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On assessing quality of therapy in non-linear distributed mathematical models for brain tumor growth dynamics

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ABSTRACT

In this paper a mathematical model for glioma therapy based on the Gompertzian law of cell growth is presented. In the common case the model is considered with non-linear spatially varying diffusion depending on a parameter. The case of the linear spatially-varying diffusion arose as a special case for a particular value of the parameter.

Effectiveness of the medicine is described in terms of a therapy function. At any given moment the amount of the applied chemotherapeutic agent is regulated by a control function with a bounded maximum. Additionally, the total quantity of chemotherapeutic agent which can be used during the treatment process is bounded.

The main goal of the work is to compare the quality of the optimal strategy of treatment with the quality of another one, proposed by the authors and called the alternative strategy. As the criterion of the quality of the treatment, the amount of the cancer cells at the end of the therapy is chosen. The authors concentrate their efforts on finding a good estimate for the lower bound of the cost-function. Thus it becomes possible to compare the quality of the optimal treatment strategy with the quality of the alternative treatment strategy without explicitly finding the optimal control function.

Introduction

Mathematical models of brain tumor growth under consideration of diffusion have been developed and studied in many papers (see for example [31–33,16,34,3,25,27,35,17,20,21,24]). An optimal-control approach to cancer treatment, especially to brain cancer treatment, is well-established (see [8,9,11,18]). In particular, a comparison of optimal and suboptimal treatment protocols was already considered for some models of tumor anti-angiogenesis in [22].

The basic model we are developing further was suggested in [31,33] and is based on the model of Murray [26]. In these models the authors assume a linear spatially-varying diffusion and the exponential growth law for the tumor cells:

$$\frac{\partial c(x,t)}{\partial t} = \nabla(D(x)\nabla c(x,t)) + \rho c(x,t), \quad \text{(see [29, from p.536])}$$

$$\frac{\partial c(x,t)}{\partial t} = \nabla(D(x)\nabla c(x,t)) + \rho c(x,t) - G(t)c(x,t), \quad \text{(see [36, 34])}$$

where the function c denotes the density of tumor cells, $D(x)$ has only two values $D(x) = D_G$, for x in gray matter and $D(x) = D_W$ for x in white matter with $D_W > D_G$, $\rho \in \mathbb{R}_+$ is a constant and $G(t) = k \in \mathbb{R}$ when the chemotherapy is being administered, and $G(t) = 0$ otherwise.

The model suggested in Section 1 is distinguished from the Murray et al. model mainly by the assumption of the Gompertzian law of cell growth and the non-linear spatially-varying diffusion depending on a parameter. The dynamics of the amount of the chemotherapeutic agent is in contrast to the model of Murray et al. a part of the model too. The class of the therapy functions considered is wider than in [31].

In the model suggested in this article we will adopt the Gompertzian growth law for the tumor cells since the Gompertzian models ensure that the growth rate of the tumor cells reduces as the maximal density of the tumor cells is approached while the exponential growth assumes unlimited growth of the density of tumor cells.

Another significant difference between the model suggested and the model from [31,33] is a non-linear spatially-varying diffusion as in [1,29]. The case of the linear spatially-varying diffusion arose as a special case for a particular parameter value. The description of the diffusion of the malignant glioma cells is still a subject of discussion (see [1,2,13,7,14,30]). In [30] it is argued that

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there is no significant difference in motility between cultures of a gross tumor and a histologically normal brain. On the other hand many authors stress an extensive non-linear character of the tumor cells distribution [12,1,13]. In [1] a non-linear diffusion in the form $\nabla(C^k\nabla C)$ depending on a parameter k is considered. For $k>0$ the tissue is modeled rather as a porous medium and for $k=0$ as a special case with a linear diffusion studied in detail in [2]. Analogous law is usually used for the description of the diffusion in porous medium (see, for instance, [4,29]). We assume this description of the diffusion for the model suggested too.

The nature of the interaction between the tumor size and the prescribed treatment is still up for debate. In the present work a wide class of increasing concave bounded therapy functions is examined.

The main goal of the work is to compare the quality of the optimal strategy of treatment with the quality of another one, proposed by the authors in Section 4 and called 'the alternative'. As the criterion of the quality of the treatment, the amount of the cancer cells at the end of the therapy is chosen. At any given moment the amount of the applied chemotherapeutic agent is regulated by a control function with a bounded maximum. Additionally, the total quantity of chemotherapeutic agent which can be used during the treatment process is bounded.

Despite the essential progress achieved in the solving of optimization problems for distributed systems (see [23]) the search for the optimal control for problems described in terms of non-linear equations of parabolic type is still mathematically very difficult. Therefore the authors concentrate their efforts in Section 3 on finding a good estimate for the lower boundary of the cost-function. Thus it becomes possible to compare the quality of the optimal treatment strategy with the quality of the alternative treatment strategy without explicitly finding the optimal control function. The corridor between the analytical lower estimate and the value of the cost-function on the alternative control enables qualitative assessments and forecasts for the results of the treatment to be made.

1. Model and optimization problem formulation

Let $\Omega\subset\mathbb{R}^3$ be a bounded domain of volume S with a smooth boundary Γ, n be the outer normal unit vector to Γ. For $f\in L_1(\Omega)$ we denote onward

$$\overline{f}:=\int_\Omega f(x)dx.$$

Let $c(x,t)\in C^1(\Omega\times[0,T])$ be the density of tumor cells and $h(x,t)$ the amount of the chemotherapeutic in $x\in\Omega$ at the moment t. We will consider the following model describing the growth of the tumor cells under the influence of chemotherapy:

$$\begin{aligned}\frac{\partial c(x,t)}{\partial t}&=\rho c(x,t)(1-\beta\ln c(x,t))+A_\alpha c(x,t)-c(x,t)G(h)\\ \frac{\partial h(x,t)}{\partial t}&=-\gamma_h h(x,t)+A_{\alpha_h}h(x,t)+u(x,t),\quad 0\leqslant t\leqslant T;\end{aligned}\tag{1.1}$$

where $\rho,\beta,d_h,\gamma_h,c_{lim},\alpha,\alpha_h\in\mathbb{R}_+$ are constants and $\beta=\frac{1}{\ln c_{lim}}$,

$$A_\alpha c(x,t):=\sum_{i=1}^3\frac{\partial}{\partial x_i}\left(D(x)\cdot c(x,t)^{2\alpha}\cdot\frac{\partial c(x,t)}{\partial x_i}\right),$$

$$A_{\alpha_h}h(x,t):=d_h\sum_{i=1}^3\frac{\partial}{\partial x_i}\left(h(x,t)^{2\alpha_h}\cdot\frac{\partial h(x,t)}{\partial x_i}\right)$$

with $D(x)=D_w$ for white matter and $D(x)=D_g$ (see [26]) for gray matter. The parameters α,α_h characterize the degree of the non-linearity of the respectively diffusions. The parameter ρ (see [26]) denotes the growth rate of tumor cells, c_{lim} the maximum density of the tumor cells, d_h is the diffusion coefficient of the medicine, γ_h the dissipation rate of the medicine, $G(h)$ describes the influence of the chemotherapeutic (called *therapy function*). We will consider the class of increasing concave bounded functions with $G(0)=0$ e.g.,

$$G(h)=\frac{\lambda h}{1+h},\quad \lambda\in\mathbb{R}^+.$$

The control function $u(x,t)\in L_\infty(\Omega\times[0,T])$ denotes the quantity of the chemotherapeutic agent applied to a patient at the moment t in $x\in\Omega$.

For the cumulative amount of the chemotherapeutic agent the following inequality

$$\int_0^T\int_\Omega h(x,t)dxdt\leqslant Q_0\tag{1.2}$$

with $Q_0>0$ holds.

Note 1. For $\alpha=0$ (respectively $\alpha_h=0$) the diffusions become linear

$$A_0c(x,t)=\nabla(D(x)\nabla c(x,t)),\quad A_0h(x,t)=d_h\Delta h(x,t).$$

The model description is completed with the following initial conditions

$$c(x,0)=c_0(x)>0,\quad h(x,0)=0\tag{1.3}$$

and some boundary conditions which prohibit the migration of the tumor cells outside the brain boundary.

It makes sense to consider two kinds of boundary conditions: either if $\alpha\geqslant 0$

$$\frac{\partial c(x,t)}{\partial n}|_{\Gamma\times(0,T]}=0,\quad \frac{\partial h(x,t)}{\partial n}|_{\Gamma\times(0,T]}=0;\tag{1.4}$$

or if $\alpha>\frac{1}{2}$

$$c(x,t)|_{\Gamma\times(0,T]}=0,\quad \frac{\partial h(x,t)}{\partial n}|_{\Gamma\times(0,T]}=0\tag{1.5}$$

(see Section 3 of the present article).

The actual optimal control problem

Let $K\subseteq L_\infty(\Omega\times[0,T])$. In what follows we will consider three possibilities to define K:

- $K_1:\{u(x,t)\in L_\infty(\Omega\times[0,T])\mid u(x,t)=\delta(x-x^*)u(t),\ x^*\in\Omega\}$ where δ be the Dirac function,
- $K_2:\{u(x,t)\in L_\infty(\Omega\times[0,T])\mid u(x,t)=u(t)\}$,
- $K_3:\{u(x,t)\in L_\infty(\Omega\times[0,T])\mid u(x,t)=\chi_C(x)u(t)\}$, where

$$\chi_C(x):=\begin{cases}1, & x\in C,\\ 0, & x\notin C\end{cases}$$

is the characteristic function of a compact set $C\subset\Omega$ of area S_C.

In each of the three cases the inequality

$$0\leqslant u(t)\leqslant q\tag{1.6}$$

must hold with $q>0$.

Consider the following optimal control problem. We need to find the time $T\in(0,\infty)$ and the control function $u(x,t)\in K$ such that $u(x,t),T$ provide the infimum to the cost-function:

$$\Phi(u,T)=\int_\Omega\ln c(x,T)dx=:\overline{\ln c}(T)\tag{1.7}$$

Let

$$\inf_{u\in K}\Phi(u,T)=\Phi(u^*,T).$$