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EFFICACY OF A COMBINATION THERAPY FOR A MATHEMATICAL MODEL OF GLIOMA

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ABSTRACT

We will present a mathematical model for a virotherapy of glioma. The action of the continuously injected herpes simplex virus will be supported by an inhibitor of the TNF-α, which will be applied to supress the innate immune response by macrophages. We will study the efficacy of the treatment measured in the radius of the tumor under different combination of the two drugs. The model may serve as a first step toward developing an optimal strategy for the treatment of glioma by the combination of TNF-α inhibitor and oncolytic virus injection.

INTRODUCTION

Oncolytic viruses are genetically altered replication-competent viruses which infect and reproduce in cancer cells but do not harm normal cells. When an infected cell dies many newly formed viruses are released and spread out infectiong neighboring tumor cells. This therapy, although based on quite promising assumptions, enounters one major obstacle; the innate immune system recognizes the infected cells and destroys them before the viruses within them get a chance to multiply [2].

It was reported in [4] that CD 163+ macrophages in the rats experiments for glioma inhibited OV therapy making it unsuccessful. The solution suggested in [4] was to use cyclophosphamide (CPA) as a suppressant of the immune response through the inhibition of CD 163+ and thus enhance the effectiveness of the OV therapy.

This approach has been studied from the mathematical point of view by Friedman et al. in [3]. The model in [3] was described by the system of PDEs and effect of the therapy with and without CPA was analyzed.

In the present paper we intend to pick up on this work, but pursue a different avenue based on a very recent paper by Auffinger et al. [1]. In that paper was suggested that in order to enable the effective action of the virotherapy one should try to block the main "weapon" used by macrophages, namely the TNF-α. It was demonstrated there that inhibition of TNF-α could significantly enhance virus replication and the efficacy of the overal treatment.

Thus our goal here it to construct a model which captures the interactions between healthy tumor cells, infected tumor cells, the viruses and macrophages and the TNF-α they produce. The model is based on the work of Friedman et al. [3]. However, here we will formulate a reduction of this model from the spatial PDE model to the population type ODE model. For this will enable us pursue detailed dynamical system analysis of the model as well as analysis of it as an optimal control problem for drug treatment. Although the spatial element has to be compromised for that, it is not entirely removed from the analysis. Indeed, we will be able to estimate the tumor radius in terms of the cells population. The efficacy of both treatments by injection of virus and TNF-α inhibitor will be analyzed in the context of the radius of the tumor.

The approach pursued in our paper will be to target the tumor by combining the two therapies: the viral injection and the TNF-α inhibitor. We will analyze the response of the system to various doses, particularly the efficacy of the therapy having as a goal the minimization of the tumor radius. The administration of the virus will be pursued through a continuous injection.

One aspect to be taken into account is determining the doses of administration of both therapetic agents: the virus and the TNF-α inhibitor have negative side-effects.

A MATHEMATICAL MODEL

Let $x(t)$ denote the density of cancer cells (uninfected), $y(t)$ the density of infected cancer cells, $v(t)$ the density of the virus, $M(t)$ the density of the macrophages, and $T(t)$ the concentration of TNF-α, $T(t)$. The model includes two controls, u_1 and u_2. The control $u_1(t)$ represents the amount of the virus that is injected into the tumor and the control $u_2(t)$ stands for the dosage of the TNF-α inhibitor.

The burst number is the number of virus that emerge from dying cancer cells. We shall take it in the range of $50 \leqslant b \leqslant 150$. Using units of $\frac{g}{cm^3}$, the parameter b is the burst size defined as $b \times \frac{mass\ of\ virus}{mass\ of\ cells} = b \times 10^{-6}$.

The dynamics of the model is expressed mathematically by the following system of the ODEs:

$$\frac{dx}{dt} = \alpha x - \beta x v - \delta_x x, \tag{1}$$

$$\frac{dy}{dt} = \beta x v - k y \frac{T}{K+T} - \delta_y y, \tag{2}$$

$$\frac{dM}{dt} = A + syM - \delta_M M, \tag{3}$$

$$\frac{dT}{dt} = \frac{\lambda}{1+u_2} M - \kappa y \frac{T}{K+T} - \delta_T T, \tag{4}$$

$$\frac{dv}{dt} = b_1 k y \frac{T}{K+T} + b\delta_y y - \rho x v - \delta_v v + u_1. \tag{5}$$

All the densities and concentrations are in unit of $\frac{g}{cm^3}$. In Eq. (1) α represents the proliferation rate of unifected cancer cells and δ_x is the death rate; β is the infection rate of x by viruses v. In Eq. (2) the term $ky\frac{T}{K+T}$ represents the necrotic death of infected celss caused by TNF-α, while δ_y is the death by apoptosis. When a cell y dies by apoptosis, b virus particles are released, while if it dies by necrosis a very small number, b_1, of viruses emerge. These are accounted by the first two terms on the right hand side of Eq. (5). In Eq. (3) the terms A and $\delta_M M$ represent the source and death of macrophages under healthy normal conditions, while syM accounts for the tumorigenic response of the immune system invoked by the infected cells y. In Eq. (4), the first term on the right-hand side is the production of TNF-α by macrophages. while the remaining two terms are loss by absorption within y cells and by natural degradation. The virus equation (5) includes virus particles from dead y cells and loss from absorption by x (i.e. $\rho x v$) and natural degradation/clearance ($\delta_v v$). We also included in the model a continuous injection u_1 of virus, as virotherapeutic drug, and a continuous injection u_2 as TNF-α inhibitor (in Eq. (4)).

In the present paper we take $u_1 \equiv const = C$ and $u_2 \equiv const = D$. We expect b_1 to be very small (viruses are damaged during necrosis) so for simplicity we shall take $b_1 = 0$. As in [3] the viruses burst (or replication) number b will play a major role in the progression of the disease and its treatment.

We denote by $n(t)$ the density of all the dead cells. Then, in addition to the dynamics given by (1)-(5), we have the equation

$$\frac{dn}{dt} = ky\frac{T}{K+T} + \delta_y y + \delta_x x + \delta_M M - \mu n, \tag{6}$$

where μ is the rate by which dead cells are cleared out of the tumor.

Table 1 gives the values of the parameters, which will be used in our analysis.

Tabela 1. Parameters of the model

Parameter	Description	Num. values	Dimension
α	Proliferation rate of uninfected tumor cells	0.2	1/day
β	Infection rate of tumor cells by viruses	$2 \cdot 10^4$	$\frac{cm^3}{g \cdot day}$
ρ	Rate of loss of viruses during infection	$4 \cdot 10^{-2}$	$\frac{cm^3}{g \cdot day}$
k	Effectiveness of the inhibitory action of TNF-α	0.4	1/day
δ_y	Infected tumor cell death rate	0.2	1/day
λ	TNF-α production rate	$2.86 \cdot 10^{-3}$	1/day
δ_T	TNF -α cell degradation rate	55.45	1/day
δ_M	Macrophages death rate	0.015	1/day
K	Carrying capacity of the TNF-α	$5 \cdot 10^{-7}$	$\frac{g}{cm^3}$
κ	Degradation of TNF-α due to its action on infected cells	$4 \cdot 10^{-10}$	1/day
δ_v	Virus lysis rate	0.5	1/day
A	Constant source of macrophages	$9 \cdot 10^{-7}$	$\frac{g}{cm^3 \cdot day}$
s	Stimulation rate of macrophages by infected cells without stimulus	0.15	$\frac{cm^3}{g \cdot day}$
δ_x	death rate of uninfected cancer cells	0.1	1/day
μ	removal rate of dead cells	0.25	1/day
θ_0	average of total densitiy of cells	0.9	g/cm^3

CALCULATION OF THE TUMOR RADIUS

We assume that the tumor is sperical with variable radius $R(t)$, volume $V(t)$ and a mass $m(t) = x(t) + y(t) + M(t) + n(t)$. Thus at each point of the sphere the density of the cells increases at the rate $\frac{dm}{dt}$. Adding up the equations (1)-(3) and (6) we get

$$\frac{dm}{dt} = \alpha x - \delta_x x + A + syM - \mu n$$

The total mass of the tumor then increases at rate

$$V(t)(\alpha\widetilde{x} - \delta_x\widetilde{x} + A + s\widetilde{yM} - \mu\widetilde{n})$$

where $\widetilde{z}$ is the average of z. Let θ_0 is be the sum of averages, $\theta_0 = \widetilde{x} + \widetilde{y} + \widetilde{M} + \widetilde{n}$.We assume that that increase in total mass causes the tumor volume to increase propotionally, that is by $\theta_0 \frac{dV}{dt}$ and that $\widetilde{yM} = \widetilde{y}\widetilde{M}$ so that

$$\theta_0 \frac{dV}{dt} = V(t)(\alpha\widetilde{x} - \delta_x\widetilde{x} + A + s\widetilde{y}\widetilde{M} - \mu\widetilde{n})$$

Since

$$\frac{dV}{dt}V = \frac{3}{R}\frac{dR}{dt}$$

we get

$$\theta_0 \frac{3}{R}\frac{dR}{dt} = (\alpha\widetilde{x} - \delta_x\widetilde{x} + A + s\widetilde{y}\widetilde{M}) - \mu\widetilde{n}$$

Hence

$$\theta_0 \frac{3}{R}\frac{dR}{dt} = (\alpha\widetilde{x} - \delta_x\widetilde{x} + A + s\widetilde{y}\widetilde{M}) - \mu(\theta_0 - \widetilde{x} - \widetilde{y} - \widetilde{M})$$

Finally we assume that x, y, M and v satisfy the same equation as the averages $\widetilde{x}$, $\widetilde{y}$, $\widetilde{M}$ and $\widetilde{v}$. Hence we get the following formula for the tumor radius:

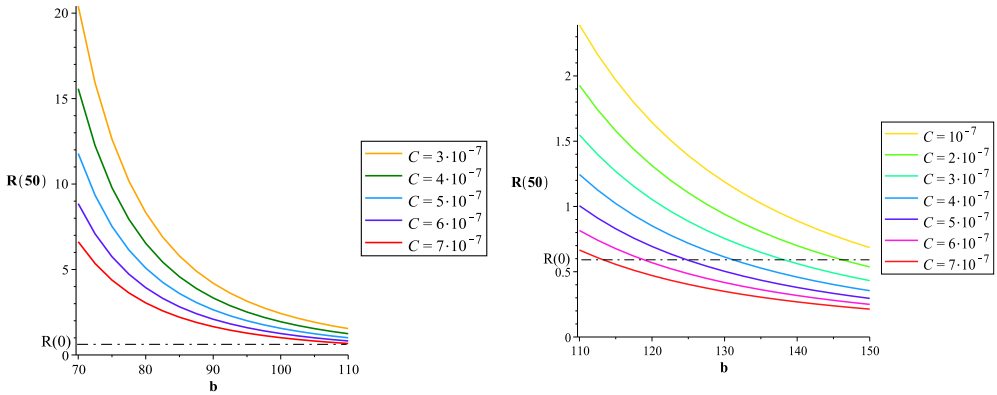
$$\theta_0 \frac{3}{R}\frac{dR}{dt} = (\alpha x - \delta_x x + A + syM) - \mu(\theta_0 - x - y - M) \tag{7}$$

RESULTS

In this section we simulate the model (1)-(7) in order to determine how the state of the system responds to a combined therapy. We assume that the process starts with the following initial conditions:

$$x(0) = 0.7,\ \ y(0) = 0.1,\ \ n(0) = 0,\ M(0) = 0.1,\ \ T(0) = 10^{-7},\ \ \frac{4\pi}{3}R(0)^3 = 0.9.$$

We assume that initially we inject dose of viruses, given by $v(0) = 10^{-6}$ and no additional therapy is given. If b is small, namely $b = 70$, the tumor radius increases to $43cm$ at $t = 50$. For $b = 90$, $R(50)$ is still large, namely $R(50) \approx 6cm$. It is only when $b = 150$ that $R(50)$ does no longer increase relative to $R(0)$. These results are in agreement with the mouse experiments in [3] in the sense that if $b = 50$ the tumor radius quickly increases while if $b = 150$ the radius begins to decrease. The simulations of $T(t)$ suggests that the initial load $v(0)$ results in massive increase of TNF-α. We also see that after initial injection of the virus, the virus is multiplying to achieve its maximum by day about 30 for $b = 70$ and 90; after that, the virus density keeps decreasing - the drug is 'too week'. As a result, the growth of R after day 30 is limited. However, the increasing amount of virus in the first 30 days causes M to growth - which leads to growth of T mentioned above. And big amounts of T restrains the replication of virus residing in infected cells y - which is bad for the therapy.



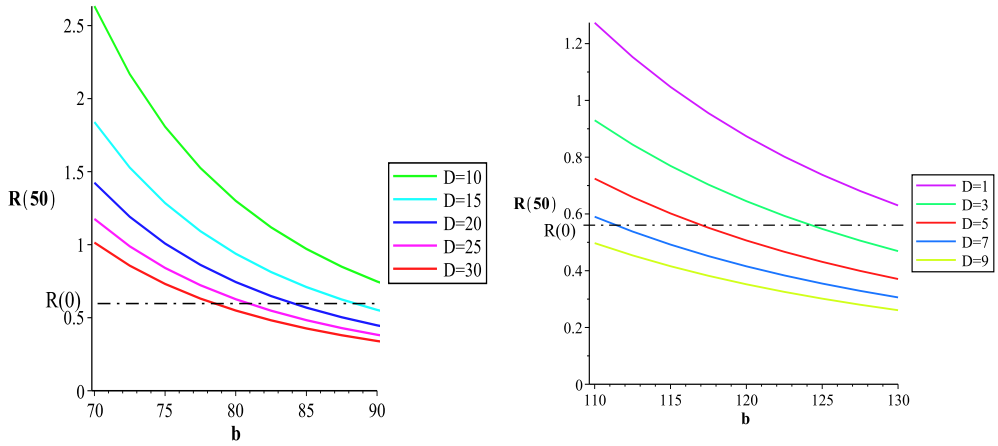
Rysunek 1. Graphs of $R(50)$ for different values of C.

We will now study behaviour of the system that we apply constant viral infusion $C = 5 \cdot 10^{-7}$. The effect of the drug on the tumor radius is as follows: for $b = 70$ and $b = 90$ the radius $R(t)$ is still increasing, although much less than in the case of $C = 0$. But for $b = 150$ function R after small initial increase, is strictly decreasing, with $R(50)$ approximately half the initial tumor

radius. Fig. 1 shows the profile of $R(50)$ as a function of b. We see that $R(50)$ is monotone decreasing function of b; furthermore for smaller b's the decline in $R(50)$, as b increases, is more steep. For each value of b, we can determine the exact value of C for which the drug will decrease $R(50)$ below its initial size. For $b < 120$ doses around 10^{-7} do not decrease R by day 50, but for $b > 120$, the smaller doses will make $R(50)$ smaller than $R(0)$.

Next we will assume that combined therapy is given at constant rates, i.e. $C = 5 \cdot 10^{-7}$ and $D = 15$. Firstly, for $b = 70$, the tumor size increases but not as much as in the case $D = 0$ (now $R(50)$ is 5 times smaller). For $b = 90$ the tumor radius, after initial increase, goes down to reach its initial size. Finally for $b = 150$ we also obtain our desired goal for tumor reduction ($R(50) \approx 0.1cm$). We note here that values of $T(t)$ are of an order of magnitude lower than in the case $D = 0$. Applying D also supports growth of v - now it is about 5 times higher.

Now it becomes natural to look closer at the therapy itself and see how the two main agents: viral infusion and TNF-α inhibitor contribute to the succes of the therapy. Fig. 2 shows how the system evolves in terms of $R(50)$ for variable replication number b while applying different D amounts. We see that even for $b = 80$ and $C = 5 \cdot 10^{-7}$ we can decrease $R(50)$ from $R(0)$ if we take $D = 30$. In the figure with $b \in [110, 130]$ we use lower C, namely $C = 3 \cdot 10^{-7}$, then even with such high burst number, with $D = 0$, $R(50) > R(0)$. This case shows the signifficant effect of small doses of D may have, namely for $b \geqslant 123$, with the low dose of D, $D = 3$ we get the desired shrinkage of the tumor radius i.e. $R(50) < R(0)$.



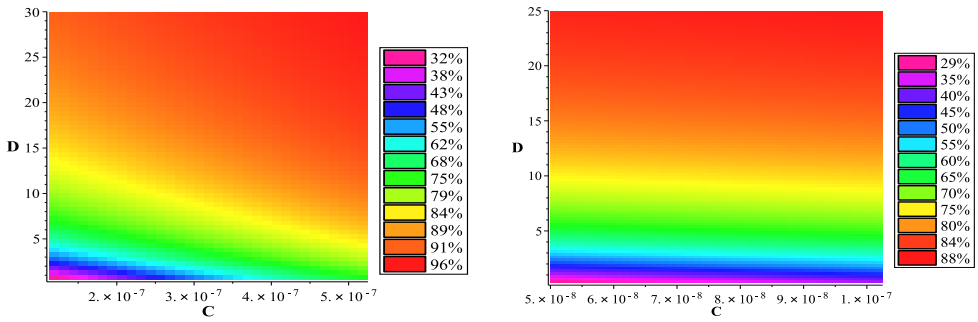
Rysunek 2. Graphs of $R(50)$ for fixed C and different values of D.

In order to capture more clearly the benefits of the dual therapy by C and D, we introduce the concept of efficacy. Let T denote the duration of the therapy. For our analysis we will choose the window of $T = 50$. We denote by $R(C, D)$ the radius of the tumor at the day T under the combined treatment with $u_1(t) \equiv C$ and $u_2(t) \equiv D$. The efficacy of the combined therapy is defined by

$$E(C, D) = \frac{R(0, 0) - R(C, D)}{R(0, 0)}.$$

Fig. 3 is an efficacy map for the case $b = 90$ showing the efficacy of the combined treatment with C varying along the horizontal axis and D along the vertical one. We can see that the efficacy of the combined treatment increases with either C or D. For small C, the efficacy goes up sharply with D. For $D > 4$ (TNF-α production is inhibited by 80%) the efficacy grows slowly with C. An efficacy map for $b = 70$ has the same features as in Fig. 3 (not shown here).

In the efficacy map for the case $b = 150$ we take a smaller range of C, $C \in [10^{-7}, 5 \cdot 10^{-7}]$. The reason is that for higher values of C, $R(50)$ will become very small even if $D = 0$. We still



Rysunek 3. Efficacy maps for $b = 90$ and $b = 150$, respectively.

see for small C a sharp increase in the efficacy as D increases, but for fixed D there is almost no increase in the efficacy as C increases.

DISCUSSION AND CONCLUSION

Following recent experiments [5] that show that blocking macrophages-produced TNF-α can enhance virotherapy treatment in glioma. We developed a mathematical model which includes both drugs, oncolytic viruses and TNF-α inhibitor. We observed that the burst number b plays a critical role in the model. Given a combined therapy (C, D) and terminal time T, the tumor radius $R(t)$ at time $t = T$ will be smaller then the initial radius $R(0)$ if and only if b exceeds certain treshold number, $b(C, D)$. Furthermore, we developed an efficacy map of treatment that depends on b. Generally the maps show the importance of the TNF-α inhibitor application in the combined therapy. Even a small dose applied we can obtain better efficacy than raising the level of viral infusion very significantly. Further work on the topic will include analysis of the model as a dynamical system with a goal of establishing long term behaviour.

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