^2}\int_0^r \eta^2(\lambda x(\eta,t) - \mu(1 - x - y - z) + syz - \omega z^2 - Pz)d\eta.$$

Thus, the tumor radius is given by

$$R'(t) = u(1,t).$$

Now we simply take out the spatial variable r from all equations in the system 1, we have

$$\begin{cases} \frac{dx}{dt} = \lambda x - \beta xv - (\lambda x - \mu n + syz - \omega z^2 - Pz)x \\ \frac{dy}{dt} = \beta xv - kyz - \delta y - (\lambda x - \mu n + syz - \omega z^2 - Pz)y \\ \frac{dz}{dt} = syz - \omega z^2 - (\lambda x - \mu n + syz - \omega z^2 - Pz)z - Pz \\ \frac{dv}{dt} = b\delta y - k_0 yv - \gamma v \\ \frac{dR}{dt} = \frac{1}{3}R(\lambda x - \mu n + syz - \omega z^2 - Pz) \end{cases} \tag{2}$$

We notice that the first four equations are decoupled from the last one, so it will be sufficient to study formed by the first four equations of 2 in order to determine the dynamics of virotherapy and the evolution of the radius of the tumor.

The coefficients were experimentally determined in [7] and they are given here in order to compute bifurcation points, and to make some numerical comparisons.

Proliferation rate of tumor cells	λ	2×10^{-2} l/h
Infected cells lysis rate	δ	$1/18$ l/h
Removal rate of necrotic cells	μ	$1/48$ l/h
Burst rate of infected cells	b	50 viruses/cell
Density of tumor cells	θ	10^6 Cells/mm^3
Infection rate	β	$7/10 \times 10^{-9}$ mm^3/h virus
Immune killing rate	k	2×10^{-8} mm^3/h immune cell
Take-up rate of viruses	k_0	10^{-8} mm^3/h immune cell
Stimulation rate by infected cells	s	5.6×10^{-7}mm^3/h infected cell
Clearance rate of immune cells	ω	20×10^{-8} mm^3/h cell
Clearance rate of viruses	γ	2.5×10^{-7} l/h

We work with relative concentrations (i.e. $\frac{x}{\theta}$, etc.). With this change the system stays literally the same, and $x + y + z + n = 1$. The time is measured in hundred of hours, the constants become

$$\lambda = 2,\ \delta = \frac{100}{18},\ \mu = \frac{100}{48},\ D = \frac{36}{10},\ \beta = \frac{7}{100}, k = 2,\ k_0 = 1,\ s = 56, \omega = 20,\ \gamma = \frac{25}{10}. \tag{3}$$

The concentration of cyclophosphamide is a piecewise defined function:

$$P(t) = \begin{cases} \frac{5}{2}, & 0 < t \leq \frac{18}{25} \\ \frac{5}{96}(120 - 100t), & \frac{18}{25} < t \leq \frac{6}{5} \\ 0, & t \geq \frac{6}{5} \end{cases}$$

Given the fact that the system (2) is polynomial in each component, we have global existence and uniqueness of solutions for any choice of initial condition. By using uniqueness of solutions and the method of the variation of constants we get that the set $Q = \{(x, y, z, v, R)|(x, y, z) \in [0, 1]^3, v \geq 0, R \geq 0\}$ is invariant set for the system (2).

3. **Hopf bifurcation and periodic solution analysis.** Let $\mathbb{F}$ be the vector field defined the system, namely, defined as follows

$$\mathbb{F}(x, y, z, v, b) = \begin{pmatrix} \lambda x - \beta xv - (\lambda x - \mu + \mu x + \mu y + \mu z + syz - \omega z^2)x \\ \beta xv - kyz - \delta y - (\lambda x - \mu + \mu x + \mu y + \mu z + syz - \omega z^2)y \\ syz - \omega z^2 - (\lambda x - \mu + \mu x + \mu y + \mu z + syz - \omega z^2)z \\ b\delta y - k_0 yv - \gamma v \end{pmatrix} \tag{4}$$

Thus the system (2) could be written

$$\begin{cases} \frac{dx}{dt} = \mathbb{F}_1(x, y, z, v, b) \\ \frac{dy}{dt} = \mathbb{F}_2(x, y, z, v, b) \\ \frac{dz}{dt} = \mathbb{F}_3(x, y, z, v, b) \\ \frac{dv}{dt} = \mathbb{F}_4(x, y, z, v, b) \end{cases}$$

We denote by $D\mathbb{F}$ the Fréchet derivative of the vector field $\mathbb{F}$ with respect to the first four variables. In order to determine the equilibrium solutions of system (2), we must solve:

$$\mathbb{F}(x, y, z, v, b) = 0_{\mathbb{R}^4}. \tag{5}$$

considering b as a parameter. We note that equation (5) is polynomial in each component and by applying the elimination method and the fundamental theorem

of algebra could be shown that is has 14 solutions. Some of the equilibrium points are quite obvious to obtain, e.g.

$$\{x = 0, y = 0, z = 0, v = 0\}, \{x = 1, y = 0, z = 0, v = 0\}, \{x = 0, y = 0, z = 1, v = 0\},$$

$$\{x = 0, \ y = 0, \ z = \frac{\mu}{\omega}, \ v = 0\}, \{x = \frac{\omega + \lambda}{\omega}, \ y = 0, \ z = -\frac{\lambda}{\omega}, \ v = 0\}$$

$$\{x = 0, \ y = \frac{-\delta + \mu}{\mu}, \ z = 0, \ v = \frac{b\delta \ (-\delta + \mu)}{-\delta \, k_0 + k_0\mu + \gamma \, \mu}\},$$

However, we are mainly interested in those equilibrium points that are satisfying $0 < x < 1$, $0 < y < 1$, $0 < z < 1$, $v > 0$. Notice b as a parameter which takes values between 50 and 1500. Such interval for b is motivated by experimentalists in [7].

Our goal now is to find and study the stability of the equilibrium solutions satisfying $x \neq 0$, $y \neq 0$, $z \neq 0$ and $v \neq 0$. In this case we can solve the system of equations resulting from (5) by elimination and obtain:

$$v = \frac{b\delta y}{k_0 y + \gamma} \tag{6a}$$

$$z = \frac{1}{\omega}\left(sy - \lambda + \frac{\beta b\delta y}{k_0 y + \gamma}\right) \tag{6b}$$

$$x = \frac{1}{\lambda + \mu}(sy - \omega z + \mu - \mu y - \mu z - syz + \omega z^2) \tag{6c}$$

where y is the root of a quartic polynomial with variable coeficients in b

$$c_4(b)y^4 + c_3(b)y^3 + c_2(b)y^2 + c_1(b)y + c_0(b) \tag{7}$$

and the coefficients are:

$$
\begin{aligned}
c_4(b) &= ks(\lambda + \mu)k_0^3 \\
c_3(b) &= -k_0 b^2 s\beta^2\delta^2 + k_0^2\left((3ks\gamma + b(k+s)\beta\delta)(\lambda + \mu) - b\beta\delta\lambda\omega\right) \\
&\quad -k_0^2(\lambda + \mu)(k\lambda - (\delta + \lambda)\omega) \\
c_2(b) &= (-b^2\beta^2\delta^2(s\gamma + b\beta\delta) + k_0\left(k\gamma(3s\gamma + 2b\beta\delta)(\lambda + \mu) + b\beta\delta(2s\gamma(\lambda + \mu)\right. \\
&\quad -2\gamma\lambda\omega + b\beta\delta(2\lambda + \mu + \omega)) - (\lambda + \mu)(3k\gamma\lambda - 3\gamma(\delta + \lambda)\omega \\
&\quad +b\beta\delta(\lambda + \omega))k_0 \\
c_1(b) &= \gamma(k\gamma(s\gamma + b\beta\delta)(\lambda + \mu) + b\beta\delta(s\gamma(\lambda + \mu) - \gamma\lambda\omega + b\beta\delta(2\lambda + \mu + \omega)) \\
&\quad -(\lambda + \mu)(3k\gamma\lambda - 3\gamma(\delta + \lambda)\omega + 2b\beta\delta(\lambda + \omega))k_0) \\
c_0(b) &= (-\gamma^2(\lambda + \mu)(k\gamma\lambda - \gamma(\delta + \lambda)\omega + b\beta\delta(\lambda + \omega))
\end{aligned}
$$

If we substitute in (7) all non-dimensionalized constants except b, we have that y is an implicit function of b and is given by:

$$
y^4 + \frac{1}{1372}\left(\frac{108829}{9} + \frac{8267b}{36} - \frac{686b^2}{27}\right)y^3 + \frac{1}{1372}\left(\frac{235445}{6} + \frac{18781b}{18} - \frac{66983b^2}{1296} - \frac{343b^3}{1944}\right)y^2
$$
$$
+ \frac{1}{1372}\left(\frac{662725}{12} + \frac{131215b}{144} + \frac{76685b^2}{2592}\right)y + \frac{1}{1372}\left(\frac{2027375}{72} - \frac{94325b}{144}\right) = 0
\tag{8}
$$

In order to study the roots of equation (7) we introduce some results from the general theory of binary forms.

Definition 3.1. *A general quartic binary form is any polynomial in x and y,*

$$q(x, y) = \sum_{k=0}^{4}\binom{4}{k}a_k x^k y^{4-k}. \tag{9}$$

Let $(c_{ij}) \in \mathrm{GL}_2(\mathbb{R})$ be a linear change of variables, i.e. a transformation of the variables x and y given by

$$x = c_{11}\bar{x} + c_{12}\bar{y}, \quad y = c_{21}\bar{x} + c_{22}\bar{y}.$$

The quartic binary form $q(x, y)$ is transformed into another quartic binary form $\bar{q}(\bar{x}, \bar{y})$ in the new variables $\bar{x}$ and $\bar{y}$ defined by

$$\bar{q}(\bar{x}, \bar{y}) = \sum_{k=0}^{4} \binom{4}{k} a_k (c_{11}\bar{x} + c_{12}\bar{y})^k (c_{21}\bar{x} + c_{22}\bar{y})^{n-k}.$$

After expanding and regrouping terms, we obtain

$$\bar{q}(\bar{x}, \bar{y}) = \sum_{k=0}^{4} \binom{4}{k} \bar{a}_k \bar{x}^k \bar{y}^{4-k}$$

where the coefficients $\bar{a}_k$ are polynomials in a_i and c_{ij}.

Definition 3.2. *A nonconstant polynomial $p(A_0, A_1, A_2, A_3, A_4)$ in the variables A_0, A_1, A_2, A_3 and A_4 is said to be an invariant of index g of the quartic binary forms if for all quartic binary forms $q(x, y)$ and all linear changes of variables we have*

$$p(\bar{a}_0, \bar{a}_1, \bar{a}_2, \bar{a}_3, \bar{a}_4) = (c_{11}c_{22} - c_{21}c_{12})^g p(a_0, a_1, a_2, a_3, a_4).$$

Below, for the convenience, we quote a few results presented in [9].

Lemma 3.1. *We have that*

$$i(a_0, a_1, a_2, a_3, a_4) = a_0 a_4 - 4a_1 a_3 + 3a_2^2$$

and

$$j(a_0, a_1, a_2, a_3, a_4) = \det \begin{pmatrix} a_0 & a_1 & a_2 \\ a_1 & a_2 & a_3 \\ a_2 & a_3 & a_4 \end{pmatrix}$$

are invariants of index 4 and of index 6, respectively, for any quartic binary forms.

Lemma 3.2. *Let $\Delta = i^3 - 27j^2$. The binary form has only simple roots (i.e. multiplicity 1) if and only if the discriminant $\Delta \neq 0$.*

The next Lemma can be shown easily by using symbolic calculation.

Lemma 3.3. *The solutions of the equation $q(1, x) = 0$, i.e. $a_4 x^4 + 4a_3 x^3 + 6a_2 x^2 + 4a_1 x + a_0 = 0$, are*

$$x_{mn} = -\frac{a_3}{a_4} + (-1)^m \sqrt{\frac{1}{6a_4^2}\left(6a_3^2 + \frac{\sqrt[3]{9}ia_4}{r} + a_4\sqrt[3]{3}r - 6a_2 a_4\right)} +$$

$$(-1)^n \sqrt{-\frac{1}{6a_4^3}\left(-12a_3^2 a_4 + \frac{\sqrt[3]{9}ia_4}{r} + a_4^2 r + 12a_2 a_4^2 + (-1)^m \frac{6\sqrt{6}(2a_3^3 - 3a_2 a_3 a_4 + a_1 a_4^2)}{\sqrt{\frac{1}{6a_4^2}\left(6a_3^2 + \frac{\sqrt[3]{9}ia_4}{r} + a_4\sqrt[3]{3}r - 6a_2 a_4\right)}}\right)} \tag{10}$$

where $m, n = 1, 2$ and $r = \sqrt[3]{-9j + \sqrt{-3\Delta}}$.

Now we return to analyzing the case for equilibrium solutions $(x(b), y(b), z(b), v(b))$ of the decoupled ODE system (2) when all components are non-zero simultaneously (i.e. $x \neq 0$, $y \neq 0$, $z \neq 0$.)

Theorem 3.1. *For the chosen set of the constant values* (3) *and any* $b \in (50, 1500)$, *the solutions of the equation* (5) *with all components non-zero simultaneously are differentiable functions of the parameter* b.

Proof. For any polynomial with variable coefficients

$$x^n + c_{n-1}(\xi)x^{n-1} + c_{n-2}(\xi)x^{n-2} + ... + c_1(\xi)x^1 + c_0(\xi)$$

it is known that the roots have the same smoothness as the coefficients if the multiplicity of the roots is constant. In general, at the points where the multiplicity of the roots changes the roots may loose the smoothness property. For the given set of constants (3) if we solve $\Delta = 0$, where Δ is the discriminant associated with the equation (8), we obtain

$$b = 0 \,(\text{with multiplicity } 6)\,, \quad b = -23.07639773, \quad b = 35.73236461,$$
$$b = -304.5746522 \pm 289.6509340\mathbf{i}, \quad b = -1.2581694375 \pm 0.4454333074\mathbf{i},$$
$$b = 89.4795363 \pm 148.8296778\mathbf{i}.$$

This shows that the discriminant Δ does not vanish for the given set of constants (3) when $b \in (50, 1500)$. By Lemma 3.3, the roots of the equation (8) are simple and therefore smooth with respect to the parameter b. Using also the set of the equations (6) we obtain the conclusion of the theorem. $\qquad\square$

It turns out, following the construction of roots for quartic polynomials written in closed form (Lemma 3.3) that, for the given set of the constant values (3), only the case $m = 1$, $n = 2$ produces a solution that concurs with the physical meaning of our problem($y(b)$ being the value of a non-zero concentration i.e. $0 < y(b) \leq 1$ when $b \in (50, 1500)$.) We would also like to point out that, by the help of Lemma 3.3 we can approximate the equilibrium solutions in this case (of all non-zero components) with arbitrary precision.

Theorem 3.2. *The system* (2), *using the given set of constant values* (3) *and* b *as a parameter, has a Hopf bifurcation point.*

Proof. In this proof we are going to check the set of well known sufficient conditions for the existence of a Hopf bifurcation point:

(H1) There exists b_0 and a smooth branch of equilibrium solutions
$(x(b), y(b), z(b), v(b), b)$ for $b \in (b_0 - \epsilon, b_0 + \epsilon)$, with
$\mathbb{F}(x(b_0), y(b_0), z(b_0), v(b_0), b_0) = 0$ and $(x(b_0), y(b_0), z(b_0), v(b_0))$ is an isolated solution of $\mathbb{F}(x, y, z, v, b_0) = 0$.

(H2) $\mathbb{F}$ is sufficiently smooth in a neighborhood of $(x(b_0), y(b_0), z(b_0), v(b_0), b_0)$

(H3) The Jacobian matrix of the vector field $\mathbb{F}$ evaluated at the equilibrium solution, i.e. $\mathrm{D}\mathbb{F}(x(b), y(b), z(b), v(b), b)$ with $b \in (b_0 - \epsilon, b_0 + \epsilon)$ has a pair of simple complex conjugate eigenvalues $\Lambda(b)$, $\overline{\Lambda(b)}$ such that $\mathbf{Im}(\Lambda(b_0)) > 0$, $\mathbf{Re}(\Lambda(b_0)) = 0$ and $\frac{d}{db}\mathbf{Re}(\Lambda(b_0)) \neq 0$

(H4) $\mathrm{D}\mathbb{F}(x(b_0), y(b_0), z(b_0), v(b_0), b_0)$ has no eigenvalues of the form $k\mathbf{Im}(\Lambda(b_0))\mathbf{i}$ where $\mathbf{i}$ is the imaginary unit and $k \in \{0, 2, 3, 4, ...\}$.

Since the vector field is polynomial in each component and by Theorem 3.1 the equilibrium solutions depend smoothly on the parameter b, condition (H2) holds. We notice that the characteristic polynomial for the Jacobian of the vector field (4) is also quartic. The discriminant of the characteristic polynomial, when $50 < b < 1500$ and consider the set of constants (3), vanishes only for $b = 51.57242982$. Thus for $52 < b < 1500$, by repeating a similar argument as in Theorem 3.1 the roots of

the characteristic polynomial are also differentiable functions of parameter b. Let $\Lambda_{mn}(b)$ where $m, n = 1, 2$ represent the roots of the characteristic polynomial (where m, n have the meaning given by Lemma 3.3). When $b = 550$ the eigenvalues are

$$(\Lambda_{m,n}(550)) = \begin{pmatrix} -7.618277765 & -3.388867230 \\ -7.3 \cdot 10^{-6} + 2.2734867506\mathrm{i} & -7.3 \cdot 10^{-6} - 2.2734867506\mathrm{i} \end{pmatrix}$$

and for $b = 551$ we have

$$(\Lambda_{m,n}(551)) = \begin{pmatrix} -7.616911353 & -3.386713853 \\ 0.000788256 + 2.273610580\mathrm{i} & 0.000788256 - 2.273610580\mathrm{i} \end{pmatrix}$$

This shows the existence of a point $550 < b_0 < 551$ that satisfies (H1). Let

$$\Lambda^4 + C_3(b)\Lambda^3 + C_2(b)\Lambda^2 + C_1(b)\Lambda + C_0(b)$$

be the characteristic polynomial. The coefficient $C_3(b)$ is

$$sy + \gamma + \delta + \lambda + \mu + \frac{(sy - \lambda)(k + \lambda)}{\omega} + y\left(k_0 - \frac{b^2 y \beta^2 \delta^2}{\omega\,(\gamma + yk_0)^2} + \frac{b\beta\delta(k - sy + 2\lambda - \omega)}{\omega\,(\gamma + yk_0)}\right) \tag{11}$$

If we substitute the non-dimensionalized constants (3) we obtain

$$\frac{475425 + 3142440y - 4410by + 2285748y^2 - 19404by^2 - 49b^2y^2 + 441936y^3 - 7056by^3}{1620(5 + 2y)^2}. \tag{12}$$

where y satisfies equation (8). It can be shown numerically that given y satisfies (8) the coefficient of Λ^3 from the characteristic polynomial cannot vanish for any $50 < b < 1500$. This fact guarantees, by a simple application of the Viète formulae, that for the given range of the parameter b the solutions of the characteristic polynomial cannot have zero real part simultaneously. Also, it can be shown numerically that $\frac{d}{db}\mathbf{Re}(\Lambda_{21}(b)) \neq 0$ when $550 < b < 551$ by using a very accurate representation of the coefficients $C_i(b)$ and implicit differentiation with respect to the characteristic equation. Thus, conditions (H3) and (H4) are also satisfied.

In [11] it describes a direct method for the computation of Hopf bifurcation points. Let $\phi_0^1 + \mathbf{i}\phi_0^2$ represent an eigenvector of the pure imaginary eigenvalue $\Lambda_{21}(b_0)$. It is shown that a Hopf bifurcation point could be located by solving the nonlinear system

$$\begin{cases} \mathbb{F}(x, y, z, v, b) = 0 \\ [(\mathrm{D}\mathbb{F}(x, y, z, v, b))^2 + \zeta I_4]\bar{p} = 0 \\ <\bar{p}, \bar{p}> -1 = 0 \\ <\bar{q}, \bar{p}> = 0 \end{cases}$$

where $\bar{q}$ is a vector in $\mathbb{R}^4$ with nonzero projection on span$\{\phi_0^1, \phi_0^2\}$. By the application of this method we find $b_0 = 550.00923219396759996$.   □

Thus we proved that the system (2) has periodic solutions for appropriate values of the parameter b. In the next section we address the natural question that arises, namely whether the periodicity of solutions intrinsically has an influence over the tumor radius in a finite time period.

4. **Numerical study and discussion.** For the numerical simulations we work with the following set of non-dimensionalized initial data are given in [7]:

$$x(0) = 0.84, \; y(0) = .10, \; z(0) = 0.06, \; 2.6 \cdot b \leq v(0) \leq 5.6 \cdot b.$$

We here numerically analyze the behavior of the velocity field given by $f(x, y, z, v) = \lambda x - \mu n + syz - \omega z^2 - Pz$. The behavior of the velocity field is directly related

to the behavior of the solutions to the system (2). We also notice that, from (2), the radius of the tumor is given by

$$R(t) = R_0 \exp\left(\frac{1}{3}\int_0^t f(x(s,b), y(s,b), z(s,b), v(s,b))ds\right) \tag{13}$$

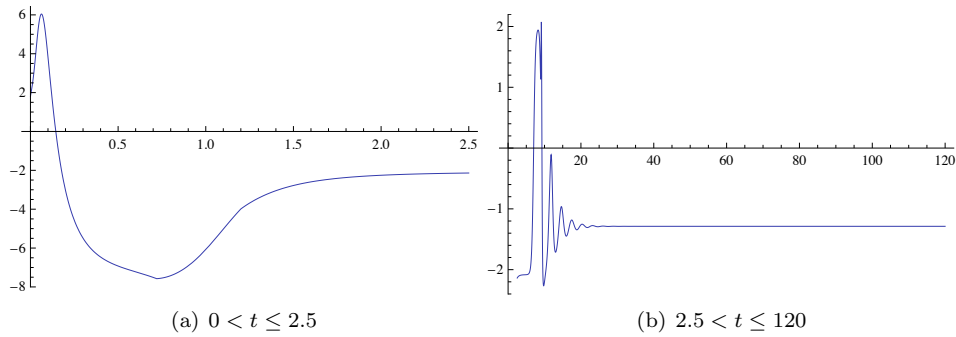where R_0 is the initial tumor radius. In the following numerical calculations $R_0 = 2mm$.

(a) $0 < t \le 2.5$ (b) $2.5 < t \le 120$

FIGURE 2. The velocity field when $b = 300$.

(a) $0 < t \le 2.5$ (b) $2.5 < t \le 120$
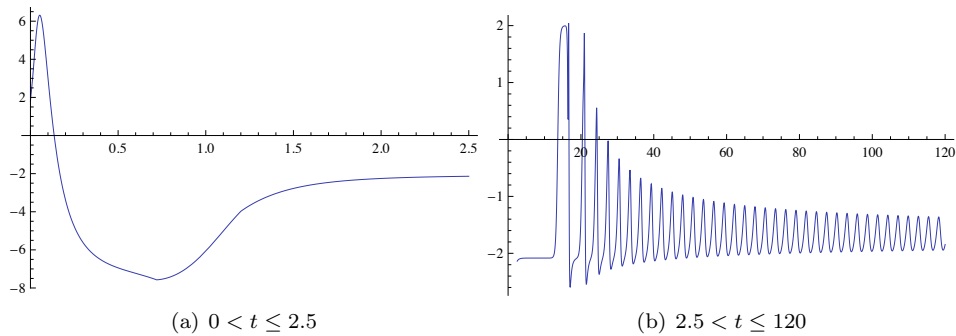
FIGURE 3. The velocity field when $b = 551$.

Figure 2 shows the profile of the velocity field when the value of the parameter b is 300. Figure 3 shows the profile of the velocity field when the value of the parameter b is 551. We notice that, up to $t = 2.5$ (which in real time means 250 hours, a little over 10 days,), the shapes of the velocity field for both $b = 300$ and $b = 551$ are almost identical. The major differences start only for $t \ge 20$ (about three months). It is interesting that both cases share an oscillation behavior between $t = 2.5$ and $t = 20$. We also notice that this oscillation is not due to the perturbation of cyclophosphamide, which may seem a somehow counterintuitive [8].

Figure 4 shows the evolution of the tumor radius under different values of the parameter b. Although the radius of the tumor eventually goes to zero, that is, the tumor will be eradicated eventually, the radius of the tumor decreases more rapidly when the value of the parameter b is big.

(a) When b=300 at $t = 15$ we have
$R = 0.0012483326090$

(b) When b=551 at $t = 15$ we have
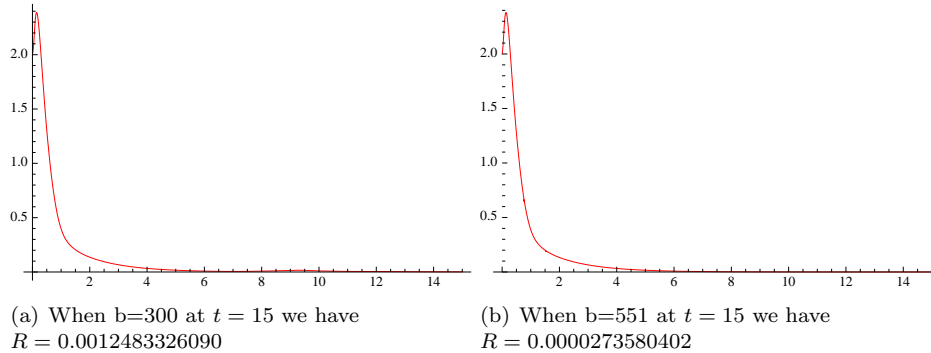$R = 0.0000273580402$

FIGURE 4. The tumor radius when $0 < t < 15$.

When $b = 550$ the solution expresses oscillations with or without the presence of cyclophosphamide. We also present a numerical comparison for the evolution of the velocity field in this case, in Figure 5 and Figure 6.

(a) When b=550 at $0 < t < 2.5$ wtih $P \equiv 0$

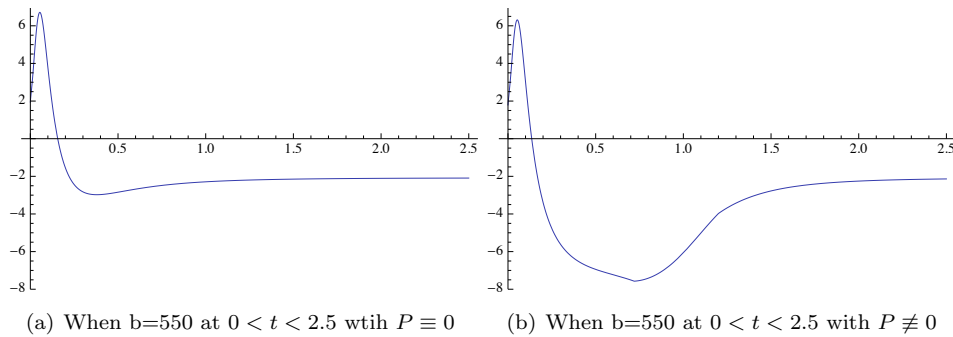(b) When b=550 at $0 < t < 2.5$ with $P \not\equiv 0$

FIGURE 5. The evolution of the tumor velocity field show that the tumor radius decreases faster in the presence of cyclophosphamide

The conclusion that we draw from this numerical comparison is that the periodicity of the solutions to system (2) may not be a major factor for shrinking of the tumor radius in the first two months period after the virotherapy treatment, but the value of the burst size b.

In this study we focus on the parameter burst size, and get a range of its values in which the system has periodic solutions once we fix all other parameters. This confirms some observation in experiments [4][5]. Since there are ten parameters, it is possible that some other parameters could also have Hopf bifurcations, and therefore produce periodic solutions of the system. The search for other Hopf bifurcations in the full parameter space is a huge amount of work. Only when we have some suggestions from experiments about parameter value, as we did here for the burst size, we can perform such a study. It may be interesting to study how sensitive of the interval of burst size value for Hopf bifurcations is dependent on the rest of the parameters. We leave this for the future consideration.

(a) When b=550 at $2.5 < t < 120$ wtih $P \equiv 0$ (b) When b=550 at $2.5 < t < 120$ with $P \not\equiv 0$
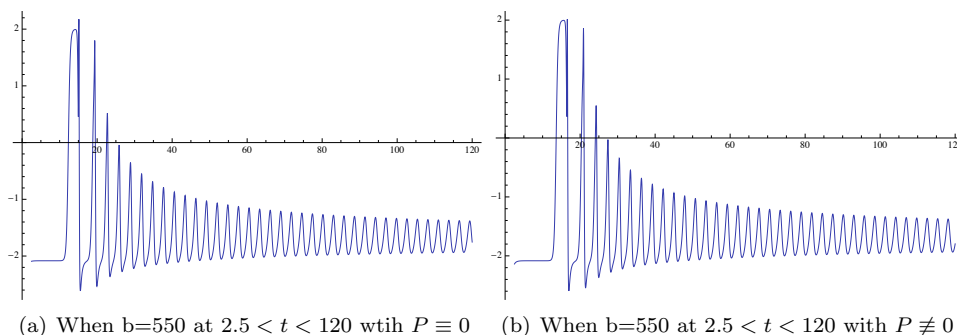
FIGURE 6. The system presents oscillations with and without cyclophosphamide and the tumor radius when $t = 15$ is
$R = 0.0024389484$ if $P \equiv 0$ and $R = 0.0001036137$ if $P \not\equiv 0$

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