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Anita Krawczyk

INHIBITING TUMOR GROWTH BY GM-CSF TREATMENT, SUFFICIENT ε-OPTIMALITY IN ONE-DIMENSIONAL SPACE

Summary

A mathematical model based on system of partial differential equations describing inhibition of tumor growth by GM-CSF treatment was created in [1]. It was assumed that tumor is a spherical model, the injection regimen was not optimized. In this paper we assume that tumor is a ball (but velocity vector $\vec{v} = [v_1, v_1]$) so we can compare results with [1]. Moreover we construct dual dynamic programming approach and formulate a sufficient ε-optimality condition for the treatment.

Keywords and phrases: mathematical model of tumor growth, tumor growth inhibiting, sufficient ε-optimality, one-dimensional space deformation

1. Introduction

In recent times many experiments concerning cancer treatment were conducted and some mathematical models were created to numerically simulate tumor growth. Some of these experiments measured the effect of inhibiting tumor growth by GM-CSF treatment on mice with HIF-1α deficient or HIF-2α deficient macrophages (see e.g. [2], [3], [4], [12], [13]). Basing on them a mathematical model consisting of a system of partial differential equations was created and presented in the paper [1]. More precisely paper [1] contains a mathematical model of a tumor that includes the interactions between live and dead tumor cells, macrophages, endothelial cells and the cytokines, such as M-CSF, GM-CSF, VEGF, sVEGFR-1, MCP-1/CCL2, and oxygen. The paper also includes the effects of HIF-1α and HIF-2α factors in GM-CSF-treated and untreated tumor growth. The model is used to predict the tumor volume growth under partial blocking of HIF-1α or stabilization of HIF-2α, with injection of GM-CSF and to compare it with the growth without injection.

For simplicity, in [1], the tumor is assumed to be a spheroid. The boundary of the tumor moves with the velocity $\vec{v}$ in the direction of the normal. For this model the sensitivity analysis was carried out with respect to the parameter list to choose the most important of them. Numerical simulations for different parameters were proceeded using Matlab, results were compared to the experimental facts. The model was used to examine the effect of different GM-CSF dosing regimens, degradation of HIF-1α, and/or stabilization of HIF-2α on tumor reduction. In the paper [1] different GM-CSF dosing protocols are compared but optimization problem is not considered at all. Moreover no verification theorem was presented so the numerical simulations do not guarantee that the calculated results (given in the form of figures) are really proper approximate solutions at least from mathematical point of view.

The main aim of this paper is to extend the approach to the GM-CSF treatment presented in [1]. In [1] tumor was assumed to be a spheroid and calculations were conducted in R^1 so only one velocity v was used and tumor size was calculated using its radius. As a computational tool we are using FreeFem++, which demands at least 2 dimensions to build triangular finite element. For this reason we conduct calculations in R^2 but assume that velocity vector $\vec{v} = [v_1, v_1]$ so results can be quite easy compared with these presented in [1]. We don't just repeat previous calculations. Due to different tool and different approach to building new boundary actually we construct different computational method so in a consequence results can be different. Moreover first we formulate the problem of GM-CSF dosing protocols as optimal control problem for simplified model, next basing on ideas presented in [6] we construct dual dynamic programming methodology for created optimal control problem and we formulate verification theorem for approximate minimum. Basing on this verification theorem we build a numerical algorithm looking for an approximate optimal solution for treatment by GM-CSF. So we have the formulae which allows us to check whether the calculated functions realize approximate optimal control problem with given $\varepsilon > 0$. It means that we know that the calculated treatment of GM-CSF is really $\varepsilon-$optimal accordingly to the mathematical model what is the most significant development comparing to the [1].

1.1. Mathematical model

The mathematical model focuses on major cells such as live and dead tumor cells, macrophages, endothelial cells (EC) and the cytokines including M-CSF, MCP-1/CCL2, GM-CSF, VEGF, sVEGFR-1, as well as oxygen molecules. Two-phase free boundary model was created where the tumor is modeled as a growing continuum $\Omega(t)$ with boundary $\partial\Omega(t)$, both evolved in time. The tumor region $\Omega(t)$ is included in a fixed domain $D \subset \mathbf{R}^2$ where the region $D \setminus \Omega(t)$ represents the healthy tissue. Live and dead tumor cells are assumed to be only in $\Omega(t)$ while macrophages, endothelial cells, cytokines and oxygen molecules are assumed to be

in both, tumor and healthy tissue; cytokines and oxygen molecules due to their size can diffuse throughout the whole domain D. A macroscopic velocity field $\mathbf{v}$ exists in $\Omega(t)$, while $\mathbf{v} = 0$ in $D \setminus \Omega(t)$. Following [1] we use below notations of densities for defining cell species and cytokines in the system of ten equations.

Cells	
$c(r,t)$	live tumor cell density $(cell/cm^3)$
$b(r,t)$	dead tumor cell density $(cell/cm^3)$
$m(r,t)$	macrophage density $(cell/cm^3)$
$e(r,t)$	endothelial cell density $(cell/cm^3)$
Cytokines	
$q(r,t)$	M-CSF (macrophage colony-stimulating factor) density (g/cm^3)
$p(r,t)$	MCP-1/CCL2 (monocyte chemoattractant protein) density (g/cm^3)
$g(r,t)$	GM-CSF (granulocyte-macrophage colony-stimulating factor) density (g/cm^3)
$h(r,t)$	VEGF (vascular endothelial growth factor) density (g/cm^3)
$s(r,t)$	sVEGFR-1 (soluble VEGF receptor-1) density (g/cm^3)
Oxygen	
$w(r,t)$	density (g/cm^3)

Due to FreeFem++ demands all equations must be written in their weak form. For this reason we introduce test functions $o_1, ..., o_{11}$ where o_1, o_2,o_{11} are Sobolev space functions $H^1(\Omega(t))$, while $o_3,\ldots,o_{10}$ are Sobolev space functions $H^1(D)$ and $t \in [1,T]$, where $T \in \mathbb{N}$.

Live tumor cells density is set up as

$$\int_{\Omega(t)} \frac{\partial c}{\partial t} o_1 dxdy + \int_{\Omega(t)} \bigtriangledown(c\overrightarrow{v}) o_1 dxdy = \int_{\Omega(t)} \lambda_1(w) c(1 - \frac{c}{c^*}) o_1 dxdy - \int_{\Omega(t)} \lambda_2(w) c o_1 dxdy - \int_{\Omega(t)} \mu_c c o_1 dxdy, \quad (1)$$

where c* is the carrying capacity of the cells, proliferation and necrosis directly depend on oxygen level thus these dependencies are described by piecewise linear approximations

$$\lambda_1(w) = \left\{ \begin{array}{ll} 0 & \text{if } w < w_h, \\ \lambda_1(w - w_h)/(w_0 - w_h) & \text{if } w_h \le w \le w_0, \\ \lambda_1 & \text{if } w > w_0, \end{array} \right\},$$

$$\lambda_2(w) = \left\{ \begin{array}{ll} \lambda_2 & \text{if } w < w_n, \\ \lambda_2(w_h - w)/(w_h - w_n) & \text{if } w_n \le w \le w_h, \\ 0 & \text{if } w > w_h, \end{array} \right\},$$

where w_0 is the normal oxygen level, while $[0, w_n]$, $(w_n, w_h]$ and $(w_h, w_o]$ are oxygen

levels in necrosis, extreme hypoxia and hypoxia, respectively.

The equation of dead tumor cells is written as

$$\int_{\Omega(t)} \frac{\partial b}{\partial t} o_2 dxdy + \int_{\Omega(t)} \bigtriangledown(b\overrightarrow{v}) o_2 dxdy = \int_{\Omega(t)} \lambda_2(w) c o_2 dxdy + \int_{\Omega(t)} \mu_c c o_2 dxdy - \int_{\Omega(t)} \mu_b \frac{w}{w_0} m b o_2 dxdy. \quad (2)$$

Two first terms of the right side (cells death due to necrosis and apoptosis) are obtained from previous equation. The last term means clearing cells by macrophages.

The equation

$$\int_D \frac{\partial m}{\partial t} o_3 dxdy + \int_{\Omega(t)} \bigtriangledown(m\overrightarrow{v}) o_3 dxdy = -\int_D \bigtriangledown(k_p m \bigtriangledown p) o_3 dxdy - \int_D \bigtriangledown(k_g m \bigtriangledown g) o_3 dxdy, \quad (3)$$

describes macrophage density. Chemotactic coefficients k_p and k_g are assumed to be constant.

The evolution equation for density of EC is

$$\int_D \frac{\partial e}{\partial t} o_4 dxdy + \int_{\Omega(t)} \bigtriangledown(e\overrightarrow{v}) o_4 dxdy = -\int_D \bigtriangledown(k_h e \bigtriangledown h) o_4 dxdy. \quad (4)$$

The chemotactic coefficient k_h is assumed to be constant as well. Diffusion was neglected in all above equations due to its not significant value.

The equation of M-CSF density is

$$\int_D \frac{\partial q}{\partial t} o_5 dxdy + \int_{\Omega(t)} \bigtriangledown(q\overrightarrow{v}) o_5 dxdy = -\int_D (D_q \bigtriangledown q) \bigtriangledown o_5 dxdy + \int_{\Gamma_2} D_q \left(N.x \frac{\partial q}{\partial x} + N.y \frac{\partial q}{\partial y} \right) o_5 dxdy + \lambda_3 \int_{\Omega(t)} c o_5 dxdy - \mu_q \int_D q o_5 dxdy, \quad (5)$$

where constant λ_3 is a secretion rate of M-CSF by tumor cells, decay rate μ_q is also constant.

The MCP-1/CCL2 is secreted by macrophages in a response to binding M-CSF by receptors

$$\int_D \frac{\partial p}{\partial t} o_6 dxdy + \int_{\Omega(t)} \bigtriangledown(p\overrightarrow{v}) o_6 dxdy = -\int_D (D_p \bigtriangledown p) \bigtriangledown o_6 dxdy + \int_{\Gamma_2} D_p \left(N.x \frac{\partial p}{\partial x} + N.y \frac{\partial p}{\partial y} \right) o_6 dxdy + \int_D \lambda_4(w) \frac{q}{q+q_0} m o_6 dxdy - \int_D \mu_p p o_6 dxdy, \quad (6)$$

decay rate μ_p is also constant. The second term of the right side of the equation depends on oxygen level being piecewise linear function λ_4 such as:

$$\lambda_4(w) = \left\{ \begin{array}{ll} 0 & \text{if } w < w_n, \\ 0.4\lambda_4 & \text{if } w_n \le w \le w_h, \\ \lambda_4 & \text{if } w > w_h. \end{array} \right\}.$$

The VEGF density is described with constant decay rate μ_h by

$$\begin{aligned} \int_D \frac{\partial h}{\partial t} o_7 dxdy + \int_{\Omega(t)} \bigtriangledown(h\overrightarrow{v}) o_7 dxdy &= -\int_D (D_h \bigtriangledown h) \bigtriangledown o_7 dxdy \\ &+ \int_{\Gamma_2} D_p \left(N.x \frac{\partial h}{\partial x} + N.y \frac{\partial h}{\partial y} \right) o_7 dxdy + \int_{\Omega(t)} \lambda_5(w) c o_7 dxdy \\ &+ \theta_1 \int_D \lambda_6(w) \frac{q}{q+q_0} m o_7 dxdy - \overline{\mu}_s \int_D sh o_7 dxdy - \mu_h \int_D h o_7 dxdy, \end{aligned} \quad (7)$$

where $\lambda_5(w) = \lambda_5 \phi(w)$ and

$$\Phi(w) = \left\{ \begin{array}{ll} 0 & \text{if } w < w_n, \\ (w - w_n)/(w^* - w_n) & \text{if } w_n \le w < w^*, \\ 1 - 0.7(w - w^*)/(w_0 - w^*) & \text{if } w^* < w \le w_0, \\ 0.3 & \text{if } w > w_0, \end{array} \right\},$$

where $w^* \in (w_h, w_0)$ refers to the threshold at which the hypoxic effect is maximal.

The equation for sVEGFR-1 density is

$$\begin{aligned} \int_D \frac{\partial s}{\partial t} o_8 dxdy + \int_{\Omega(t)} \bigtriangledown(s\overrightarrow{v}) o_8 dxdy &= -\int_D (D_s \bigtriangledown s) \bigtriangledown o_8 dxdy \\ &+ \int_{\Gamma_2} D_s \left(N.x \frac{\partial s}{\partial x} + N.y \frac{\partial s}{\partial y} \right) o_8 dxdy + \theta_2 \lambda_7 \int_D \frac{g + \overline{v} g_0}{g + g_0} m o_8 dxdy \\ &- \overline{\mu}_h \int_D sh o_8 dxdy - \mu_s \int_D s o_8 dxdy, \end{aligned} \quad (8)$$

where coefficient θ_2 equals 1 for normal mice whereas it is much smaller than 1 for mice with HIF-2α deficient macrophages. Small factor $\overline{v}$ was added because normally macrophages secret relatively small amount of this cytokine. Coefficient g_0 is a saturation, the last term μ_s is a constant decay rate.

All main elements influencing oxygen level are described in

$$\begin{aligned} \int_D \frac{\partial w}{\partial t} o_9 dxdy + \int_{\Omega(t)} \bigtriangledown(w\overrightarrow{v}) o_9 dxdy &= -\int_D (D_w \bigtriangledown w) \bigtriangledown o_9 dxdy \\ &+ \int_{\Gamma_2} D_w \left(N.x \frac{\partial w}{\partial x} + N.y \frac{\partial w}{\partial y} \right) o_9 dxdy + \lambda_8 \int_D e o_9 dxdy \\ &- \lambda_9 \int_D mw o_9 dxdy - \lambda_{10} \int_D cw o_9 dxdy. \end{aligned} \quad (9)$$

Oxygen is diffused from the vascularate (first term of the right side) and delivered by endothelial cells (second term of the right side), it is consumed by macrophages (third term of the right side) and live tumor cells (fourth term of the right side) at the same time.

The last equation

$$\int_D \frac{\partial g}{\partial t} o_{10} dxdy + \int_{\Omega(t)} \bigtriangledown(g\overrightarrow{v}) o_{10} dxdy = -\int_D (D_g \bigtriangledown g) \bigtriangledown o_{10} dxdy$$
$$+ \int_{\Gamma_2} D_g \left(N.x \frac{\partial g}{\partial x} + N.y \frac{\partial g}{\partial y} \right) o_{10} dxdy + \int_D u(t) o_{10} dxdy - \mu_g \int_D g o_{10} dxdy, \quad (10)$$

describes GM-CSF density. It depends mainly on injection (control) $u(t)$, being periodic function. Decay rate μ_g is constant just like in case of previous equations.

We take that $c + b + m + e = \theta_3 c^*$, where θ_3 represents the volume fraction of the cells in the tumor. We initiate the tumor as a ball with radius $R_0 = 0,625$ mm what constitutes volume $1mm^3$ i.e. $\Omega(0) = B(0, R_0)$ (ball with center at zero and radius R_0). We also set up following initial conditions: $c(r,0) = c_0$, $b(r,0) = 0$, if $r \in \Omega(0)$, $m(r,0) = m_0$, $e(r,0) = \frac{e_0}{1+e^{(5R_0 - r)/\epsilon}}$, $w(r,0) = w^* + \frac{\tilde{r}^2}{\tilde{L}^2}(w_0 - w^*)$, if $r \in D$, where $\epsilon > 0$ is small, $\tilde{r} = \|r\|$, $\tilde{L} = volD$ and parameters c_0, m_0, e_0, w_0 are average densities of cells in tumor, macrophages, EC and oxygen in healthy issue. All cytokines are assumed to have zero initial conditions: $q(r,0) = p(r,0) = s(r,0) = h(r,0) = g(r,0) = 0$, if $r \in D$. Zero flux boundary conditions are assumed as boundary conditions for: q, p, s, h, g on ∂D, i.e. $q = p = s = h = g = 0$ if $r \in \partial D$ and $w = w_0$ if $r \in \partial D$ and $t \in [0, T]$. In [1] the above model for simplicity is considered to be a spherical model so D is a closed, fixed spherical domain with radius $r = L$ and $\Omega(t)$ is a spheroid with time-dependent radius $r = R(t)$.

We assume that tumor is a two-dimensional ball during whole calculations. We derive two vector components ($v_1 = v_1$) from the algebraic equation $c + b + m + e = \theta_3 c^*$ and equations (1)-(4) and we get:

$$\theta_3 c^* \nabla \cdot [v_1, v_1] = \lambda_1(w) c (1 - \frac{c}{c^*}) - \mu_b \frac{w}{w_0} mb$$
$$- \bigtriangledown \cdot (k_p m \bigtriangledown p) - \bigtriangledown \cdot (k_g m \bigtriangledown g) - \bigtriangledown \cdot (k_h e \bigtriangledown h). \quad (11)$$

And its weak form

$$\theta_3 c^* \int_{\Omega(t)} [v_1, v_1] \bigtriangledown o_{11} dxdy = \int_{\Omega(t)} \lambda_1(w) c (1 - \frac{c}{c^*}) o_{11} dxdy - \int_{\Omega(t)} \mu_b \frac{w}{w_0} mb o_{11} dxdy$$
$$- \int_{\Omega(t)} \bigtriangledown (k_p m \bigtriangledown p) o_{11} dxdy - \int_{\Omega(t)} \bigtriangledown (k_g m \bigtriangledown g) o_{11} dxdy - \int_{\Omega(t)} \bigtriangledown (k_h e \bigtriangledown h) o_{11} dxdy. \quad (12)$$

For simplicity let us denote by:
x the vector of ten variables $x = (c, b, m, e, q, p, h, s, w, g)$, by $\nabla \cdot (x\mathbf{v}) = (\nabla \cdot (c\mathbf{v}), \nabla \cdot (b\mathbf{v}), \nabla \cdot (m\mathbf{v}), \nabla \cdot (e\mathbf{v}), \nabla \cdot (q\mathbf{v}), \nabla \cdot (p\mathbf{v}), \nabla \cdot (h\mathbf{v}), \nabla \cdot (s\mathbf{v}), \nabla \cdot (w\mathbf{v}), \nabla \cdot (g\mathbf{v}))$, $\Delta x = (0, 0, 0, 0, \bigtriangledown \cdot (D_q \bigtriangledown q), \bigtriangledown \cdot (D_p \bigtriangledown p), \bigtriangledown \cdot (D_h \bigtriangledown h), \bigtriangledown \cdot (D_s \bigtriangledown s), \bigtriangledown \cdot (D_w \bigtriangledown w), \bigtriangledown \cdot (D_g \bigtriangledown g))$ and by $f(t, r, x, u)$ the vector consisting of right hand sides of the above ten equations (1)-(10), having in mind that the function c in (5) and (7) equations

is restricted only to the domain $\Omega(t)$, i.e.

$$f(t,r,x,u) = (f_1(t,r,c), f_2(t,r,b), f_3(t,r,m), f_4(t,r,e), f_5(t,r,q),$$
$$f_6(t,r,p), f_7(t,r,h), f_8(t,r,s), f_9(t,r,w), f_{10}(t,r,g,u))$$

and for equation (11) we denote

$$R = \lambda_1(w)c(1-\frac{c}{c^*}) - \mu_b\frac{w}{w_0}mb - \bigtriangledown\cdot(k_p m \bigtriangledown p) - \bigtriangledown\cdot(k_g m \bigtriangledown g) - \bigtriangledown\cdot(k_h e \bigtriangledown h),$$

and we put $R = (R_1, R_1)$, $\mathbf{v} = (v_1, v_1)$.

As we consider equations in weak form we also introduce vector of test functions $o = (o_1, o_2, o_3, o_4, o_5, o_6, o_7, o_8, o_9, o_{10})$ and o_{11} where o_1,o_2,$o_{11} \in H^1(\Omega(t))$, while o_3,...,$o_{10} \in H^1(D)$ and $t \in [1,T]$, where $T \in \mathbb{N}$.

Then we can rewrite system of (1)-(11) equations as

$$\int_D (\frac{\partial x}{\partial t}o + \nabla\cdot(x\mathbf{v})o + (\bigtriangledown x \bigtriangledown o))dr - \int_{\partial D}(\bigtriangledown\cdot(x_{10}))(o_{10})dr \tag{13}$$
$$= \int_D f(t,r,x,u)odr,\ t \in [0,T],$$
$$\theta_3 c^* \int_{\Omega(t)}(\mathbf{v} \bigtriangledown o_{11}))dr = \int_{\Omega(t)}(Ro_{11}))dr,\ t \in [0,T].$$

The cost functional for our control problem should minimize the quantity of injection and minimize the tumor size. Thus our optimal control problem takes the form: minimize the functional

$$J(x,u) = \frac{1}{I}\int_0^T u(t)dt + \int_{\Omega(T)} c(r,T)dr \tag{14}$$

subject to (13) where $u \in U = L^\infty(0,T;[0,I])$, $I > 0$.

We tell that a pair (x,u) is admissible if $u \in U$ and there exists corresponding to it solution x to (13) satisfying mentioned above initial and boundary conditions.

In [6] theory applied to the above control problem was presented for two- dimensional space, with two independent velocity vectors. In the next section we present the most important notions from mentioned dual dynamic programming theory to derive verification theorem: sufficient ε-optimality conditions for approximate solution of problem (14)-(13). The aim of the verification theorem is to give conditions formulated in terms of dual dynamic programming method which allow to verify that the $(u_\varepsilon, x_\varepsilon)$ is an approximate (ε-optimal) pair for J. We should keep in mind that in general we are not able to solve (1)-(10) with described boundary conditions. What is more we do not even know if that system has any solution at all. This is one of the reasons why we use verification theorem. The approximate approach to our optimal control problem allows us to create numerical algorithm ensuring construction of ε-optimal pair so also building optimal control treatment resulting in

minimizing tumor size. In the last subsection of section 4 we present several examples demonstrating the value of the algorithm - finding injection regime resulting in tumor shrinking using relatively small quantity of drugs. Moreover we compare our results with these presented in [1].

2. Dual Formulation of Control Problem

In this paper we present dual dynamic programming theory for the control problem (14). Dual approach for dynamic programming was introduced and developed in several papers ([5], [8], [9], [10], [11]) describing different optimal control problems. In [6] that theory was applied to the our control problem but for two-dimensional space, with two independent velocity vectors. We use this theory for simplified model. In this section we present just main theory notions.

Using this approach we assume that we do not cope with a value function directly, instead of it we use some auxiliary function defined in a dual set satisfying dual dynamic equation. Then we derive sufficient optimality conditions for primal value function. Thus, let introduce the definition of a dual set first. Let $P \subset \mathbb{R}^{14}$ be an open set of the variables $(t, r, p) = (t, r, y^0, y)$, $y \in \mathbb{R}^{10}$, $y^0 \leq 0$, $(t, r) \in Q = [0, T] \times D$. Denote by $\mathbf{P}$ its projection on the space of variables (y^0, y). We shall also use the set

$$P_\Gamma = \{(t, r, p) : \ t \in (0, T), \ r \in \Gamma = \partial D, \, (y^0, y) \in \mathbf{P}\}, \tag{15}$$

$$P_{\Gamma(t)} = \{(t, r, p) : \ t \in (0, T), \ r \in \Gamma(t) = \partial\Omega(t) \, (y^0, y) \in \mathbf{P}\}. \tag{16}$$

Denote by $W^{1:2}(P)$ the specific Sobolev space of functions of three variables (t, r, p) having the first order weak or generalized derivative with respect to t, r and up to the second order weak derivatives with respect to the variable p. Our notation for the function space is used for the functions of time t and depending on the primal variable x, and the dual variable p. The primal and dual variables are independent and the functions in the space $W^{1:2}(P)$ have different properties with respect to t, r and p. Let $V(t, r, p)$ of $W^{1:2}(P)$ be an auxiliary function defined on P and satisfying the following condition:

$$V(t, r, p) = y^0 V_{y^0}(t, r, p) + y V_y(t, r, p) = p V_p(t, r, p), \tag{17}$$

for $(t, r, p) \in P$. V_{y^0}, V_y and V_p denote the partial derivatives with respect to the dual variables y^0, y and $p = (y^0, y)$, respectively. Now, we denote by $p(t, r)$, $(t, r) \in Q$, the dual trajectory, while $x(t, r)$, $(t, r) \in Q$ mean the primal trajectory. Let us put

$$\mathbf{x}(t, r, p) = -V_y(t, r, p), \quad \text{for } \ (t, r, p) \in P. \tag{18}$$

Using the function $\mathbf{x}$ it is possible to come back from the dual trajectories $p(t, r)$ lying in P to the primal function $x(t, r)$, $(t, r) \in Q$. Further, we delimit ourselves only to these admissible trajectories $x(\cdot)$ for which exist functions $p(t, r) = (y^0, y(t, r))$,

$(t,r,p(t,r)) \in P$, $y(\cdot) \in H^1(Q)$, $y(T,r) = 0$, $(T,r) \in Q$, such that $x(t,r) = \mathbf{x}(t,r,p(t,r))$, for $(t,r) \in Q$. Thus, denote

$$\begin{aligned} Ad_{\mathbf{x}} = \{(x,u) \in Ad: \text{ there exist } p(t,r) = (y^0, y(t,r)), \\ y(\cdot) \in H^1(Q),\ y(T,r) = 0,\ (T,r) \in Q,\ (T,r,p(T,r)) \in P, \\ (T,r) \in Q, \psi : \mathbb{R}^3 \mapsto \mathbb{R}^{10},\ y(0,r) = \psi(r), (0,r,y^0,\psi(r)) \in P,\ r \in D, \\ \psi(\cdot) \in H^1(\Omega) - \text{ fixed, such that } x(t,r) = \mathbf{x}(t,r,p(t,r)),\ (t,r) \in Q\}. \end{aligned}$$

Actually, it means that we are going to study problem (14) in smaller set $Ad_{\mathbf{x}}$ determined by the functions (18).

Next for any fixed $\bar{y}^0 < 0$ we define a dual optimal value $S_D^{\mathbf{x},\bar{y}^0}$ for problem (14) by the formula:

$$S_D^{\mathbf{x},\bar{y}^0} = \inf_{(x,u) \in Ad_{\mathbf{x}}} -\bar{y}^0 J(x,u). \tag{19}$$

Each value $S_{\varepsilon D}^{\mathbf{x},y_\varepsilon^0}$ satisfying inequality:

$$S_D^{\mathbf{x},\bar{y}^0} \le S_{\varepsilon D}^{\mathbf{x},y_\varepsilon^0} \le S_D^{\mathbf{x},\bar{y}^0} - \varepsilon y_\varepsilon^0$$

for any fixed $y_\varepsilon^0 < 0$ will be called dual ε-optimal value for problem (14).

The above means that we are looking for such control u_ε which will bring on the state x_ε to give the number of tumor cells $\int_{\Omega(T)} c_\varepsilon(r,T)dr$ under sum of injections $\int_0^T u_\varepsilon(t)dt$ such a value that

$$J(x_\varepsilon, u_\varepsilon) \le J(x,u) + \varepsilon$$

for all $(x,u) \in Ad_{\mathbf{x}}$. In order to prove the verification theorem we require that the auxiliary function $V(t,r,p)$ satisfies the second order partial differential inequality of dual dynamic programming in a weak form with any fixed $y_\varepsilon^0 < 0$:

$$\begin{aligned} \varepsilon y_\varepsilon^0 \le \sup_{u \in U} \{ \langle \frac{\partial}{\partial t} V(t,\cdot,p), v(t,\cdot) \rangle_{L^2(D)} \\ + \langle \bigtriangledown \cdot (V(t,\cdot,p)\mathbf{v}) v(t,\cdot) \rangle_{L^2(D)} + \langle \bigtriangledown V(t,\cdot,p), \bigtriangledown v(t,\cdot) \rangle_{L^2(D)} \\ - \int_\Gamma (-V_{y_{10}}(t,r,p))(y_{10}(t,r)) v(t,r) dr \\ + \langle y f(t,\cdot,-V_y(t,\cdot,p), u(t)), v(t,\cdot) \rangle_{L^2(\Omega)} \\ + y_\varepsilon^0 \langle u(t) v(t,\cdot) \rangle_{L^2(D)} \} \le 0,\ t \in [0,T],\ p \in \mathbf{P}, \end{aligned} \tag{20}$$

for all $v \in L^2((0,T); H^1(D))$, with end and boundary conditions in below form:

$$\begin{aligned} &V_{y^0}(T,r,p) = -V_{y_1}(T,r,p),\ r \in \Omega(T),\ (T,r,p) \in P, \\ &V_{y^0}(T,r,p) = 0, \quad r \in D \backslash \Omega(T),\ (T,r,p) \in P. \end{aligned} \tag{21}$$

$$V_{y_i}(t,r,p) = 0,\ i = 1,2,3,4,5,6,7,8,9, (t,r,p) \in P_\Gamma, \tag{22}$$

where for $\mathbf{v}$ we assume $\mathbf{v} = (v_1, v_1)$ and

$$v_1 = (\lambda_1(V_{y_9})V_{y_1}(1 - \frac{V_{y_1}}{c^*})) - \mu_b \frac{V_{y_9}}{w_0} V_{y_3} V_{y_2} - \nabla \cdot (k_p(V_{y_3})\nabla V_{y_6})$$
$$-\nabla \cdot (k_g(V_{y_3})\nabla V_{y_{10}}) - \nabla \cdot (k_h(V_{y_4})\nabla V_{y_7})$$
$$-k_g(-V_{y_3})\frac{\partial(-V_{y_{10}})}{\partial r_1} - k_h(-V_{y_4})\frac{\partial(-V_{y_7})}{\partial r_1}),$$

We have a relation between both systems having V we calculate x by formula

$$x(t,r) = -V_y(t,r,p(t,r)).$$

Define the set

$$\mathcal{P} = \{p(t,r) = (y_\varepsilon^0, y(t,x)), (t,r) \in Q; (t,r,p(t,r)) \in P,$$
$$y(\cdot) \in H^1(Q), \text{ exist } (u,x) \in Ad_{\mathbf{x}},\ x(t,r) = -V_y(t,r,p(t,r)),$$
$$(t,r) \in Q,\ y(T,r) = 0,\ (T,r) \in Q\}.$$

Having the above notions and inequality, in the next section we present main theorem (formulated in [6]) so called verification theorem being in fact sufficient ε-optimality conditions for our problem (14).

3. Sufficient ε-optimality conditions

In order to formulate verification theorem regarding ε -optimality conditions we consider a solution V to dual dynamic programming inequality (20) and the set $Ad_{\mathbf{x}}$ defined by $-V_y$. Thus, lets assume that we have any solution $V \in W^{1:2}(P)$ of (20) with (22) satisfying (17). Next define $\mathbf{x}_\varepsilon(t,r,p) = -V_y(t,r,p)$, $(t,r,p) \in P$ and denote

$$Ad_{\mathbf{x}_\varepsilon} = \{(x,u) \in Ad : \text{ there exist } p(t,r) = (y^0, y(t,r)),$$
$$y(\cdot) \in H^1(Q),\ y(T,r) = 0,\ (T,r) \in Q,\ (T,r,p(T,r)) \in P,$$
$$(T,r) \in Q, \psi : \mathbb{R}^3 \mapsto \mathbb{R}^{10},\ y(0,r) = \psi(r), (0,r,y^0,\psi(r)) \in P,\ r \in D,$$
$$\psi(\cdot) \in H^1(D) - \text{fixed, such that } x(t,r) = \mathbf{x}_\varepsilon(t,r,p(t,r)),\ (t,r) \in Q\}.$$

Theorem 1 Let $(x_\varepsilon, u_\varepsilon) \in Ad_{\mathbf{x}_\varepsilon}$ and $p_\varepsilon(t,r) = (y_\varepsilon^0, y_\varepsilon(t,r))$, $y_\varepsilon(\cdot) \in H^1(Q)$, $p_\varepsilon \in \mathcal{P}$, $y_\varepsilon(T,r) = 0$, $(T,r) \in Q$, be a function such that $x_\varepsilon(t,r) = -V_y(t,r,p_\varepsilon(t,r))$, $(t,r) \in Q$. Suppose that

$$\varepsilon y_\varepsilon^0 \le \langle \frac{\partial}{\partial t} V(t,\cdot,p_\varepsilon(t,\cdot)), v(t,\cdot)\rangle_{L^2(D)} \tag{23}$$

$$+ \langle \bigtriangledown \cdot (V(t,\cdot,p_\varepsilon(t,\cdot))\mathbf{v}), v(t,\cdot)\rangle_{L^2(D)} + \langle \bigtriangledown V(t,\cdot,p_\varepsilon(t,\cdot)), \bigtriangledown v(t,\cdot)\rangle_{L^2(D)}$$
$$- \langle -V_{y_{10}}(t,\cdot,p_\varepsilon) y_{10}(t,\cdot), v(t,\cdot)\rangle_{L^2(\Gamma)}$$
$$+ \langle y_\varepsilon(t,\cdot) f(t,\cdot,-V_y(t,\cdot,p_\varepsilon(t,\cdot)), u_\varepsilon(t)), v(t,\cdot)\rangle_{L^2(\Omega)} + y_\varepsilon^0 \langle u(t) v(t,\cdot)\rangle_{L^2(D)}$$
$$V_{y^0}(T,r,(y_\varepsilon^0, y_\varepsilon(T,r))) = x_{1\varepsilon}(r,T),\ r \in \Omega(T).$$

Then $(x_\varepsilon, u_\varepsilon)$ is an optimal pair relative to all $(x, u) \in Ad_{\mathbf{x}_\varepsilon}$.

Proof for above theorem can be found in [6]. From the proof we infer that knowing the auxiliary function V satisfying (20) and (23) we can give the explicit formula for optimal value of J in term of V_{y^0} and $p_\varepsilon(0, x) = (y^0_\varepsilon, \psi(0, x))$ i.e. we have the following

Corollary 1 Assume the same as in the above Theorem. Then optimal value of the functional J is expressed as

$$-y^0_\varepsilon J(x_\varepsilon, u_\varepsilon) = -y^0_\varepsilon \int_D V_{y^0}(0, r, y^0_\varepsilon, \psi(r))dr.$$

4. Numerical algorithm

We use numerical algorithm presented in [6] based on verification theorem described in previous section to calculate suboptimal pair $(u_\varepsilon, x_\varepsilon)$ such that J satisfies $J(u_\varepsilon, x_\varepsilon) \leq J(u, x) + \varepsilon$ for all $(u, x) \in Ad_{\mathbf{x}_\varepsilon}$ in fixed time T. Below we present the algorithm ensuring that we find $\varepsilon-$optimal pair in finite number of steps.

Algorithm:

1. Fix $\varepsilon > 0$ and calculate auxiliary function V from (20)-(22).

2. Form $Ad_{\mathbf{x}_\varepsilon}$ as a finite family of N pairs $(u(\cdot), x(\cdot))$:

   a) Define controls u_n, $n = 1, \ldots, N$, in the interval $[0, T]$.

   b) For each given u_n calculate x_n, $n = 1, \ldots, N$ solving equations (1)-(10).

3. Find minimal value of $J(u_n)$, $n = 1, \ldots, N$ and corresponding to it pair denote by $(\hat{u}, \hat{x})$.

4. Assume $y^0_\varepsilon = -1$ and determine $\hat{y}(\cdot)$ from the relation

$$\hat{x}(t, r) = -V_y(t, r, -1, \hat{y}(t, r)).$$

5. For V and $(\hat{u}(\cdot), \hat{y}(\cdot))$ check the inequalities (23)

   a) If V and $(\hat{u}(\cdot), \hat{y}(\cdot))$ satisfy (23) then $(\hat{u}(\cdot), \hat{x}(\cdot)$ is an ε-optimal pair and $J(\hat{u}, \hat{x})$ is an ε -optimal value.

   b) If V and $(\hat{u}(\cdot), \hat{y}(\cdot))$ do not satisfy (23) then go to 2.

4.1. Numerical calculations

In order to illustrate our numerical method and to compare results we use the same values of parameters as in [1].

Parameter	Dimensionless value	Parameter	Dimensionless value
μ_c	1.2	D_w	20
μ_b	2.4	D_g	3
μ_q	12	λ_3	57.6
μ_p	5	λ_4	960
μ_s	4.97	λ_5	272
$\overline{\mu}_s$	29.7	λ_6	915
μ_h	31.6	λ_7	543
$\overline{\mu}_h$	89.3	λ_8	30
μ_g	4	λ_9	28.11
k_p	0.006	λ_{10}	72
k_g, k_h	0.001	θ_3	0.9
D_p, D_q	2	c^*	1.28
D_h, D_s	1		

To make calculations we used FreeFem++-cs 14.3 package from the site https://www.ljll.math.upmc.fr/lehyaric/ffcs/install.php (with implemented engine FreeFem++ version 3.26-3). We used analogous algorithm as presented in [6]. The crucial difference can be found in new boundary building. Thanks to the simplification and using just one vector v no issues occurred when building new boundary. Moreover program execution time decreased almost 10 times comparing to the full two-dimensional model.

We implemented following steps:

1. Build meshes $Th1$, $Th2$ (with appropriate triangulation) in spaces $Vh1$, $Vh2$ with boundaries $\Gamma_1 = \partial\Omega(t)$ and $\Gamma_2 = \partial D$

We build two meshes $Th1$, $Th2$. Mesh $Th1(\Omega(0))$ representing a tumor is a circle of radius $r = 0,625$. Mesh $Th2$ representing the healthy tissue is a region $D \setminus \Omega(0)$. In the Figure 1 we present triangular finite elements created by FreeFem++ in both regions.

2. Choose several controls (injection regimes)

We examine below injection regimes. For each of them we go through the whole algorithm.

- $u(t) = 1$ where $t \in [0, 20]$;
- $u(t) = 5$ where $t \in [0, 20]$;
- $u(t) = 10$ where $t \in [0, 20]$;
- $u(t) = 15$ where $t \in [0, 20]$;
- $u(t) = 20$ where $t \in [0, 20]$;
- $u(t) = 25$ where $t \in [0, 20]$;
- $u(t) = 30$ where $t \in [0, 20]$;
- $u(t) = 35$ where $t \in [0, 20]$;
- $u(t) = 50$ where $t \in [0, 20]$;

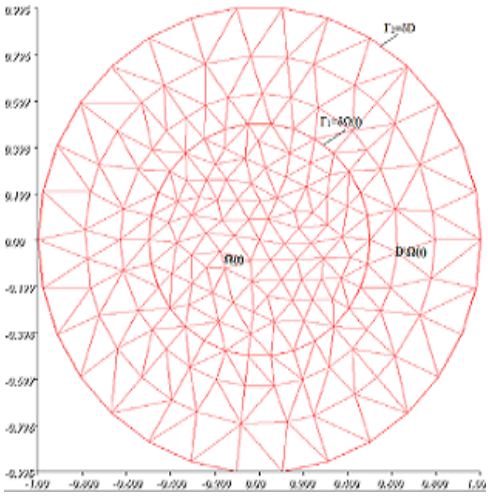

Fig. 1. Meshes Th1, Th2 in t=1 with triangulation.

- $u(t) = 100$ where $t \in [0, 20]$;
- if $t < 5$ then $u(t) = 100$ else $u(t) = 10$ where $t \in [0, 20]$;
- if $t < 5$ then $u(t) = 200$ else $u(t) = 50$ where $t \in [0, 20]$;
- if $t < 5$ then $u(t) = 50$ else $u(t) = 10$ where $t \in [0, 20]$;
- if $t < 5$ then $u(t) = 20$ else $u(t) = 10$ where $t \in [0, 20]$;
- if $cos(\pi * t) < 0$ then $u(t) = 100$ else $u(t) = 1$ where $t \in [0, 20]$;
- if $cos(\pi * t) < 0$ then $u(t) = 10$ else $u(t) = 1$ where $t \in [0, 20]$;
- if $cos(\pi * t) < 0$ then $u(t) = 20$ else $u(t) = 0$ where $t \in [0, 20]$;
- if $sin(\pi * t) < 0$ then $u(t) = 10$ else $u(t) = 1$ where $t \in [0, 20]$;
- if $sin(\pi * t) < 0$ then $u(t) = 10$ else $u(t) = 0$ where $t \in [0, 20]$;
- if $sin(\pi * t) < 0$ then $u(t) = 20$ else $u(t) = 0$ where $t \in [0, 20]$.

3. Solve equations (1)-(11) with defined boundary and initial conditions

We set up the following initial conditions: $c = b = m = e = q = p = s = h = g = w = 1$ if $r \in D$ in numerical calculations. As boundary conditions we assume zero flux boundary conditions for: $q = p = s = h = g = 0$ and $w = w_0$ if $r \in \partial D$, where $w_0 = 1$. We consider a free boundary problem hence we assume no boundary conditions on $\partial\Omega(t)$.

4. Find new boundary $\Gamma_1(t) = \partial\Omega(t + 1)$

As boundary $\Gamma_1(t)$ is a circle we use its radius r to calculate its size in each following time step. In each step $t > 0$ we calculate average velocity on the boundary $vbavg$ (by checking v_1 values in each point of border $\Gamma_1(t)$). New boundary $\Gamma_1(t+1)$ is created by summing radius r and average velocity $vbavg$ in current step t. Positive $vbavg$ value means tumor increase while negative value its shrinking.

5. Build meshes $Th1(t+1)$, $Th2(t+1)$

6. Repeat steps 2-5 in 20 **time steps for each control**

From all considered solutions we choose the optimal one using verification theorem and algorithm described in previous section. Among all checked injection regimes the one minimizing functional J (14) was $u(t) = 10$ where $t \in [0, 20]$. For this injection functional value equals $J = 2.1184$. The verification theorem was fulfilled with $\varepsilon = 0.0009$ so it means that we found $\varepsilon-$optimal state $S^{x,y^0_\varepsilon}_{\varepsilon D}$ such that $S^{x,\bar{y}^0}_D \leq S^{x,y^0_\varepsilon}_{\varepsilon D} \leq S^{x,\bar{y}^0}_D - \varepsilon y^0_\varepsilon$. Figure 2 compares integral of c values (live tumor cells density) with and without treatment. We can notice that tumor volume increase rapidly without treatment while its growth is stopped by using chosen $\varepsilon-$optimal injection. In [1] such a small dosage (10ng) was not presented, the smallest used in calculations was 25ng while the majority of calculations was conducted for 100ng. We also tested dosage 100ng however this value was not optimal as tumor size was smaller on only 3% while total amount of used GM-CSF was bigger 10 times comparing to the chosen dosage. For this reason we cannot compare exact values just results trends.

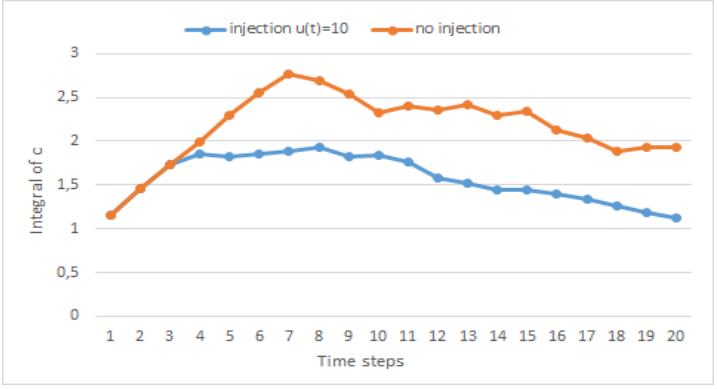

Fig. 2. Integral of c value with and without injection.

GM-CSF treatment has the major impact on tumor size but we cannot forget about influence of HIF-1α and HIF-2α factors. In numerical calculations HIF-1α deletion and HIF-2α deletion or stabilization are simulated by modification of θ_1 and θ_2 parameters values. Experimental data suggests that HIF-1α deficiency significantly reduces tumor growth by reducing VEGF production. Figure 3 shows integral of c values including HIF-1α deletion.

We can notice that its deficiency additionally reduces tumor size (even without GM-CSF treatment), what confirms both experimental and computational [1] data.

As tumor size modification observed in case of HIF-1α deletion is actually caused by VEGF production reduction we should analyze its density as well. Figure 4 presents average VEGF densities including GM-CF treatment/or not and HIF-1α

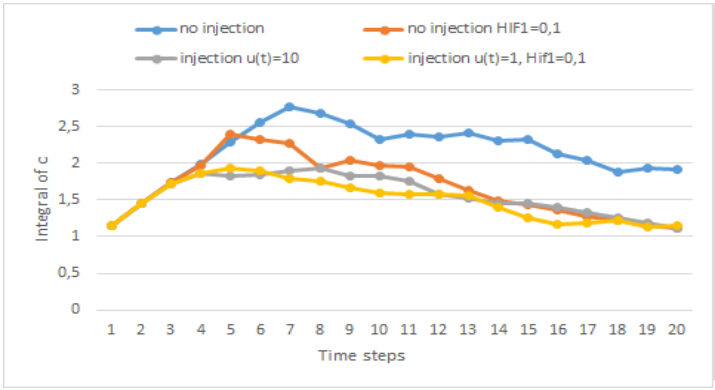

Fig. 3. Integral of c value with and without injection, including HIF-1α deletion.

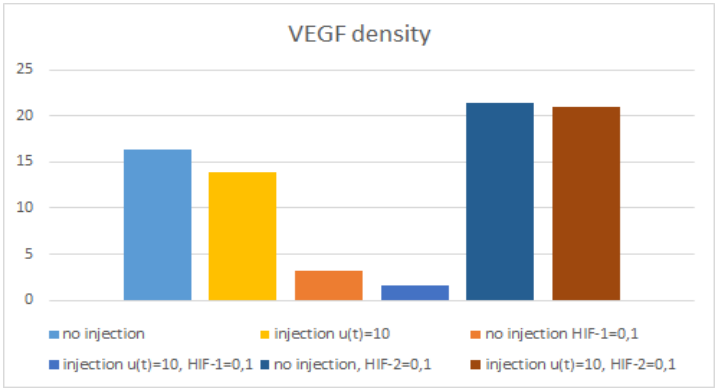

Fig. 4. Average VEGF density. Comparison of values including GM-CSF and HIF-1α variability.

deletion/or not. Application of GM-CSF injection leads to VEGF density reduction. This effect is additionally reinforced by HIF-1α deletion. HIF-1α deficiency significantly reduces VEGF production even without any injection. Similar results were achieved in [1], just the difference in VEGF density under treatment and not was higher, what can be caused by higher dose.

Experimental data suggests also that HIF-2α deletion significantly reduces the production of sVEGFR-1, but has no effect on VEGF production. Figure 5 presents average sVEGFR-1 density depending on treatment and HIF-1α or HIF-2α modifications. Just like in previous case in [1] we can find analogous results but with higher differences in sVEGFR-1 density depending on using or not GM-CSF treatment.

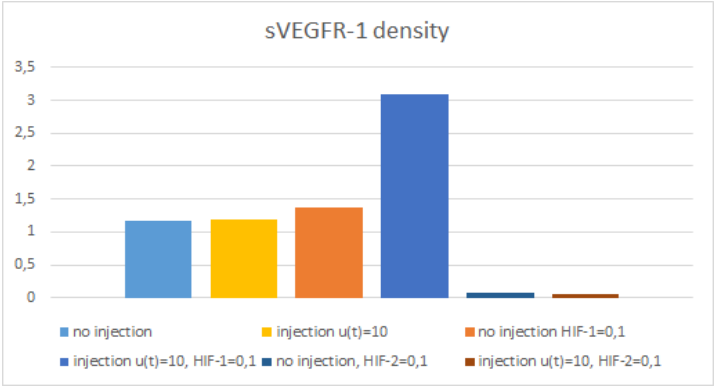

Fig. 5. Average sVEGFR-1 density. Comparison of values including GM-CSF and HIF-1α variability.

5. Conclusions

We study mathematical model of tumor growth presented in [1] where model was simplified to one-dimensional sphere. We use two-dimensional model but assume that tumor shape is a ball so results can be easily compared. The main advantage of our paper is that we formulate an optimal control problem to predict $\varepsilon-$optimal GM-CSF treatment to reduce the tumor volume. To study the optimal control problem, we developed approximate dual dynamic programming approach. Using this approach, we formulate the verification theorem resulting in sufficient $\varepsilon-$optimal conditions for the considered problem. That theorem was a basis to build numerical algorithm calculating approximate minimum of the functional containing volume of the tumor under chosen injection of GM-CSF (being the problem control). Using chosen set of controls, we calculate corresponding states x and found minimal value of the functional J for this set. For the suspected suboptimal pair (u, x) and corresponding to its dual trajectory y we checked verification condition (29) with $\varepsilon = 0.0009$. The inequality was fulfilled what means that for the injection $u(t) = 10$, $t \in [0, 20]$ the value of the functional $J = 2.1184$ and it differs from the optimal value on $\varepsilon = 0.0009$. However, we should remember that received $\varepsilon-$optimal control doesn't mean that the tumor volume is the smallest among all checked injection regimens, it's $\varepsilon-$ optimal including also drug usage. Drug dosage (100ng of GM-CSF) used in the majority of numerical calculations in [1] also in our case cause higher tumor size decrease than chosen injection (10ng). However, tumor size is smaller on only 3% while total amount of used GM-CSF is bigger 10 times, so such dosage cannot be called the optimal.

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Faculty of Mathematics and Computer Science
University of Łódź
Banacha 22, PL-90-238 Łódź
Poland
E-mail: krawczyk@math.uni.lodz.pl

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HAMOWANIA WZROSTU GUZA NOWOTWOROWEGO PRZY ZASTOSOWANIU LECZENIA GM-CSF, WARUNKI WYSTARCZAJĄCE ε-OPTYMALNOŚCI W PRZESTRZENI JEDNOWYMIAROWEJ

S t r e s z c z e n i e

Rozważany w pracy matematyczny model rozwoju guza nowotworowego przy zastosowaniu leczenia GM-CSF został zaczerpnięty z [1]. Składa się on z dziecięciu równań różniczkowych cząstkowych z których cztery pierwsze są nieliniowe pierwszego rzędu, a pozostałe nieliniowe typu parabolicznego. W części obliczeniowej [1] model teoretyczny sprowadzono do jednowymiarowego modelu sferycznego. Dawkowanie zastrzyków GM-CSF nie zostało zoptymalizowane. W niniejszym artykule zakładamy, że guz jest kulą, jednocześnie wektor prędkoci sterujący zmianami brzegu przyjmuje postać: $\vec{v} = [v_1, v_1]$, w związku z czym wyniki mogą być odnoszone do cytowanej pracy. Równanie opisujące wektor prędkości zostało wyprowadzone z czterech pierwszych równań modelu oraz zależności algebraicznej. W niniejszym artykule nie powtarzamy jednak tylko poprzednich obliczeń, ponieważ podobnie jak w [6] formułujemy zadanie optymalizacji. Co więcej, w oparciu o dualne programowanie dynamiczne stosujemy ε - optymalne warunki wystarczające dla zadania, a także wykorzystujemy algorytm numeryczny zaproponowany w [6], stosując jednak wektor prędkości odpowiedni do kuli reprezentującej guz. Obliczenia prezentowane w artykule dokonywane były przy użyciu pakietu FreeFem++, w związku z czym wszystkie równania zostały przedstawione w postaci wariacyjnej. Zmiany rozmiaru guza reprezentowane są poprzez zmiany obszaru siatki elementw skończonych wygenerowanej w pakiecie.

Słowa kluczowe: matematyczny model rozwoju guza, hamowania wzrostu guza, warunki wystarczające ε-optymalności