MATHEMATICAL BIOSCIENCES
AND ENGINEERING
Volume **10**, Number **3**, June **2013**

doi:10.3934/mbe.2013.10.565

pp. **565–578**

MATHEMATICAL MODELING OF GLIOMA THERAPY USING ONCOLYTIC VIRUSES

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Abstract. Diffuse infiltrative gliomas are adjudged to be the most common primary brain tumors in adults and they tend to blend in extensively in the brain micro-environment. This makes it difficult for medical practitioners to successfully plan effective treatments. In attempts to prolong the lengths of survival times for patients with malignant brain tumors, novel therapeutic alternatives such as gene therapy with oncolytic viruses are currently being explored. Based on such approaches and existing work, a spatio-temporal model that describes interaction between tumor cells and oncolytic viruses is developed. Conditions that lead to optimal therapy in minimizing cancer cell proliferation and otherwise are analytically demonstrated. Numerical simulations are conducted with the aim of showing the impact of virotherapy on proliferation or invasion of cancer cells and of estimating survival times.

1. **Introduction.** Cancer is a collection of diseases with the common feature of uncontrolled cellular growth. Most tissues in the body can give rise to cancer, some even yield several types, and each cancer has unique features. Cancer cells normally escape the usual controls on cell proliferation and proliferate excessively to form a neoplastic growth or tumor. We are particularly interested in cancer gliomas in this article. Diffuse infiltrative gliomas are by far the most common primary brain tumors in adults [1]. In contrast to almost all other brain tumors, such diffuse gliomas are characterized by extensive, diffuse infiltration of tumor cells in the neuropil, which is, the dense network of interwoven neuronal and glial cell processes. Unlike solid tumors, for which simple exponential or geometric expansion represents expansion of volume, gliomas consist of motile cells that can migrate as well as proliferate [29]. Glioma growth patterns have been studied extensively by Hans-Joachim Scherer [8, 25], one of the pioneers in the area. Individual glioma cells are highly motile, with the ability to invade most of the neural axis of rats

2010 *Mathematics Subject Classification.* Primary: 92C37, 35B35; Secondary: 35B40.
Key words and phrases. Cancer gene therapy, oncolytic viruses, mathematical model.

in less than one week following implantation and are known to be viable even long distances from the bulk lesion in humans [28].

Cancer gene therapy is a promising treatment strategy. Advances in knowledge of the biology of viruses have been used to consider replicating vectors preferentially in tumors that can significantly amplify the expression of gene therapy. Among these viruses, some have a mutation or a deletion in their genome that affect replication in normal cells but not in cancer cells. Within a tumor cell, loss of the requisite proteins may be compensated in trans by the mechanisms involved in tumorigenesis. Oncolytic viruses have been shown to possess a significant antitumor activity [16, 18]. Such viruses infect tumor cells and replicate inside them, without harming healthy normal cells, and eventually cause lysis. However, this introduces a new level of complexity. Although much progress has been made in both the theoretical study and clinical trials of oncolytic viruses [10, 13, 31, 34, 35, 37, 38], problems still remain to be addressed with regards to their interactions with the immune system or the specificity of infection, replication, and diffusion.

Currently, available therapeutic modalities for high grade malignant gliomas often fail to improve patient prognosis. Standard therapy is limited by a low therapeutic index and by the cross-resistance between chemotherapeutic drugs. Within this context, gene therapy is a promising therapeutic strategy for malignant gliomas, potentially offering both tumor targeting and novel cell-killing mechanisms. Recombinant adenoviruses appear promising as gene therapy vectors for glioma, on the merit of their ability to infect both dividing and quiescent tumor cells, instigate genome plasticity, facilitate mild pathogenicity in humans, and generate safety as shown in gene therapy clinical trials for glioma.

As a way of supporting practical clinical measures and quantifying the effectiveness of treatment it is necessary to develop new mathematical formulations for gliomas since it is practically impossible either to measure the growth rate or to determine the spatio-temporal infiltration of gliomas and the way that replicating viruses spread to the region of the tumor. It is within this framework that this article is written.

Replication-conditional, oncolytic adenoviruses [22], such as ONYX-015, are emerging as powerful tools in the warfare on cancer. The ability to modify cell-specific infectivity or tissue-specific replication machinery, as well as the possibility of modifying viral-cellular protein interactions with cellular checkpoint regulators are emerging as new trends in the design of safer and more effective adenoviruses. ONYX-015 is an oncolytic adenovirus that lacks the E1B-55K gene product required for p53 degradation and therefore was predicted to selectively replicate in tumor cells with inactive p53 pathways [2, 19]. The successful entry of the viral particle into target cells is strongly dependent on the presence of the main receptor for adenovirus, the Coxsackievirus and Adenovirus Receptor (CAR) [11]. Mitogen-activated protein kinase (MEK) inhibitors have been shown to promote CAR expression, and could be used to increase the susceptibility of target cells to ONYX-015 infection. However, MEK inhibitors interfere with adenovirus replication due to resulting G1-phase cell cycle arrest [7]. Therefore, enhanced efficacy will depend on treatment protocols that productively balance these competing effects. Tao and Guo [32] suggested that greater tumor treatment is achieved when oncolytic adenovirus infection and MEK inhibitor treatment occur at the same time. Bagheri and others [3] investigated combinatorial treatment strategies using a mathematical model that predicts the impact of MEK inhibition on tumor cell proliferation, ONYX-015

infection, and oncolysis. They postulated that treating cells with CI1040 prior to infection, followed by its removal at the time of ONYX-015 infection, would maximize virus uptake due to increased up-regulation of CAR, and maximize cell death due to the release of cells from G1-phase arrest. But the mechanism underlying virus replication in G1-arrested cells remains unclear and warrants further investigation.

The structure of this paper is as follows. In Section 2, we introduce the mathematical model and define various quantities that make up the model. In Section 3 we provide an exact traveling wave solution to the model in the untreated case of glioma development. Model analysis is provided in Section 4 where conditions of optimal therapy that stabilize the tumor are determined. Section 5 is devoted to estimating the survival time of patients when the tumor cannot be stabilized. The last section is set aside for discussions and conclusions.

2. **The mathematical model.** The model takes into account the dynamical interactions between a growing population of tumor cells, a population of susceptible and uninfected tumor cells, V_1; a population of infected tumor cells, V_2; and a population of free virus, that is, virus in the extracellular tissue, V_3. Unlike the model developed in [39], we assume that the tumor follows a logistic growth, which can be slowed down by an inhibitor, captured through the expression $1-u$. Thus, the tumor admits a maximum size and density defined by the carrying capacity K.

When the virus is administered, the dynamic interactions between the virus and tumor cell population is described by the following system of reaction-diffusion equations in the tumor region Ω,

$$\begin{cases} \dfrac{\partial V_1(t,x)}{\partial t} &= \varepsilon_1 \Delta V_1 + \rho(1-u)V_1\Big(1-\dfrac{V_1}{K}\Big) - dV_1 - \dfrac{\beta r V_1 V_3}{1+\varepsilon V_3}, \quad t>0, \\ \dfrac{\partial V_2(t,x)}{\partial t} &= \varepsilon_2 \Delta V_2 + \dfrac{\beta r V_1 V_3}{1+\varepsilon V_3} - dV_2 - a(1-u)V_2, \quad t>0, \\ \dfrac{\partial V_3(t,x)}{\partial t} &= \varepsilon_3 \Delta V_3 + k(1-u)V_2 - bV_3, \quad t>0,. \end{cases} \tag{1}$$

The model is explained as follows. The intensity of MEK inhibitor application is captured by the parameter u. In order to use the model to study the possible optimal timing of MEK inhibitor, we here assume that $u = const$, which ranges from zero to one. If $u = 0$, there is no drug treatment, that is no cells enter $G1$ arrest and there is no production of the CAR molecule. If $u = 1$, the drug has the maximum possible effect and all cells enter $G1$ arrest and the production of the CAR molecule is at its theoretical maximum. The population of uninfected tumor cells replicates at a rate ρ and has a natural death rate, d. When the virus meets susceptible cells, infection can occur. This requires the interaction of free virus with a CAR receptor on a susceptible cell, which occurs at a rate $\beta r V_1 V_3$. The infection rate is thus proportional to the average number of receptors on the cell surface, r, the concentration of free virus V_3, and the concentration of susceptible cells V_1. A tissue is defined as receptor-positive when the measured DLU/mm^2 (digital light units per millimetre squared) in the total binding section is at least twice as high compared to the non-specific binding section, defined by Paganelli et al. [23]. Mean receptor density values r are only calculated from the receptor-positive tissues.

As the virus becomes hyper-abundant relative to the uninfected cells, multiple infections of already infected cells become more likely than infection of uninfected cells, so the infection rate saturates with V_3 as the term $1/(1+\varepsilon V_3)$. The saturation effect accounts for the fact that the number of contacts of an individual cell reaches

some maximal value as the immune system evolves to stop a virus just as the virus evolves to enter cells and replicate [36].

The infected cells can die due to two mechanisms: the natural death rate denoted by the parameter d and the virus-induced death rate represented by parameter a. The virus-induced death rate is proportional to $1-u$. That is, as the activity of the inhibitor is increased, the rate of virus induced cell death declines. The reason is that virus induced cell death requires virus production and this does not occur in the presence of the inhibitor because the cells are arrested in $G1$. Infected cells produce new virus particles with a rate k, and this is again diminished in the presence of the inhibitor. Free virus particles decay with a rate b.

3. **Exact solution of untreated Glioma model.** For untreated gliomas, we neglect the complex interplay between the tumor and its environment. This complex interplay, treated in [6] established conditions of periodic dynamics existence for a treated glioma. The system can be reduced to the the following equation:

$$\frac{dV_1(t,x)}{dt} = \varepsilon_1 \Delta V_1 + (\rho - d)V_1\Big(1 - \frac{V_1}{K\frac{(\rho-d)}{d}}\Big) \tag{2}$$

This formulation is completed by the adoption of boundary conditions that impose no migration of cells beyond the brain boundary with initial conditions $V_1(x,0) = f(x)$, where $f(x)$ defines the initial spatial distribution of malignant cells.

Accordingly, equation (2) is a reaction-diffusion partial differential equation that describes the density of glioma cancer cells in terms of two net rates: proliferation $(\rho - d)$ and invasion (ε_1). These parameters can be estimated from routinely available pre-treatment MRIs (magnetic resonance images) [15]. This model, known as proliferation and invasion model [21, 29, 30], has been successful in predicting untreated growth and invasion kinetics for each patient [15], providing predictions related to surgical resection, chemotherapy [29], and radiation therapy [26].

Since we are interested in the traveling wave solution of equation (2), we specify a travelling coordinate $z = x - ct$, where c is the growth velocity of an untreated glioma. We let $V_1(x,t) = V(z)$ and by defining the new variable $V^{'} = \dfrac{dV}{dz}$, equation (2) can be formulated as:

$$\varepsilon_1 V^{''} + cV^{'} + (\rho - d)V_1\Big(1 - \frac{V_1}{K\frac{(\rho-d)}{d}}\Big) = 0. \tag{3}$$

Using the hyperbolic tangent-function method [12], $V^{'}$ could be expressed by,

$$\frac{dV}{dz} = F(V) = a_1 V + a_2 V^{\frac{3}{2}}, \tag{4}$$

where F is a solution of the following equation

$$\varepsilon_1 \; F\frac{dF}{dV} + cF + (\rho - d)V_1\Big(1 - \frac{V_1}{K\frac{(\rho-d)}{d}}\Big) = 0. \tag{5}$$

Substituting (3) into (5), we deduce that

$$\begin{cases} a_1 = \pm\sqrt{\dfrac{2(\rho-d)}{3\varepsilon_1}} \\ a_2 = \pm\sqrt{\dfrac{2\rho}{3\varepsilon_1 K}} \\ c = \mp\sqrt{\dfrac{25}{6}\varepsilon_1(\rho-d)} \end{cases} \tag{6}$$

Thus the equation has the following exact solution:

$$V_1(x,t) = \frac{(a_1\Theta)^2 \exp\left(a_1(x-ct)\right)}{\left(1 - a_2\Theta \exp\left(\frac{1}{2}a_1(x-ct)\right)\right)^2}, \tag{7}$$

where Θ is a constant of integration.

An interesting consequence of the Tanh method for traveling wave solutions is to provide the exact numerical value $\left(c = \sqrt{\dfrac{25}{6}\varepsilon_1(\rho-d)}\right)$ of glioma velocity in comparison with the value defined by Fisher's approximation ($c = 2\sqrt{(\rho-d)\varepsilon_1}$). Thus we obtain a better approximation of survival time since it is well known that tumor growth velocity is negatively correlated with patient survival [20, 24, 30]. These traveling waves are of great importance because, when they exist, the tumor invades the healthy tissue at its full potential. This first analysis is used to represent traveling wave solutions in the case of untreated glioma proliferation and invasion.

4. **Study of steady state solutions.** Wang and Li [33] studied the connection between additive D-stability and reaction-diffusion models, and gave several algebraic sufficient conditions by checking the signs of principal minors of a matrix A, which guarantee either stability or instability in the presence of diffusion. We recall that such a matrix A is said to be additively D-stable if $A - D$ remains Hurwitz for all nonnegative diagonal matrices D [14]. Additive D-stability is particularly useful for the study of reaction-diffusion systems where the matrix A represents the linearization of the reaction dynamics at a steady-state.

In this respect we discuss in this section the stability of the equilibrium solutions of our model system (1). Analysis reveals that there are precisely two homogeneous equilibrium solutions; one is the trivial steady state $S^0 = (0,0,0)$ and and the other is given by $S^* = (S_1, S_2, S_3)$ that satisfies the equations,

$$\begin{cases} S_1 &= \dfrac{K\left[\rho(1-u) - d - \dfrac{\beta r}{\varepsilon}\right] + K\sqrt{\delta}}{4\rho(1-u)}, \\ S_2 &= \dfrac{\beta r S_1}{\varepsilon[d + a(1-u)]} - \dfrac{b}{\varepsilon k(1-u)}, \\ S_3 &= \dfrac{k(1-u)S_2}{b}, \end{cases} \tag{8}$$

where,

$$\delta = \left(\rho(1-u) - d - \frac{\beta r}{\varepsilon}\right)^2 + \frac{4b\rho}{\varepsilon k K}\Big(d + a(1-u)\Big). \tag{9}$$

To investigate the stability of the constant steady-state S^0, we employ the minors condition method for reaction-diffusion systems developed by Wang and Li [33]. We recall this method by noting the following:

Definition 1. A matrix

$$P = \begin{pmatrix} p_{11} & p_{12} & p_{13} \\ p_{21} & p_{22} & p_{23} \\ p_{31} & p_{32} & p_{33} \end{pmatrix}$$

satisfies the minors condition if

$$p_{11} \leq 0,\ p_{22} \leq 0, p_{33} \leq 0,\ \det(P) \leq 0, \tag{10}$$

$$\det \begin{pmatrix} p_{11} & p_{12} \\ p_{21} & p_{22} \end{pmatrix} \geq 0,\ \det \begin{pmatrix} p_{11} & p_{13} \\ p_{31} & p_{33} \end{pmatrix} \geq 0, \det \begin{pmatrix} p_{22} & p_{23} \\ p_{32} & p_{33} \end{pmatrix} \geq 0. \tag{11}$$

Theorem 1. *Assume that* $1 - \dfrac{d}{\rho} < u < 1 + \dfrac{d}{a}$, *then the equilibrium solution* S^0 *is asymptotically stable.*

Proof. Let J_{S^0} be the Jacobian matrix of (1) at S^0,

$$J_{S^0} = \begin{pmatrix} \rho(1-u) - d & 0 & 0 \\ 0 & -d - a(1-u) & 0 \\ 0 & k(1-u) & -b \end{pmatrix} \tag{12}$$

By Definition 1, it is straightforward to conclude that the Jacobian matrix J_{S^0} satisfies the minors condition. □

The tumor could be eradicated with a sufficiently high dose of MEK inhibitor; however, this is not feasible since it is unlikely that a tolerable dose of MEK inhibitor could effectively lock the tumor in $G1$ arrest, considering that the natural death rate of the cells is likely to be too slow to result in effective clearance. Thus, for the purposes of this study, we assume that it is impossible to apply MEK inhibitor in a dose that is sufficient enough to result in eradication, that is, $u < 1$. Therefore, the strategy consists of minimizing the homogeneous equilibrium S^* and stabilizing it. As such, from equations (8), we let

$$S_1(r) = \frac{K\left[\rho(1-u) - d - \dfrac{\beta r}{\varepsilon}\right] + K\sqrt{\delta}}{4\rho(1-u)} \tag{13}$$

Then

$$\frac{dS_1(r)}{dr} = -\frac{\beta K}{4\varepsilon\rho(1-u)}\left[1 + \left(\rho(1-u) - d - \frac{\beta r}{\varepsilon}\right)\right]\delta^{-1/2} < 0.$$

Thus, $S_1(r)$ is a decreasing function which satisfies $\lim\limits_{r\to+\infty} S_1(r) = 0$, so there exists a certain maximum threshold $r_{\max}$ for which $S_1(r)$ is minimal. One way to reduce the density of cancerous cells is to determine the maximum density of CAR molecules. From this density, we determine the minimum density of infected non-cancerous cells in homogeneous equilibrium and then determine the conditions for stability of this equilibrium.

The Jacobian matrix of the linearized system at the equilibrium point S^* has the form:

$$J_{S^*} \equiv \begin{pmatrix} \rho(1-u)\Big(1-\dfrac{2}{K}S_1\Big) - d - \dfrac{\beta r S_3}{1+\varepsilon S_3} & 0 & -\dfrac{\beta r S_1}{(1+\varepsilon S_3)^2} \\ \dfrac{\beta r S_3}{1+\varepsilon S_3} & -d-a(1-u) & \dfrac{\beta r S_1}{(1+\varepsilon S_3)^2} \\ 0 & k(1-u) & -b \end{pmatrix}$$

As a consequence, we obtain the following:

Theorem 2. *Assume that* $1 - \dfrac{d}{\rho} < u < 1$*, then the endemic equilibrium* S^* *is asymptotically stable.*

Proof. Under the conditions of Theorem 1, it is straightforward to observe that all the diagonal entries of J_{S^*} are negative.

In addition, we have

$$\det \begin{pmatrix} \rho(1-u)\Big(1-\dfrac{2}{K}S_1\Big) - d - \dfrac{\beta r S_3}{1+\varepsilon S_3} & 0 \\ \dfrac{\beta r V_3}{1+\varepsilon V_3} & -d-a(1-u) \end{pmatrix} \geq 0,$$

$$\det \begin{pmatrix} \rho(1-u)\Big(1-\dfrac{2}{K}S_1\Big) - d - \dfrac{\beta r S_3}{1+\varepsilon S_3} & -\dfrac{\beta r S_1}{(1+\varepsilon S_3)^2} \\ 0 & -b \end{pmatrix} \geq 0,$$

$$\det \begin{pmatrix} -d-a(1-u) & \dfrac{\beta r S_1}{(1+\varepsilon S_3)^2} \\ k(1-u) & -b \end{pmatrix} = \frac{\varepsilon \beta r k (1-u) S_1 S_3}{(1+\varepsilon V_3)^2} \geq 0.$$

Thus by Definition 1, we have shown that the Jacobian matrix J_{S^*} satisfies the minors condition. Therefore, the endemic equilibrium is stable. □

Model analysis shows that the intensity of MEK inhibitor u plays an important role in the stability of the tumor. This intensity must be large enough and must depend on the proliferation and death rates of cancer cells to stabilize the tumor. This is buttressed by noting that the conditions of Theorem (2) are valid only when the tumor is close to the endemic equilibrium. With this in mind, it becomes important to introduce the following:

Theorem 3. *Assume that* $1 - \dfrac{bd}{kK\beta r - ab} < u < 1$*, then the endemic equilibrium* S^* *is globally asymptotically stable.*

Proof. Consider the function

$$l(V_1, V_2, V_3) = \int_{S_1}^{V_1} \frac{\eta - S_1}{\eta}\, d\eta + \int_{S_2}^{V_2} (\eta - S_2)\, d\eta + \int_{S_3}^{V_3} (\eta - S_3)\, d\eta,$$

and we denote $L(V_1, V_2, V_3) = \int_\Omega l(V_1, V_2, V_3)\, dx$. We aim at proving that L is a Lyapunov function with a negative orbital derivative:

$$\begin{aligned}\frac{dL}{dt} &= \int_\Omega \frac{V_1 - S_1}{V_1}\Big[\varepsilon_1 \Delta V_1 + \rho(1-u)V_1\Big(1 - \frac{V_1}{K}\Big) - dV_1 - \frac{\beta r V_1 V_3}{1+\varepsilon V_3}\Big]\, dx \\ &\quad + \int_\Omega (V_2 - S_2)\Big[\varepsilon_2 \Delta V_2 + \frac{\beta r V_1 V_3}{1+\varepsilon V_3} - dV_2 - a(1-u)V_2\Big]\, dx \\ &\quad + \int_\Omega (V_3 - S_3)\Big[\varepsilon_3 \Delta V_3 + k(1-u)V_2 - bV_3\Big]\, dx \\ &= I_1 + I_2 + I_3 + I_4.\end{aligned}$$

It follows from the boundary condition that

$$I_1 = \int_\Omega \Big[\varepsilon_1 \Delta V_1 \frac{V_1 - S_1}{V_1} + \varepsilon_2 \Delta V_2 (V_2 - S_2) + \varepsilon_3 \Delta V_3 (V_3 - S_3)\Big]\, dx < 0.$$

From the endemic equilibrium expression, we have

$$\begin{aligned}I_2 &= \int_\Omega \frac{V_1 - S_1}{V_1}\Big[\rho(1-u)V_1\Big(1 - \frac{V_1}{K}\Big) - dV_1 - \frac{\beta r V_1 V_3}{1+\varepsilon V_3}\Big]\, dx \\ &= \int_\Omega (V_1 - S_1)\Big[\rho(1-u)\Big(1 - \frac{V_1}{K}\Big) - d - \frac{\beta r V_3}{1+\varepsilon V_3} \\ &\quad - \rho(1-u)\Big(1 - \frac{S_1}{K}\Big) + d + \frac{\beta r S_3}{1+\varepsilon S_3}\Big]\, dx \\ &= -\frac{\rho(1-u)}{K}\int_\Omega (V_1 - S_1)^2\, dx - \beta r \int_\Omega \frac{(V_1 - S_1)(V_3 - S_3)}{(1+\varepsilon V_3)(1+\varepsilon S_3)}\, dx.\end{aligned}$$

By the same argument, we can write

$$\begin{aligned}I_3 &= \int_\Omega (V_2 - S_2)\Big[\frac{\beta r V_1 V_3}{1+\varepsilon V_3} - dV_2 - a(1-u)V_2\Big]\, dx \\ &= -(d + a(1-u))\int_\Omega (V_2 - S_2)^2\, dx + \beta r \int_\Omega (V_2 - S_2)\Big(\frac{V_1 V_3}{1+\varepsilon V_3} - \frac{S_1 S_3}{1+\varepsilon S_3}\Big)\, dx \\ &= -(d + a(1-u))\int_\Omega (V_2 - S_2)^2\, dx + \beta r \int_\Omega (V_2 - S_2)(V_3 - S_3)\frac{V_1}{1+\varepsilon V_3}\, dx \\ &\quad + \beta r \int_\Omega (V_2 - S_2)(V_1 - S_1)\frac{S_3}{(1+\varepsilon V_3)(1+\varepsilon S_3)}\, dx,\end{aligned}$$

and,

$$\begin{aligned}I_4 &= \int_\Omega (V_3 - S_3)\Big(k(1-u)V_2 - bV_3\Big)\, dx \\ &= -b\int_\Omega (V_3 - S_3)^2\, dx + k(1-u)\int_\Omega (V_3 - S_3)(V_2 - S_2)\, dx.\end{aligned}$$

Thus,

$$I_2 + I_3 + I_4 = -\Big(V_1 - S_1, V_2 - S_2, V_3 - S_3\Big) B \Big(V_1 - S_1, V_2 - S_2, V_3 - S_3\Big)^T,$$

where,

$$B = \begin{pmatrix} \dfrac{\rho(1-u)}{K} & -\dfrac{\beta r S_3}{(1+\varepsilon V_3)(1+\varepsilon S_3)} & 0 \\ 0 & d + a(1-u) & -k(1-u) \\ \dfrac{\beta r}{(1+\varepsilon V_3)(1+\varepsilon S_3)} & -\dfrac{\beta r V_1}{1+\varepsilon V_3} & b \end{pmatrix} \tag{14}$$

Under the assumption of Theorem 3, one can verify that all the principal submatrices of B have a positive determinant, thus B is a positive-definite matrix. Then, $\dfrac{dL}{dt}(V_1, V_2, V_3) < 0$, for all $(V_1, V_2, V_3) \neq S^*$. In addition, we have $L(S^*) = 0$, therefore, L is a Lyapounov function and S^* is globally asymptotically stable. □

Theorem 3 has an important biological implication. In fact, when the intensity of MEK inhibitor is bigger than $1 - \dfrac{bd}{kK\beta r - ab}$, the virotherapy always fails. This failure is determined by the replication ability of the oncolytic virus, and it does matter what the initial tumor size, the initial infected portion of the tumor, and the initial amount of injected virus are, as long as they are in the domain Ω.

5. **Numerical simulation of Glioma invasion and proliferation.** Analysis of observations made of actual patients [4, 5, 9, 17, 27] reveals that gliomas that are detectable on enhanced computer tomography (CT), had already reached a fatal size of 3 to 6 cm in diameter making it impossible for the tumor burden to be eradicated. Under such circumstances, we estimate the survival time of patients by determining the time it takes for the tumor to grow from 3 to 6 cm in average diameter. We numerically simulate the spatio-temporal patterns and tumor blow up in the case in which the endemic equilibria S^* is unstable. In fact, from Theorem (2), if $u < 1 - \dfrac{d}{\rho}$, S^* may be unstable for certain values of diffusion coefficients. The estimation of parameter values was obtained from [13, 29, 30, 34].

In Figure 1 and Figure 2 the solutions of model (1) and (2) are analyzed in a one-dimensional spatial domain $\Omega = [0\ ;\ 50\ mm]$, with Neumann boundary conditions. The evolution of the tumor at different times is shown in Figure 1 (a) for an untreated cancer (equation (2)), and Figure 1 (b), for cancer controlled by viruses (first equation of system (1)). Using model (1), Figure 2 (a) shows, after 365 days, infected cancer cell density, uninfected cancer cell density and virus free density. For cancers having the same initial spatial distribution, Figure 2 (b) represents, after 365 days, the spatial distribution of uninfected cancer cells (model (1)), and untreated glioma (model (2)). Figures 1 and 2 (b) allow a comparative study of invasion and proliferation dynamics between untreated glioma and glioma controlled by viruses. Thus, Figure 2 (b) shows that viruses can greatly reduce the proliferation dynamics, however, their effectiveness in stopping the invasion is less significant. This is explained by the fact that the survival rate of viruses is quite low in areas where cancer is absent. This implies that if viruses replicate only in areas where the cancer is already present, then the invasion of the virus should be delayed relative to that of cancer cells. The spatio-temporal cancer dynamics is simulated in 2D space in $\Omega = [0\ ;\ 80\ mm] \times [0\ ;\ 80\ mm]$ with Neumann boundary conditions meaning the system (1) is self-contained with zero flux across the boundary. In Figure 3 we represent the spatial patterning and density distribution after 365 days, of free-virus-infected cancer cells and uninfected cancer cells. This 2D

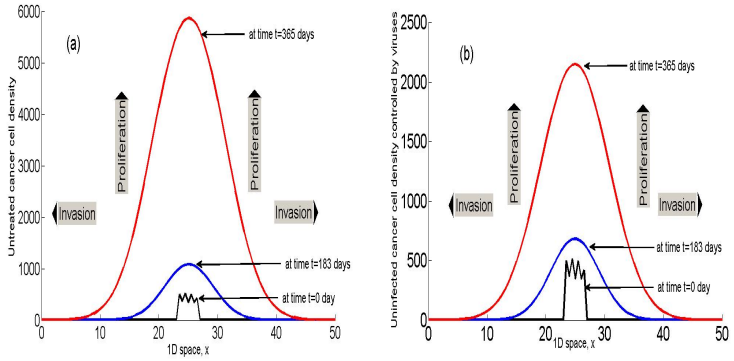

FIGURE 1. 1D space evolution of densities of untreated cancer cells and controlled cancer-virus system.

representation gives, at fixed time, a more accurate measure of the tumor diameter which is an important factor for patient survival estimation. Thus by varying the times of observations, we obtain in Figure 4, the evolution of the tumor size that tends to estimate survival of the patient before the fatal tumor diameter is reached.

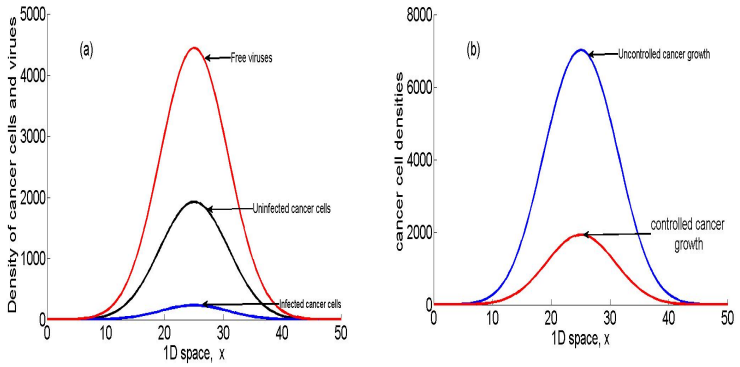

FIGURE 2. The densities, in 1D space after 365 days, of controlled cancer-virus system (model (1)) and untreated cancer (model (2)).

Table 1 gives the model parameter values and their units.

6. **Discussion and conclusion.** Oncolytic virus therapy presents a number of novel challenges because tumor eradication or control depends on the establishment of an infection and virus amplification. In this paper, we have presented a mathematical model of glioma therapy by oncolytic viruses. Conceptually, this approach is connected to the theoretical considerations of Wodarz et. al. [34, 35, 39] on cancer therapy. However, in our work, we have gone further to develop a refined mathematical model that takes into account the spatio-temporal dynamics of tumor cells and the spread of inoculated viruses. We have shown that if the intensity u of

TABLE 1. Parameter Values

Parameters	Description	Numerical values	Dimensions
a	Virus-induced cells death rate	$1/48$	$1/h$
b	Clearance rate of viruses	0.025	$1/h$
d	Natural death rate of cells	0.05	$1/h$
k	Replicating rate of viruses in infected cells	[20, 50]	$virus/cell\ h$
K	Maximal density of tumor cells	10^6	$cells/mm^2$
r	Average number of receptors on the cell surface	[0, 800000]	DLU/mm^2
ρ	Proliferation rate of cells	0.02	$1/h$
β	Infection rate of cells by viruses	79×10^{-9}	mm^2/h virus
ε_1, ε_2	Diffusion coefficient of cells	$[0.0054, 0.027]$	mm^2/h
ε_3	Diffusion coefficient of viruses	0.036	mm^2/h

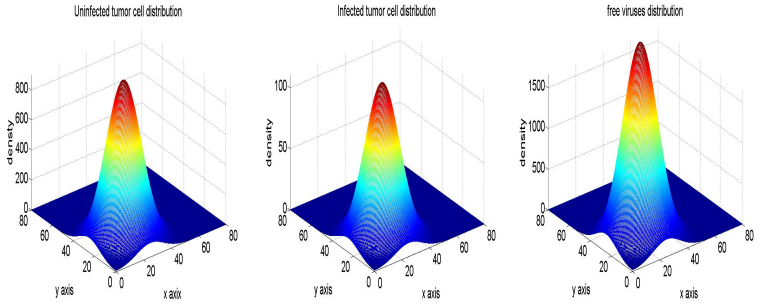

FIGURE 3. 2D spatial distribution of cancer cells and free viruses after 1 year.

the application of the inhibitor, **MEK**, is greater than 1, the tumor is theoretically treatable by the approach of genetically modified viruses. However in reality u is between 0 and 1 and this presents an inability to completely eradicate the cancer. We have determined in such circumstances, conditions of cancer persistence and conditions of optimal therapy in minimizing cancer cell proliferation. A comparison of the untreated cancer model to the model of cancer virotherapy leads to the conclusion that cancer virotherapy model significantly reduces cancer cell proliferation and slows down cancer invasion in certain circumstances. Model analysis

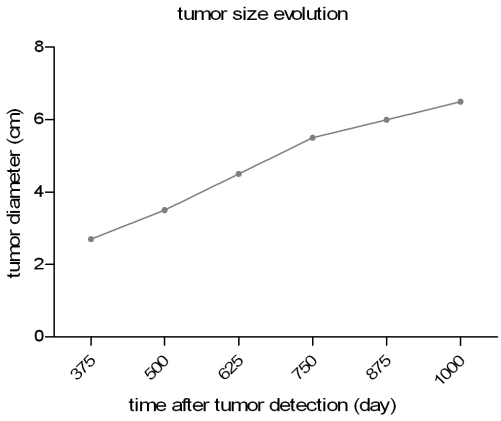

FIGURE 4. The tumor sizes were periodically measured after viral injection. Each data point represents the average tumor diameter at the corresponding time.

suggests that in situations where both the tumor and the virus populations coexist with unstable dynamics, the densities of various populations depend on a periodic administration of viruses. Indeed, under conditions where the tumor cannot be removed, we have shown by numerical simulations that the survival time of patients may be increased when the viruses are inoculated in a region near the tumor to increase their efficiency (see Fig.4).

Acknowledgments. Our thanks to the anonymous referees whose valuable comments and suggestions aided in the revision of this paper.

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Received June 11, 2012; Accepted February 01, 2013.

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