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## MODELING THE SPATIOTEMPORAL DYNAMICS OF VIROTHERAPY AND IMMUNE RESPONSE AS A TREATMENT FOR CANCER

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**Abstract.** Oncolytic virotherapy is a promising treatment for cancer, which uses viruses that selectively target and kill cancer cells. In this article, we developed a system of partial differential equations, which describes the spatiotemporal dynamics of cancer cells under virotherapy and immune response. We carried out numerical simulations of the system and analyzed the important biological parameters. The numerical results suggest that high viral infection plays an important role in improving the treatment outcomes. Moreover, strong immune response can improve the result of virotherapy along with a high immune killing rate of cancer cells. This model could be validated by using patients' data; and thus it may help oncologists choose the optimal therapy to eradicate cancer.

**Keywords:** cancer; drug delivery; immune response; mathematical modeling; oncolytic viruses.

**2010 AMS Subject Classification:** 46N60, 62P10, 35Q92.

### 1. INTRODUCTION

Recently, there has been a remarkable development in treatments for cancer. The efficacy of a treatment depends on its ability to eliminate the tumor in a short time, without damaging the surrounding healthy tissue. In the field of genetic engineering, researchers have been able

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to find a new treatment for cancer with genetically altered viruses [1]. Oncolytic virus is a promising treatment for cancer because it specifically infects the cancer cells and multiplies within them, eventually leading to its lysis. New virus molecules are then released to infect the neighboring cancer cells [2]. Virotherapy is administered into the body via different delivery methods, for example, intratumoral and intravenous [3–8]. Intratumoral delivery is restricted to easily reachable solid tumors, whereas intravenous delivery is a good option for advanced, metastatic, or unreachable cancer [9]. Clinical trials have shown success in the treatment of cancer using these two delivery methods [10–13].

By mathematical modeling we can describe the interaction between oncolytic virotherapy and tumor growth. Moreover, numerical analysis can predict the optimal strategies to ensure the effectiveness of virotherapy. Wu et al. [14] built a mathematical model consisting of a system of partial differential equations (PDEs), describing tumor growth during virotherapy. They discussed three strategies for injecting the virus: (1) uniform injection (injecting the entire tumor), (2) core injection, and (3) rim injection. They concluded through the analysis of a simplified ordinary differential equation (ODE) model that the virus injected into the tumor has the ability to control its growth. Friedman and Tao [15] developed a PDE model similar to the previous one, where the virus is injected into the tumor, but included a diffusion term for viral density. They analyzed the model to find the effect of injecting the virus on reducing tumor size and found that if viral density is large enough, it minimizes tumor size in a very short time.

One of the most important obstacles that limits the efficiency of virotherapy is the presence of immune response because it destroys both viruses and infected cancer cells (blocking the spread of viral infection) [16]. Some studies have shown how the evolution of nanotechnology has contributed to overcoming this problem. Encapsulating the oncolytic virus by nanomaterials leads to stabilization of the drug in the bloodstream [17]. There are mathematical modeling approaches to understand the immune response against virotherapy. Wein et al. [18] added into their earlier model [14] an immune response that kills virus-infected cancer cells, and they used recent preclinical and clinical data to validate the model and estimate key parameter values. They concluded that an effective immune response contributes to the removal of the virus before complete elimination of the tumor. Therefore, complete control of the tumor is

achieved using the oncolytic virus together with immune suppressors. Later, Tao and Guo [19] developed the previous model by adding a diffusion term for both viral density and immune response density [18]. Through their analysis of the model, they found a threshold for the strength of immune response to control tumor growth during virotherapy. Another model, which describes the effect of immune response on infected cancer cell population and virus population, is proposed by Phan and Tian [20]. The analysis of the model shows that if the burst size of the virus is not too big, then the immune response may complicate virotherapy by creating more equilibria.

There is still a growing need to understand how to improve the efficiency of virotherapy by combining it with other treatments. Therefore, some mathematical models have examined the effect of virotherapy in combination with immune suppressors and inhibitors [21, 22]. Friedman et al. [21] presented a mathematical model for spherical glioma, a type of cancer, undergoing virotherapy by injecting into its center. The model also includes the effect of cyclophosphamide (a chemotherapy drug that suppresses the immune response). They concluded that tumor size would decrease to being very small even without cyclophosphamide if the burst size is big. Furthermore, repeated cyclophosphamide treatment decreases the density of uninfected tumor cells and thus reduces the risk of a secondary tumor. Tao and Guo [22] developed a mathematical model describing the effect of combined treatment using an oncolytic virus and mitogen-activated protein kinase (MEK) inhibitors on tumor size. MEK inhibitors enhance the coxsackie-adenovirus receptor to ensure the entry of the virus into the tumor cell, but it can also prevent the proliferation of the virus. As a result, they studied the optimal dose and timing of MEK inhibitors. They found that the injection of the virus and MEK inhibitors at the same time achieved more effectiveness for the combined treatment.

Our goal is to understand the dynamics of virotherapy in the presence of immune response. Cancer cells have the ability to escape from the immune system [16]; however, the presence of viruses could stimulate immune cells and help them recognize and, thus, attack cancer cells [23]. We developed the model by Phan and Tian [20] by considering the effect of the immune system on uninfected cancer cells (to be published). We also added a death term for these uninfected cancer cells. The model consists of four nonlinear ODEs, describing the interaction between

tumor growth and virotherapy, along with the effect of immune response. In this article, we develop this ODE model by incorporating the spatial evolution of cells because the virus spreads into the tumor. Therefore, we added a diffusion term for viral density. The main purpose of this article is to determine the optimal strategy for viral treatment. The model would be solved numerically for different values of parameters, where the virus is given at a constant rate for a certain period of time. The latter can be accomplished by nanotechnology [24]. In Section 2, we present the model, and then in Section 3, we carry out numerical solutions of the model for different parameter values. Finally, discussion and future work are presented in Section 4.

## 2. MATHEMATICAL MODEL

Our mathematical model describes the dynamics of tumor growth under oncolytic virotherapy in the presence of immune response. In particular, we present a PDE model that takes into account the spatiotemporal evolution of cancer cells. We assume that the domain is spherically symmetric, and thus, the variables depend on time  $t$  and radial distance  $r$ . The virus is delivered through a blood vessel and diffuses into the tumor, with no flux at the boundary (right). Also, the virus is released at a constant rate for a certain time interval. We hypothesize that cancer cells depend on the closest blood vessel, which has the radius  $r_b$ . Therefore, we estimate the radius of the spherical region supported by the blood vessel by  $\frac{r_b}{\sqrt{BVF}}$ , where BVF is the blood volume fraction [25, 26].

Supposing that the oncolytic virus diffuses into the tumor, infects the cells, and then becomes inactive, the cancer cells can be divided into uninfected and infected cells. We assume that the uninfected cells grow logistically and die with a constant rate. The infected cells would eventually die, thus releasing new viruses (the virus replicates inside the infected cell). Moreover, we assume that the virus would either die naturally or by the immune system. The presence of cancer cells (uninfected and infected) stimulates the immune system, thus causing their death by natural killer cells. Finally, the immune cells die naturally. Therefore, we have the following system of PDEs:

$$\begin{aligned}
(1) \quad \frac{\partial x}{\partial t} &= \lambda x \left(1 - \frac{x+y}{C}\right) - \beta xv - \alpha xz - dx, \\
\frac{\partial y}{\partial t} &= \beta xv - \mu yz - \delta y, \\
\frac{\partial v}{\partial t} &= D\nabla^2 v + b\delta y - \beta xv - kvz - \gamma v, \\
\frac{\partial z}{\partial t} &= s_1 yz + s_2 xz - \rho z,
\end{aligned}$$

where the homogenous initial and boundary conditions are as follows:

$$\begin{aligned}
(2) \quad x(r, 0) &= x_0, \quad y(r, 0) = y_0, \quad v(r, 0) = \hat{v}_0, \quad z(r, 0) = z_0, \\
(3) \quad v(r_b, t) &= v_0, \quad \frac{\partial v}{\partial r} \left( \frac{r_b}{\sqrt{BVF}}, t \right) = 0.
\end{aligned}$$

The model variables are

$x = x(r, t)$  is the density of uninfected tumor cells,

$y = y(r, t)$  is the density of infected tumor cells,

$v = v(r, t)$  is the density of oncolytic viruses, and

$z = z(r, t)$  is the density of immune cells.

The parameters and their description, values, and units are summarized in Table 1. Note that our model is similar to the one in [20], where the new terms involve the parameters  $D$ ,  $\alpha$ ,  $d$ , and  $s_2$ . Also, we consider the spatial dependence of variables because of the diffusion of the drug. Note that  $v_0$  can depend on the time at which the virus is injected according to a specific dosing and timing regimen (e.g., bolus treatment). Here, we only consider a drug that is continuously administered for a period of time at a constant dose  $v_0$ , as suggested by Borges et al. [27] for chemotherapy. This can be done by nanotechnology, which reinforces the stability of the drug in the bloodstream [17].

### 3. NUMERICAL SOLUTION

In this section, we study the model (1) numerically with initial conditions (2) and boundary conditions (3). We discretize in space and time and use the fourth-order Runge–Kutta method [30] for time discretization and the finite difference method [31] for space discretization. For

TABLE 1. The parameters, their description and values for model (1).

Parameter	Description	Value	Units	Reference
$\lambda$	Tumor growth rate	0.02	1/h	[21]
$C$	Carrying capacity of the tumor cells	$10^6$	cells/mm <sup>3</sup>	[28]
$d$	Death rate of uninfected tumor cells	0.0042	1/h	[29]
$\beta$	Infection rate of the virus	$7/10 \times 10^{-9}$	mm <sup>3</sup> /h virus	[21]
$\delta$	Death rate of infected tumor cells	1/18	1/h	[21]
$D$	Diffusion coefficient of viruses	$5 \times 10^{-7}$	mm <sup>2</sup> /h	estimated
$b$	Burst size of the virus	500	virus/cell	estimated
$\gamma$	Clearance rate of the virus	0.025	1/h	[21]
$\alpha$	Immune killing rate of uninfected tumor cells	$3 \times 10^{-9}$	mm <sup>3</sup> /h immune cell	estimated
$\mu$	Immune killing rate of infected tumor cells	$2 \times 10^{-8}$	mm <sup>3</sup> /h immune cell	[21]
$k$	Immune killing rate of virus	$10^{-8}$	mm <sup>3</sup> /h immune cell	[21]
$s_1$	Stimulation rate of the immune response by infected cells	$5.6 \times 10^{-7}$	mm <sup>3</sup> /h infected cell	[21]
$s_2$	Stimulation rate of the immune response by uninfected cells	$6 \times 10^{-8}$	mm <sup>3</sup> /h uninfected cell	estimated
$\rho$	Clearance rate of the immune response	0.002	1/h	[20]

each numerical simulation, we use the parameter values as given in Table 1, unless otherwise stated. The initial and boundary conditions are chosen as follows:

$$(4) \quad \begin{aligned} x(r, 0) &= 0.5 \times 10^6, \quad y(r, 0) = 0.01 \times 10^6, \quad v(r, 0) = 0.5 \times 10^6, \\ z(r, 0) &= 0.01 \times 10^6, \end{aligned}$$

$$(5) \quad v(r_b, t) = 0.5 \times 10^6, \quad \frac{\partial v}{\partial r} \left( \frac{r_b}{\sqrt{BVF}}, t \right) = 0,$$

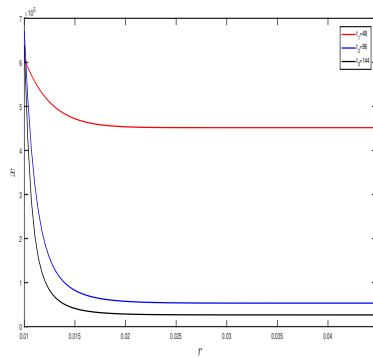
where  $r_b = 0.01$  and  $BVF=0.05$ .

We calculate  $f_x$  that represents the ratio of the uninfected (viable) cancer mass to its initial mass. This is done by integrating the density  $x$  at each time step over the spherically symmetric domain around the blood vessel, as follows:

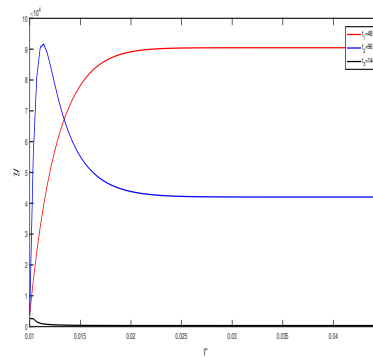
$$(6) \quad \begin{aligned} f_x(t) &= \frac{M}{M_0} = \frac{1}{x_0 V} \int_0^{2\pi} \int_{r_b}^{r_b/\sqrt{BVF}} x r dr d\theta \\ &= \frac{2\pi}{x_0 V} \int_{r_b}^{r_b/\sqrt{BVF}} x r dr, \end{aligned}$$

where  $V = \pi \left[ \left( r_b / \sqrt{BVF} \right)^2 - (r_b)^2 \right]$ . Similarly,  $f_y$ ,  $f_v$ , and  $f_z$  are calculated.

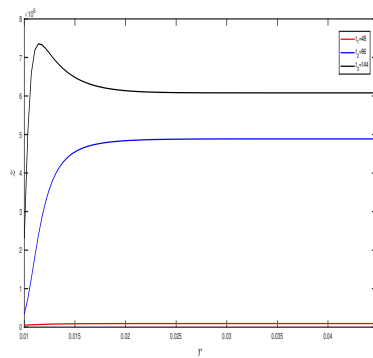
Before varying the parameters and considering the effect of the treatment on cancer growth, we solve the model (1) with the conditions (4), (5) and parameter values from Table 1, as shown in Figure 1. The time  $t$  varies from 0 to 504, which represents virotherapy given for 3 weeks. The plots in Figure 1(a)-(d) show the densities  $x$ ,  $y$ ,  $z$ , and  $v$  after the 2nd, 4th, and 6th day, respectively, of the treatment. The legend indicates the time in hours. As we are interested in viable cancer cells, we plotted the ratio of the viable cancer mass to its initial mass in Figure 1(e). Note that  $f_x = 0$  means that uninfected cells either died or became infected. Either results is our optimal goal as infected cells are damaged and would eventually die. The simulation shows that for 3 weeks of the treatment, cancer grows in the beginning of the treatment. Then, after approximately 10 days,  $f_x \approx 0.04$ . This means that the cancer mass is reduced to reach approximately 4% of its original mass.



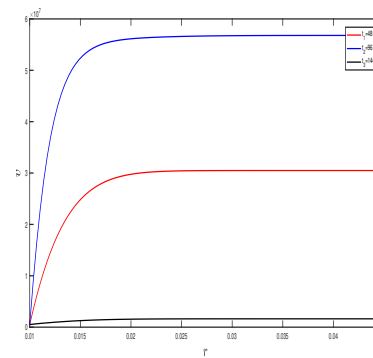
(a) Density of uninfected cells



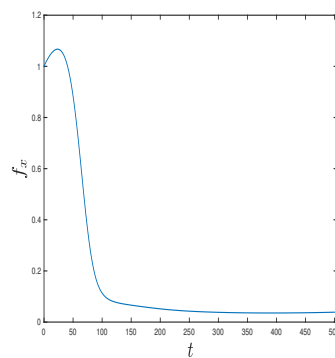
(b) Density of infected cells



(c) Density of immune cells



(d) Virus density



(e) Ratio of the uninfected cancer mass to its initial mass

FIGURE 1. Numerical simulations of (1) with the conditions (4), (5) and parameter values from Table 1. In (a)-(d), the variables are plotted after the 2nd, 4th, and 6th day of the treatment as indicated in the legend ( $t$  is given in hours). In (e), the ratio of the uninfected cancer mass to its initial mass is plotted for the whole treatment which is 3 weeks.



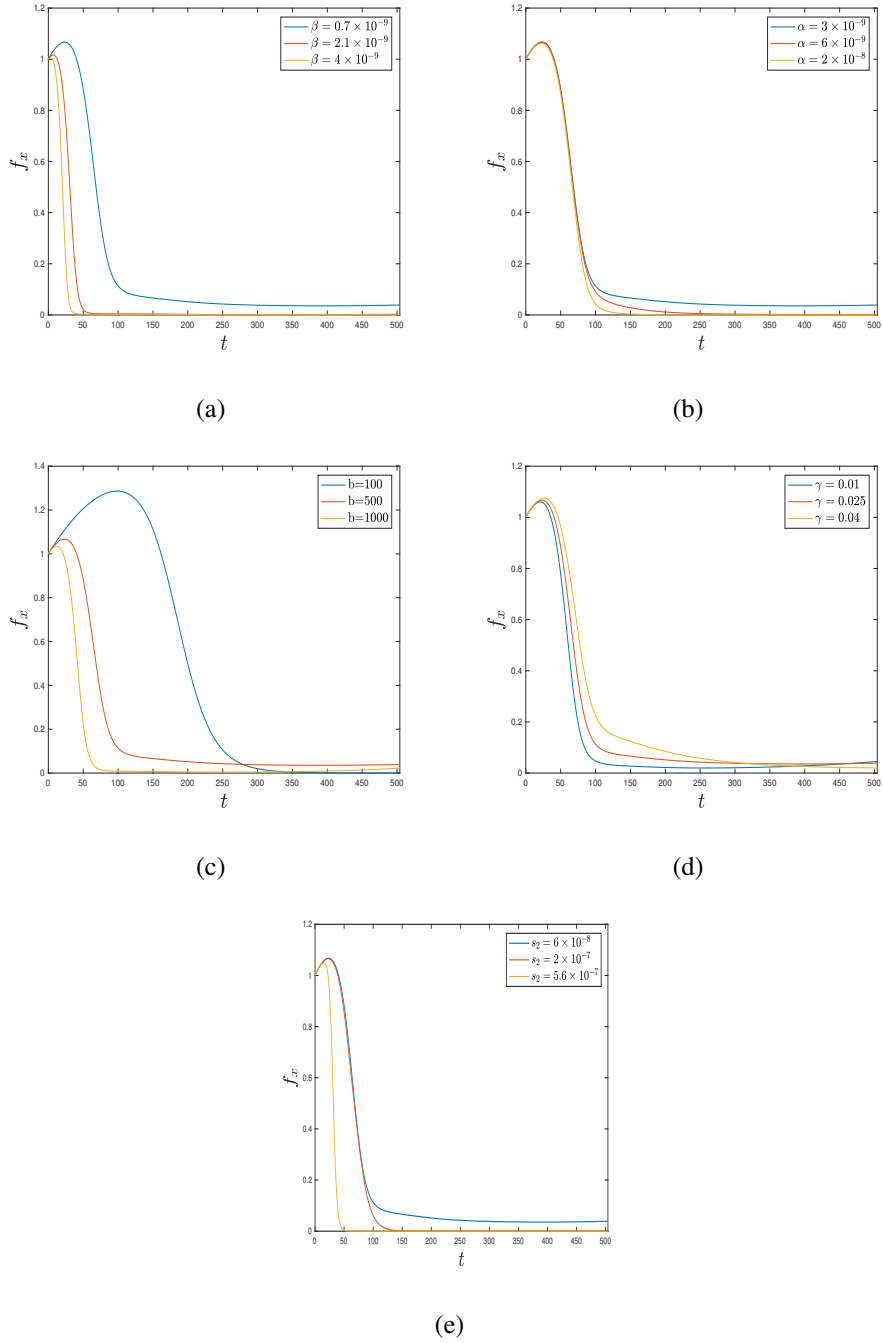


FIGURE 2. The ratio of the uninfected cancer mass to its initial mass is plotted for different values of the parameters as shown in the legend (the other parameter are taken from Table 1). In all simulations the initial and boundary conditions are as given in (4), (5).

**3.1. Parameter analysis.** In this section, we vary the parameters in the model. We focus on the infection rate of the virus ( $\beta$ ), burst size ( $b$ ), immune killing rate of uninfected cancer cells ( $\alpha$ ), clearance rate of viruses ( $\gamma$ ), and stimulation rate of immune cells by uninfected cells ( $s_2$ ). The parameters  $\beta$ ,  $b$ , and  $\gamma$  depend on the type of the virus, and thus, by varying them we consider different types of treatments. Moreover,  $\alpha$  and  $s_2$  are related to the immune response to cancer (uninfected cells). Therefore, by varying these parameters we consider cases where the immune system is stimulated by the presence of the virus or by, for example, monoclonal antibodies [32] and vaccine [33].

First, in Figure 2(a), we vary the parameter  $\beta$  (the infection rate of the virus), as indicated in the legend. For the first value of  $\beta$  (blue curve),  $f_x$  (the relative viable cancer mass) almost reaches a steady state. Then, as the infection rate increases,  $f_x$  decreases and we get a better result. For larger values of  $\beta$ ,  $f_x$  reaches zero in a short time because of the strong impact of virotherapy. For the case where  $\alpha$  (the immune killing rate of uninfected cells) is varied,  $f_x$  is almost similar at the beginning of the simulation (Figure 2(b)). Then, it is eradicated in a short time for larger values of  $\alpha$ . This shows the important role of the immune system. Now in Figure 2(c), we study the effect of the burst size ( $b$ ). The smallest value of  $b$  gives the best result; however, it takes a long time. As  $b$  increases ( $=500$ ),  $f_x$  almost reaches a steady state. This steady state becomes closer to zero as  $b$  increases to 1000. Regarding  $\gamma$  (the clearance rate of viruses), Figure 2(d) shows the impact of increasing its value. For larger values of  $\gamma$ , which means that the virus would die faster,  $f_x$  would increase as shown in the figure (yellow curve). Then, after a long time,  $f_x$  would reach smaller values than those in the other two cases (red and blue curves). Perhaps as viruses die fast (which means less viruses), the immune system kills uninfected cells. Finally, we vary the rate at which uninfected cells stimulate the immune system ( $s_2$ ), as demonstrated in Figure 2(e). It is expected that as we increase this rate,  $f_x$  would decrease and reach zero in a short time, as shown in the figure (yellow curve). This is because the strong response of the immune system would lead to the killing of uninfected cells.

#### 4. DISCUSSION AND FUTURE WORK

Virotherapy is a promising therapeutic approach for the treatment of cancer that uses genetically modified viruses to target and destroy cancer cells. The immune response is a major

obstacle that limits the efficacy of virotherapy by the eradication of viruses as well as infected cancer cells. Alternatively, new clinical studies revealed that the virus can alert the immune system to the presence of the tumor and can, thus, eradicate it [34, 35]. Therefore, we developed a mathematical model describing the spatiotemporal dynamics of virotherapy with the effect of immune response. In our model, we incorporated the impact of immune cells on uninfected cancer cells. In this article, we solved and studied the spatiotemporal dynamics of the model numerically. We varied the important parameters to examine the behavior of cancer cells in order to identify the optimal values that lead to better outcomes.

From our analysis, we found that the success of virotherapy depends on the viral infection rate. Indeed, virotherapy could be effective in controlling tumor size, provided that the viral infection rate is high. This result is in agreement with our ODE model (to be published). Furthermore, we concluded that a high immune killing rate of cancer cells leads to lower tumor growth, and high stimulation of immune cells significantly diminishes the tumor size. Also, the results show a better outcome for high values of the burst size and low clearance rate of the virus. Our results could be helpful in designing therapeutic protocols that improve the efficacy of virotherapy. This can be achieved by genetically engineering viruses with a high infection rate and burst size. It may be helpful to combine virotherapy with other therapies that stimulate the immune system to effectively recognize and attack cancer cells, for example, monoclonal antibodies [32] and vaccine [33]. Another combined therapy could include virotherapy and chemotherapy [36] or radiotherapy [37].

### **Conflict of Interests**

The author(s) declare that there is no conflict of interests.

### **REFERENCES**

- [1] H. Fukuhara, Y. Ino, T. Todo, Oncolytic virus therapy: a new era of cancer treatment at dawn, *Cancer Sci.* 107 (2016), 1373-1379.
- [2] A. Howells, G. Marelli, N. R. Lemoine, Y. Wang, Oncolytic viruses-interaction of virus and tumor cells in the battle to eliminate cancer, *Front. Oncol.* 7 (2017),195-209.
- [3] J. Maroun, M. Muñoz-Alfa, A. Ammayappan, A. Schulze, K. W. Peng, S. Russell, Designing and building oncolytic viruses, *Future Virol.* 12 (2017), 193-213.

- [4] J. Nemunaitis, F. Khuri, I. Ganly, J. Arseneau, M. Posner, E. Vokes, J. Kuhn, T. McCarty, S. Landers, A. Blackburn, L. Romel, B. Randlev, S. Kaye, D. Kirn, Phase II trial of intratumoral administration of ONYX-015, a replication-selective adenovirus, in patients with refractory head and neck cancer, *J. Clin. Oncol.* 19 (2001), 289-298.
- [5] J. R. Hecht, R. Bedford, J. L. Abbruzzese, S. Lahoti, T. R. Reid, R. M. Soetikno, D. H. Kirn, S. M. Freeman, A phase I/II trial of intratumoral endoscopic ultrasound injection of ONYX-015 with intravenous gemcitabine in unresectable pancreatic carcinoma, *Clin. Cancer Res.* 9 (2003), 555-561.
- [6] J. Nemunaitis, C. Cunningham, A. Buchanan, A. Blackburn, G. Edelman, P. Maples, G. Netto, A. Tong, B. Randlev, S. Olson, D. Kirn, Intravenous infusion of a replication-selective adenovirus (ONYX-015) in cancer patients: safety, feasibility and biological activity, *Gene Ther.* 8 (2001), 746-759.
- [7] A. I. Freeman, Z. Zakay-Rones, J. M. Gomori, E. Linetsky, L. Rasooly, E. Greenbaum, S. Rozenman-Yair, A. Panet, E. Libson, C. S. Irving, E. Galun, T. Siegal, Phase I/II trial of intravenous NDV-HUJ oncolytic virus in recurrent glioblastoma multiforme, *Mol. Ther.* 13 (2006), 221-228.
- [8] E. J. Small, M. A. Carducci, J. M. Burke, R. Rodriguez, L. Fong, L. V. Ummersen, D. C. Yu, J. Aimi, D. Ando, P. Working, D. Kirn, G. Wilding, A phase I trial of intravenous CG7870, a replication-selective, prostate-specific antigen-targeted oncolytic adenovirus, for the treatment of hormone-refractory, metastatic prostate cancer, *Mol. Ther.* 14 (2006), 107-117.
- [9] M. S. Ferguson, N. R. Lemoine, Y. Wang, Systemic delivery of oncolytic viruses: hopes and hurdles, *Adv. Virol.* 2012 (2012).
- [10] F. R. Khuri, J. Nemunaitis, I. Ganly, J. Arseneau, I. F. Tannock, L. Romel, M. Gore, J. Ironside, R. H. Macdougall, C. Heise, B. Randlev, A. M. Gillenwater, P. Brusco, S. B. Kaye, W. K. Hong, D. H. Kirn, A controlled trial of intratumoral ONYX-015, a selectively-replicating adenovirus, in combination with cisplatin and 5-fluorouracil in patients with recurrent head and neck cancer, *Nat. Med.* 6 (2000), 879-885.
- [11] R. Gollamudi, M. H. Ghalib, K. K. Desai, I. Chaudhary, B. Wong, M. Einstein, M. Coffey, G. M. Gill, K. Mettinger, J. M. Mariadason, S. Mani, S. Goel, Intravenous administration of reolysin®, a live replication competent RNA virus is safe in patients with advanced solid tumors, *Invest. New Drugs*, 28 (2010), 641-649.
- [12] V. Papanastassiou, R. Rampling, M. Fraser, R. Petty, D. Hadley, J. Nicoll, J. Harland, R. Mabbs, M. Brown, The potential for efficacy of the modified (ICP 34.5-) herpes simplex virus HSV1716 following intratumoural injection into human malignant glioma: a proof of principle study, *Gene Ther.* 9 (2002), 398-406.
- [13] I. R. Eissa, I. Bustos-Villalobos, T. Ichinose, S. Matsumura, Y. Naoe, N. Miyajima, D. Morimoto, N. Mukoyama, W. Zhiwen, M. Tanaka, H. Hasegawa, S. Sumigama, B. Aleksic, Y. Kodera, H. Kasuya, The current status and future prospects of oncolytic viruses in clinical trials against melanoma, glioma, pancreatic, and breast cancers, *Cancers*, 10 (2018), 356-375.

- [14] 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.
- [15] A. Friedman, Y. Tao, Analysis of a model of a virus that replicates selectively in tumor cells, *J. Math. Biol.* 47 (2003), 391-423.
- [16] G. Marelli, A. Howells, N. R. Lemoine, Y. Wang, Oncolytic viral therapy and the immune system: a double-edged sword against cancer, *Front. Immunol.* 9 (2018), 866-873.
- [17] K. Aoyama, S. Kuroda, T. Morihira, N. Kanaya, T. Kubota, Y. Kakiuchi, S. Kikuchi, M. Nishizaki, S. Kagawa, H. Tazawa, T. Fujiwara, Liposome-encapsulated plasmid DNA of telomerase-specific oncolytic adenovirus with stealth effect on the immune system, *Sci. Rep.* 7 (2017), 14177-14186.
- [18] L. M. Wein, J. T. Wu, D. H. Kirn, Validation and analysis of a mathematical model of a replication-competent oncolytic virus for cancer treatment: implications for virus design and delivery, *Cancer Res.* 63 (2003), 1317-1324.
- [19] Y. Tao, Q. Guo, The competitive dynamics between tumor cells, a replication-competent virus and an immune response, *J. Math. Biol.* 51 (2005), 37-74.
- [20] T. A. Phan, J. P. Tian, The role of the innate immune system in oncolytic virotherapy, *Comput. Math. Methods Med.* 2017 (2017), 1-17.
- [21] 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 (2006), 2314-2319.
- [22] Y. Tao, Q. Guo, A mathematical model of combined therapies against cancer using viruses and inhibitors, *Sci. China, Ser. A*, 51 (2008), 2315-2329.
- [23] N. L. Komarova, D. Wodarz, *Targeted cancer treatment in silico*, Birkhäuser Boston (2014).
- [24] K. T. Nguyen, Targeted nanoparticles for cancer therapy: promises and challenge, *J. Nanomed. Nanotechnol.* 2 (2011), 5.
- [25] J. Pascal, E. L. Bearer, Z. Wang, E. J. Koay, S. A. Curley, V. Cristini, Mechanistic patient-specific predictive correlation of tumor drug response with microenvironment and perfusion measurements, *Proc. Nat. Acad. Sci. (PNAS)*, 110 (2013), 14266-14271.
- [26] Z. Wang, R. Kerketta, Y. Chuang, P. Dogra, J. D. Butner, T. A. Brocato, A. Day, R. Xu, H. Shen, E. Simbawa, A. S. AL-Fhaid, S. R. Mahmoud, S. A. Curley, M. Ferrari, E. J. Koay, V. Cristini, Theory and experimental validation of a spatio-temporal model of chemotherapy transport to enhance tumor cell kill, *PLoS Comput. Biol.* 12 (2016).
- [27] F. S. Borges, K. C. Iarosz, H. P. Ren, A. M. Batista, M. S. Baptista, R. L. Viana, S. R. Lopes, C. Grebogi, Model for tumour growth with treatment by continuous and pulsed chemotherapy, *Biosyst.* 116 (2014), 43-48.
- [28] J. Malinzi, A. Eladdadi, P. Sibanda, Modelling the spatiotemporal dynamics of chemovirotherapy cancer treatment, *J. Biol. Dyn.* 11 (2017), 244-274.

- [29] E. Ratajczyk, U. Ledzewicz, H. Schättler, Optimal control for a mathematical model of glioma treatment with oncolytic therapy and TNF- $\alpha$  inhibitors, *J. Optim. Theory App.* 176 (2018), 456-477.
- [30] R. L. Burden, J. D. Faires, *Numerical Analysis*, Brooks/Cole (2011).
- [31] D. R. Lynch, *Numerical partial differential equations for environmental scientists and engineers: a first practical course*, Springer (2004).
- [32] I. Kimiz-Gebologlu, S. Gulce-Iz, C. Biray-Avci, Monoclonal antibodies in cancer immunotherapy, *Mol. Biol. Rep.* 45 (2018), 2935-2940.
- [33] L. A. Emens, Breast cancer immunotherapy: facts and hopes, *Clin. Cancer Res.* 24 (2017), 511-520.
- [34] A. Ribas, R. Dummer, I. Puzanov, A. VanderWalde, R. H. I. Andtbacka, O. Michielin, A. J. Olszanski, J. Malvehy, J. Cebon, E. Fernandez, J. M. Kirkwood, T. F. Gajewski, L. Chen, K. S. Gorski, A. A. Anderson, S. J. Diede, M. E. Lassman, J. Gansert, F. S. Hodi, G. V. Long, Oncolytic virotherapy promotes intratumoral T cell infiltration and improves anti-PD-1 immunotherapy, *Cell*, 170 (2017), 1109-1119.
- [35] M. Kim, M. Nitschké, B. Sennino, P. Murer, B. J. Schriver, A. Bell, A. Subramanian, C. E. McDonald, J. Wang, H. Cha, M.-C. Bourgeois-Daigneault, D. H. Kirn, J. C. Bell, N. D. Silva, C. J. Breitbach, D. M. McDonald, Amplification of oncolytic vaccinia virus widespread tumor cell killing by sunitinib through multiple mechanisms, *Cancer Res.* 78 (2018), 922- 937.
- [36] S. T. Wennier, J. Liu, G. McFadden, Bugs and drugs: oncolytic virotherapy in combination with chemotherapy, *Curr. Pharm. Biotechnol.* 13 (2012), 1817-1833.
- [37] Y. Touchefeu, P. Franken, K. J. J. Harrington, Radiovirotherapy: principles and prospects in oncology, *Curr. Pharm. Des.* 18 (2012), 3313-3320.