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Numerical Algorithm of Effective Cancer Treatment Based on the Fisher-Kolmogorov Equation

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Abstract

An inverse extremal problem for the Fisher-Kolmogorov model of tumor growth is studied. It is required to minimize the normalized density of tumor cells in a given subdomain, while the drug concentration in the tissue must be limited to specified values. The solvability of the inverse extremal problem is established. An algorithm to find its solution is constructed. The numerical experiments illustrate its efficiency.

1 Introduction

To date, mathematical models of tumor growth based on systems of differential equations have been widely developed. (see, e.g., [3, 8, 13]). Many of these models are quite complex and describe the behavior of several state variables. So, the work [13] considers a model that contains five state variables including the volume fractions of proliferative and necrotic tumor cells. A model studied in [3] describes the behavior of seven state variables including the volume fractions of proliferative, hypoxic, and necrotic tumor cells. A model considered in [8] contains eleven state variables including three types of tumor cells. Note that the models considered in the works [3, 8, 13] also describe the influence of anti-tumor drug therapy on tumor growth.

A series of works on mathematical modeling of tumor evolution consider reaction-diffusion models in which tumor cells are not divided into different types (see, e.g., [1, 2, 4, 12], where results of numerical simulation of tumor growth are discussed). Many diffusion models on tumor evolution contain nonlinear reaction terms. Moreover, the equation for glioma cell growth in [1], in addition to the nonlinear reaction term, also includes a nonlinear diffusion term.

Optimal control of the tumor evolution under the influence of drug therapy can be applied to form an effective treatment plan. Many works on the optimal control of tumor treatment consider models based on ordinary differential equations not accounting for the spatial distribution of tumors (see, the review in [10]). Optimal control problems for reaction-diffusion models of tumor treatment are studied, for example, in [2, 11].

In the current paper, we consider the nonlinear Fisher-Kolmogorov model of tumor growth under the influence of drug therapy. The model describes the behavior of two state variables:

tumor cells' normalized density and drug concentration. An inverse extremal problem for the considered model is studied. The problem consists of minimization of the density of tumor cells in a given subdomain, while the drug concentration in tissue is limited to the specified minimum and maximum values. The solvability of the optimal control problem is proved. An algorithm for solving the optimal control problem by minimizing the objective functional with a penalty is constructed and implemented. A numerical example demonstrates the efficiency of the algorithm. The work is a development of the previous study [7], which solves a similar problem, but for a linear model of tumor growth. The use of the nonlinear Fisher-Kolmogorov equation requires the use of a different technique for proving the main theoretical results and deriving the optimality system.

2 Problem formulation

Let Ω be a Lipschitz bounded domain, $Q = \Omega \times (0,T)$, $\Sigma = \Gamma \times (0,T)$. We denote by L^p, $1 \le p \le \infty$, the Lebesgue space, by H^1 the Sobolev space W_2^1, and by $L^p(0,T;X)$ the Lebesgue space of functions from L^p, defined on $(0,T)$, with values in Banach space X. Also let $H = L^2(\Omega)$, $V = H_0^1(\Omega) = \{v \in H^1(\Omega) : \ v|_\Gamma = 0\}$, and the space V' be the dual to V. Then we identify H with its dual space H' such that $V \subset H = H' \subset V'$, and denote by $\|\cdot\|$ the norm in H, and by (h,v) the value of functional $h \in V'$ on the element $v \in V$ coinciding with the inner product in H if $h \in H$.

In the formulation of the optimal control problem, two state variables, the normalized tumor cell density y and the normalized drug concentration s, are used. Also, a control u describing the drug entering the body is used. We define the control space $U = L^2(0,T)$ and the state space,

$$Y_\infty = Y \cap L^\infty(Q), \ \text{ where } \ Y = \{y \in L^2(0,T;V) \colon y' = dy/dt \in L^2(0,T,V')\}.$$

Next, we define the operator $A \colon V \to V'$ as follows:

$$(Ay, v) = (k\nabla y, \nabla v) \quad \forall\, y, v \in V.$$

Problem (P) Let λ be a given positive constant. It is necessary to minimize the objective functional

$$J(y,u) = \frac{1}{2}\|y\|^2_{L^2(Q)} + \frac{\lambda}{2}\|u\|^2_{L^2(0,T)} \to \inf \tag{1}$$

on functions $y \in Y_\infty$, $u \in U$, satisfying the conditions

$$s'(t) + M_0 s(t) = u(t), \ \ t \in (0,T); \ \ s(0) = 0; \tag{2}$$

$$y' + Ay = d(s)\varphi(y), \ \ t \in (0,T); \ \ y(0) = y_0, \tag{3}$$

such that

$$s(t) \le s_+, \ \ t \in [0,T]; \quad s(t) \ge s_-, \ \ t \in [t_0,T]. \tag{4}$$

Here, $\varphi(y) = y(1-y)$, and M_0, $s_- = Const > 0$.

Additionally, we assume that the model parameters satisfy the following conditions:

(i) $\ y_0 \in L^\infty(\Omega), \ \ 0 \le y_0 \le 1.$

(ii) $\ d(s)(s - s_c) < 0, \ \ s \ne s_c, \ \ |d(s_1) - d(s_2)| \le L_r|s_1 - s_2| \ \ \forall\, |s_{1,2}| \le r.$

3 Solvability of the inverse extremal problem

Let us first consider the properties of solutions of initial value problem (2) and initial-boundary value problem (3). We define the operator $B : L^2(0,T) \to H^1(0,T)$ such that $s = B(u)$ if s is a solution to the problem (2).

Lemma 1. *For $s = B(u)$ the following inequalities are valid:*

$$|s(t)| \le \sqrt{t}\|u\|_U, \quad \|s\|_U \le T\|u\|_U, \quad \|s'\|_U \le (1 + M_0T)\|u\|_U. \tag{5}$$

Proof. The first two inequalities in (5) follow from the following representation of the solution to the problem (2),

$$s(t) = \int_0^t e^{-M_0(t-\tau)}u(\tau)d\tau.$$

The inequality $\|s'\|_U$ follows from the equation (2) and the inequality $\|s\|_U$. □

Lemma 2. *Let conditions (i), (ii) hold. Then for $u \in U$ there exists a unique solution $y \in Y_\infty$, $0 \le y \le 1$, of the initial-boundary value problem (3), where $s = B(u)$.*

Proof. Let $\chi = d(s)$. By Lemma 1, $|s| \le r$, where $r = \sqrt{T}\|u\|_U$, and therefore

$$|\chi| \le |d(0)| + |d(s) - d(0)| \le |d(0)| + L_r r = r_1.$$

Let us consider a problem with truncated nonlinearity.

$$y' + Ay = \chi F(y), \quad t \in (0,T); \quad y(0) = y_0, \tag{6}$$

where $F(y) = \varphi(y)$ if $0 \le y \le 1$ and $F(y) = 0$ otherwise. Note that the solution $y \in Y$ of problem (6) satisfies the inequalities $0 \le y \le 1$. Indeed, by multiplication in the sense of inner product of equation (6) by $\psi = \max\{y - 1, 0\} \in L^2(0,T;V)$, we obtain

$$\frac{1}{2}\frac{d}{dt}\|\psi\|^2 + (k\nabla\psi, \nabla\psi) = \chi(F(y), \psi) = 0, \quad \psi(0) = 0.$$

Therefore, $\psi = 0$, $y \le 1$. Similarly, setting $\psi = \min\{y, 0\}$, we obtain $y \ge 0$. Thus, the solution to problem (6) will be the solution to problem (3). Let us prove the local solvability of (6). Let us define the operator $\Phi : L^2(0,T_1;H) \to L^2(0,T_1;H)$ such that $w = \Phi(z)$ if

$$w' + Aw = \chi F(z), \quad t \in (0,T_1); \quad w(0) = y_0. \tag{7}$$

Let $z = z_1 - z_2$, $w = \Phi(z_1) - \Phi(z_2)$. Then

$$w' + Aw = \chi(F(z_1) - F(z_2)), \quad t \in (0,T_1); \quad w(0) = 0.$$

Multiplying in the sense of the inner product the resulted equation by w and taking into account the boundedness of the derivative of the function F, we obtain

$$\frac{1}{2}\frac{d}{dt}\|w\|^2 + (k\nabla w, \nabla w) \le r_1\|z\| \cdot \|w\|.$$

Therefore, it is easy to obtain the estimate $\|w\|_{L^2(0,T_1;H)} \le r_1T_1\|z\|_{L^2(0,T_1;H)}$, from which it follows that the operator Φ is the contraction if $r_1T_1 < 1$. The fixed point of this operator will be a solution (6) on the interval $(0,T_1)$ and, by the obtained a priori estimates, this solution can be extended to the entire interval $(0, T)$. This proves the existence of a solution $y \in Y_\infty$ to the problem (3) such that $0 \le y \le 1$. Let us show the uniqueness of the solution. If $y_{1,2} \in Y_\infty$ is a solution to the problem (3), $\widehat{y} = y_1 - y_2$, then

$$\widehat{y}' + A\widehat{y} = \chi(\varphi(y_1) - \varphi(y_2)), \ \ t \in (0, T); \ \ \widehat{y}(0) = 0.$$

Multiplying in the sense of the inner product the obtained equality by $\widehat{y}$ and taking into account the boundedness of the functions $y_{1,2}$, we come to the following inequality:

$$\frac{1}{2}\frac{d}{dt}\|\widehat{y}\|^2 \le C\|\widehat{y}\|^2.$$

Here, $C > 0$ depends only on r_1, y_1, y_2. Applying Gronwall's inequality, we obtain $\widehat{y} = 0$ that is $y_1 = y_2$. □

Theorem 1. *Let conditions (i), (ii) hold and the following inequality be valid:*

$$\big(1 - e^{-M_0 T}\big)s_- \le \big(1 - e^{-M_0 t_0}\big)s_+. \tag{8}$$

Then there is a solution to problem (P).

Proof. Let us show that the set of controls ensuring the fulfillment of the inequalities (4) is non-empty. Indeed, if we take

$$u := M_0(1 - e^{-M_0 t_0})^{-1}s_-$$

as a control, then the solution to problem (2) has the form $s(t) = u(1 - e^{-M_0 t})/M_0$ and then $s(t) \ge s_-, \ \ t \in [t_0, T]$. Condition (8) provides that $s(t) \le s_+, \ \ t \in [0, T]$.

Let us consider the sequence $\{y_m, u_m\}$ satisfying the problem,

$$y_m' + Ay_m = d(s_m)\varphi(y_m), \ \ s_m = B(u_m), \ \ t \in (0, T); \ \ y_m(0) = y_0, \tag{9}$$

providing fulfillment of the constraints

$$s_m(t) \le s_+, \ \ t \in [0, T], \quad s_m(t) \ge s_-, \ \ t \in [t_0, T],$$

and convergence $J(y_m, u_m) \to j = \inf J$.

The structure of J implies the estimate $\|u_m\|_U \le C$, and therefore, by Lemmas 1 and 2,

$$|s_m(t)| \le C, \quad \|s_m\|_{H^1(0,T)} \le C, \quad |d(s_m(t))| \le C, \quad 0 \le y_m \le 1.$$

Here and below, $C > 0$ denotes constants that do not depend on m. Multiplying in the sense of the inner product the equation for y_m in (9) by y_m and taking into account the estimates of s_m, we derive the inequality

$$\frac{1}{2}\frac{d}{dt}\|y_m\|^2 + k_0\|\nabla y_m\|^2 \le C.$$

Integrating this inequality over t and applying Gronwall's lemma, we obtain the estimate $\|y_m\|_Y \le C$. Based on the estimates obtained, passing to subsequences if necessary, we conclude that there exist functions $u \in U$, $s \in H^1(0, T)$, $y \in Y_\infty$ such that

$$u_m \to u \ \text{ weakly in } U, \quad s_m \to s \ \text{ weakly in } H^1(0, T), \ \text{ strongly in } U,$$

$$y_m \to y \ \text{ weakly in } L^2(0, T; V), \ \text{ strongly in } L^2(0, T; H).$$

Moreover, the Lipschitz property of d provides that $d(s_m) \to d(s)$ in $U = L^2(0,T)$. The obtained convergences allow us to pass to the limit in (9). As a result, we obtain that $\{y, s, u\}$ satisfy the following conditions:

$$y' + Ay = d(s)\varphi(y), \quad s = B(u), \quad t \in (0,T); \quad y(0) = y_0,$$

$$s(t) \le s_+, \ \ t \in [0,T], \quad s(t) \ge s_-, \ \ t \in [t_0,T].$$

Since the objective functional is weakly lower semicontinuous, then

$$j \le J(y,u) \le \liminf J(y_m,u_m) = j$$

and therefore the pair $\{y, u\}$ is a solution to problem (P). □

4 Penalty problem

Let us define the constraint operator

$$F: \ Y_\infty \times H^1(0,T) \times U \ \to \ L^2(0,T;V') \times U \times H \times \mathbb{R},$$

$$F(y,s,u) = \{y' + Ay - d(s)\varphi(y), \ \ s' + M(s) - u, \ \ y(0) - y_0, \ \ s(0)\}.$$

Problem (P$_\varepsilon$) Let ε be a given positive constant. It is necessary to minimize the objective functional

$$J_\varepsilon(y,s,u) = J(y,u) \ + \ \frac{1}{\varepsilon}\int_0^T f_1(s(t))dt \ + \ \frac{1}{\varepsilon}\int_{t_0}^T f_2(s(t))dt \to \inf, \quad F(y,s,u) = 0, \quad u \in U.$$

Here,

$$f_1(s) = \begin{cases} 0, & \text{if } s \le s_+; \\ (s-s_+)^2, & \text{if } s > s_+. \end{cases} \qquad f_2(s) = \begin{cases} 0, & \text{if } s \ge s_-; \\ (s-s_-)^2, & \text{if } s < s_-. \end{cases}$$

Estimates of the solution of the controlled system allow us to prove the solvability of the problem with a penalty (P$_\varepsilon$) similarly to the proof of Theorem 1. As a result, the following theorem takes place.

Theorem 2. *Let conditions (i), (ii) hold. Then a solution of the problem (P$_\varepsilon$) exists.*

The following theorem establishes the approximation properties of the solution to the penalty problem (P$_\varepsilon$) with respect to the original problem (P).

Theorem 3. *Let conditions (i), (ii) hold and $\{y_\varepsilon, s_\varepsilon, u_\varepsilon\}$ be a solution to the problem (P$_\varepsilon$) for $\varepsilon > 0$. Then there is a sequence $\varepsilon \to +0$ such that*

$$u_\varepsilon \to \widehat{u} \ \ \textit{weakly in } U, \ \ y_\varepsilon \to \widehat{y} \ \ \textit{strongly in } L^2(0,T;H), \ \ s_\varepsilon \to \widehat{s} \ \ \textit{strongly in } U.$$

where $\{\widehat{y}, \widehat{u}\}$ is a solution to Problem (P), $\widehat{s} = B(\widehat{u})$.

Proof. Let a pair $\{y, u\}$ be a solution to problem (P). The existence of the solution follows from Theorem 1. Since $s = B(u)$ satisfies the inequalities (4), then $f_1(s(t)) = 0,\ t \in [0, T]$, and $f_2(s(t)) = 0,\ t \in [t_0, T]$, and hence

$$J(y_\varepsilon, u_\varepsilon) + \frac{1}{\varepsilon}\int_0^T f_1(s_\varepsilon(t))dt + \frac{1}{\varepsilon}\int_{t_0}^T f_2(s_\varepsilon(t))dt \le J(y, u),$$

where $s_\varepsilon = B(u_\varepsilon)$. Therefore

$$J(y_\varepsilon, u_\varepsilon) \le J(y, u), \quad \int_0^T f_1(s_\varepsilon(t))dt + \int_{t_0}^T f_2(s_\varepsilon(t))dt \le \varepsilon J(y, u). \tag{10}$$

From the first inequality (10) it follows that $\|u_\varepsilon\|_U \le C$, in addition $0 \le y_\varepsilon \le 1$ and similarly to the proof of Theorem 1, the following estimates are derived:

$$|s_\varepsilon(t)| \le C, \quad \|s_\varepsilon\|_{H^1(0,T)} \le C, \quad |d(s_\varepsilon(t))| \le C, \quad \|y_\varepsilon\|_Y \le C.$$

Here and below, $C > 0$ are constants that do not depend on ε. Based on the obtained estimates obtained and passing to subsequences if necessary, we obtain that there are functions $\widehat{u} \in U$, $\widehat{s} \in H^1(0, T)$, $\widehat{y} \in Y_\infty$ such that

$$u_\varepsilon \to \widehat{u} \ \text{ weakly in } U, \quad s_\varepsilon \to \widehat{s} \ \text{ weakly in } H^1(0, T), \ \text{ strongly in } U,$$

$$y_\varepsilon \to \widehat{y} \ \text{ weakly in } L^2(0, T; V), \ \text{ strongly in } L^2(0, T; H).$$

Moreover, $d(s_\varepsilon) \to d(\widehat{s})$ in $U = L^2(0, T)$. The obtained convergences allow us to pass to the limit in the equality $F(y_\varepsilon, s_\varepsilon, u_\varepsilon) = 0$. As a result we come to the relation $F(\widehat{y}, \widehat{s}, \widehat{u}) = 0$. In addition,

$$\int_0^T f_1(s_\varepsilon(t))dt \to \int_0^T f_1(\widehat{s}(t))dt, \quad \int_{t_0}^T f_2(s_\varepsilon(t))dt \to \int_{t_0}^T f_2(\widehat{s}(t))dt,$$

and since by (10) these limits are equal to 0, then $\widehat{s}(t) \le s_+,\ t \in [0, T]$, and $\widehat{s}(t) \ge s_-,\ t \in [t_0, T]$. Therefore, the pair $\{\widehat{y}, \widehat{u}\}$ is admissible for problem (P). Note that

$$j = \inf J \le J(\widehat{y}, \widehat{u}) \le \liminf J(y_\varepsilon, u_\varepsilon) \le J(y, u) = j,$$

and therefore $\{\widehat{y}, \widehat{u}\}$ is a solution to problem (P). □

5 Optimality conditions in the penalty problem

The derivation of optimality conditions is based on estimates of the derivative of the mapping "control $\mapsto$ state". Consider for a fixed $\varepsilon > 0$ the solution $\{y, s, u\}$ of the problem (P_ε). Choose an arbitrary element $v \in U$ and for any $\nu \in (0, 1)$ set

$$u_\nu = u + \nu v, \quad q = \frac{1}{\nu}(s_\nu - s), \quad g_\nu = \frac{1}{\nu}(y_\nu - y), \quad \eta_\nu = \frac{d(s_\nu) - d(s)}{s_\nu - s}, \quad \psi_\nu = \frac{\varphi(y_\nu) - \varphi(y)}{y_\nu - y}.$$

Here, $s_\nu = B(u_\nu)$, $y_\nu \in Y_\infty$ is the solution of the problem (3), where $s := s_\nu$.

By virtue of Lemmas 1, 2, the following estimates are valid:

$$0 \le y \le 1, \quad 0 \le y_\nu \le 1, \quad \|s_\nu\|_{H^1(0,T)} \le K, \quad |\eta_\nu| \le K, \quad |\psi_\nu| \le K. \tag{11}$$

Here, $K > 0$ denotes various constants that do not depend on ν. Note also that the following equalities are valid

$$g_\nu' + Ag_\nu = \eta_\nu q\varphi(y_\nu) + d(s)\psi_\nu g_\nu, \quad q' + M_0 q = v, \quad t \in (0,T), \quad g_\nu(0) = 0, \quad q(0) = 0. \tag{12}$$

Let us consider the following condition:

(iii) the function $d : \mathbb{R} \to \mathbb{R}$ is differentiable.

Lemma 3. *Let the conditions (i) – (iii) hold and $\{y, s, u\}$ be a solution to problem (P_ε). Then for each $v \in U$ there exists a function $g \in Y$ such that*

$$g' + Ag = qd'(s)\varphi(y) + d(s)\varphi'(y)g, \;\; t \in (0,T); \quad g(0) = 0. \tag{13}$$

The function $q \in H^1(0,T)$ is a solution to the Cauchy problem

$$q' + M_0 q = v, \;\; t \in (0,T), \;\; q(0) = 0. \tag{14}$$

Moreover,

$$\int_0^T ((y,g) + \lambda uv)\, dt + \frac{1}{\varepsilon}\int_0^T (f_1'(s) + \chi(s,t))\, q dt = 0. \tag{15}$$

Here, $\chi(s,t) = f_2'(s)$ if $t \in [t_0, T]$ and $\chi(s,t) = 0$ if $t \in [0, t_0)$.

Proof. From (12), using the inequalities (11), the following estimate is derived in a standard way: $\|g_\nu\|_Y \le C$, where the constant $C > 0$ does not depend on ν. Further, we conclude, passing as $\nu \to +0$ to a subsequence if necessary, that there exists a function $g \in Y$ such that the following convergences take place:

$$g_\nu \to g \;\text{ weakly in }\; L^2(0,T;V), \;\; \text{strongly in } L^2(Q);$$
$$y_\nu - y = \nu g_\nu \to 0 \;\text{ strongly in } L^2(Q). \tag{16}$$

Moreover, $\eta_\nu \to d'(s)$ in $L^2(0,T)$, $\psi_\nu \to \varphi'(y)$ in $L^2(Q)$. These convergence results allow us to pass to the limit in (12) to obtain (13). Passing to the limit in the inequality

$$\nu^{-1}(J_\varepsilon(y_\nu, s_\nu, u_\nu) - J_\varepsilon(y, s, u)) \ge 0$$

we obtain that

$$\int_0^T ((y,g) + \lambda uv)\, dt + \frac{1}{\varepsilon}\int_0^T (f_1'(s) + \chi(s,t))\, q dt \ge 0.$$

Replacing v with $-v$, we come to (15). □

Theorem 4. *Let conditions (i) – (iii) hold and $\{y, s, u\}$ be a solution of the problem (P_ε) for $\varepsilon > 0$. Then there is a unique solution $\{p_1, p_2\} \in Y \times H^1(0,T)$ of the dual system*

$$-p_1' + Ap_1 - d(s)\varphi'(y)p_1 = -y, \;\; t \in (0,T); \;\; p_1(T) = 0; \tag{17}$$

$$-p_2' + M_0 p_2 + \frac{1}{\varepsilon}(f_1'(s) + \chi(s,t)) = d'(s)(\varphi(y), p_1), \;\; t \in (0,T); \;\; p_2(T) = 0. \tag{18}$$

Wherein $u = p_2/\lambda$.

Proof. Let us make a replacement

$$\widetilde{p}_1(t) = p_1(T-t), \quad y_1(t) = y(T-t), \quad s_1(t) = s(T-t).$$

Then instead of (17) we get the problem

$$\widetilde{p}_1' + A\widetilde{p}_1 - d(s_1)\varphi'(y_1)\widetilde{p}_1 = -y_1, \quad t \in (0,T); \quad \widetilde{p}_1(0) = 0. \tag{19}$$

The unique solvability of the linear parabolic problem (19) for $\widetilde{p}_1$ with right-hand side $-y_1 \in L^\infty(Q)$ and bounded coefficient of $\widetilde{p}_1$ follows from [9, Ch.3, Th.1.2]. The existence of a unique solution $p_2 \in H^1(0,T)$ of the Cauchy problem for the linear ordinary differential equation (18) is obvious. Let us show the validity of the equality $\lambda u = p_2$.

For an arbitrary $v \in U$, we multiply in the sense of inner product the equation (13) by p_1 and the equation (17) by g, subtract the resulting equalities and integrate over time interval $(0,T)$ taking into account that $g(0) = 0$ and $p_1(T) = 0$. Then

$$\int_0^T (qd'(s)(\varphi(y), p_1) + (y, g))\, dt = 0.$$

Similarly, multiplying (14) by p_2 and (18) by q, subtracting the resulting equalities and integrating with respect to t, we obtain

$$\int_0^T \left(p_2 v - d'(s)q(\varphi(y), p_1) + \frac{1}{\varepsilon}\left(f_1'(s) + \chi(s,t)\right) q \right) dt = 0.$$

Further, subtracting the resulting equalities from (15), we come to the relation

$$\int_0^T (\lambda u - p_2) v dt = 0$$

and since $v \in U$ is arbitrary, we come to the statement of the theorem. □

6 Numerical algorithm

The following iterative algorithm is applied to find the optimal treatment plan:

Algorithm 1 Iterative algorithm

1: Set a relative accuracy of calculation γ.

2: Set the initial approximation u_0 of the control u.

3: Initialize the counter: $m \leftarrow 0$.

4: Find y_m, s_m that is a solution of problem (2), (3) when $u = u_m$.

5: Find $p_m = \{p_{1m}, p_{2m}\}$ that is a solution of problem (17), (18) when $y = y_m$, $s = s_m$.

6: Find $u_{m+1} = u_m - \delta(\lambda u_m - p_{2m})$.

7: **if** $\|(u_{m+1} - u_m)/u_{m+1}\| < \gamma$ **then** Stop.

8: **else** $m \leftarrow m + 1$; Go to 4.

The value of the parameter δ is chosen to ensure a balance between the convergence rate of the iterative algorithm and the stability of the computational process.

7 Numerical experiment

A square with an edge of 3 cm was chosen as the computational domain. Tumor cells occupy a circle with a diameter of 1 cm located in the center of the square. The values of the problem parameters were chosen as follows: $d = 5 \cdot 10^{-6} \, (s_c - s) \; (\mathrm{s}^{-1})$, $s_c = 0.2$, $s_- = 0.4$, $s_+ = 0.8$, $T = 28$ (days). Following [6], the diffusion coefficient k was set as $2.5 \cdot 10^{-9}$ (cm^2/s) . The initial distribution of the control was set as follows: it equals 0.00014 (s^{-1}) during one hour of each day. The value of the penalty coefficient ε was set equal to 0.1. When implementing the computational algorithm, it was enough to perform 10 iterations.

The implementation of the computational algorithm was fulfilled by the finite element method software FreeFEM++ [5]. When generating the computational grid, the following partition was used: 40 segments for each edge of the computational domain and 80 segments for the boundary of the circle, which is initially occupied by tumor cells. The behavior of the objective functional J_ε in dependence on the number of iterations is shown in Fig. 1. A further increase in the number of iterations does not produce a noticeable change in the behavior of the solution of the optimal control problem.

Figure 2 shows the behavior of the controls u_ε obtained at the 6th iteration (red plot) and at the last 10th iteration (blue plot) during all observation period of 28 days. The final approximation of control shows that the first days of treatment are characterized by an increased level of the incoming drug. Then the dosage of the incoming drug is reduced with some fluctuations. Figure 3 shows the behavior of the drug concentration in tissue s_ε (blue plot) compared with the selected limitations (s_- and s_+, red lines). Some violation of constraints on function s_ε is explained by the use of an insufficiently small value of the penalty parameter ε.

To evaluate the effectiveness of the obtained optimal scenario of antitumor therapy, the dynamics of changes in tumor cell density throughout the entire observation period were considered. In Figure 4, the distributions of tumor cell density y_ε in the central cross-section of the computational domain for different time moments (initial time moment, 1 week, 2 weeks, 3 weeks, and 4 weeks) are shown. As it can be seen, during the whole time interval, a monotonic decrease in tumor cell density is observed.

8 Conclusion

The inverse extremal problem for the nonlinear Fisher-Kolmogorov model of tumor growth under the influence of drug therapy has been studied. The solvability of the problem has been proved. An auxiliary problem of optimal control with a penalty is proposed. Approximation properties of the problem's solution with a penalty to the solution of the original inverse extremal problem are established. An iterative algorithm for solving the problem with a penalty has been constructed and implemented.

The proposed approach may form the basis for the development of optimal anti-tumor treatment plans. The direction of further research will be related to the study of a model of tumor evolution that describes the behavior of two or more types of tumor cells and takes into account other state variables that influence tumor growth.

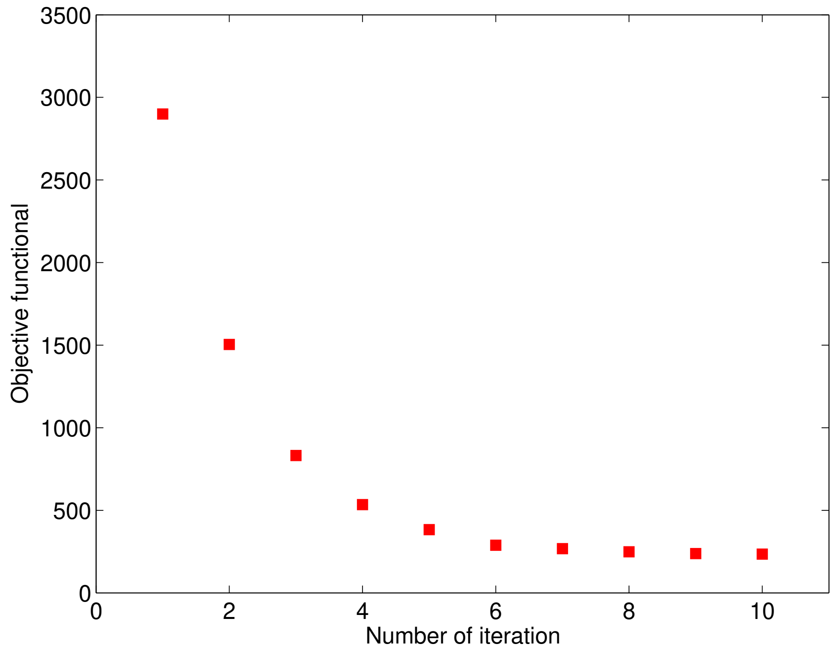

Figure 1: Objective functional J_ε.

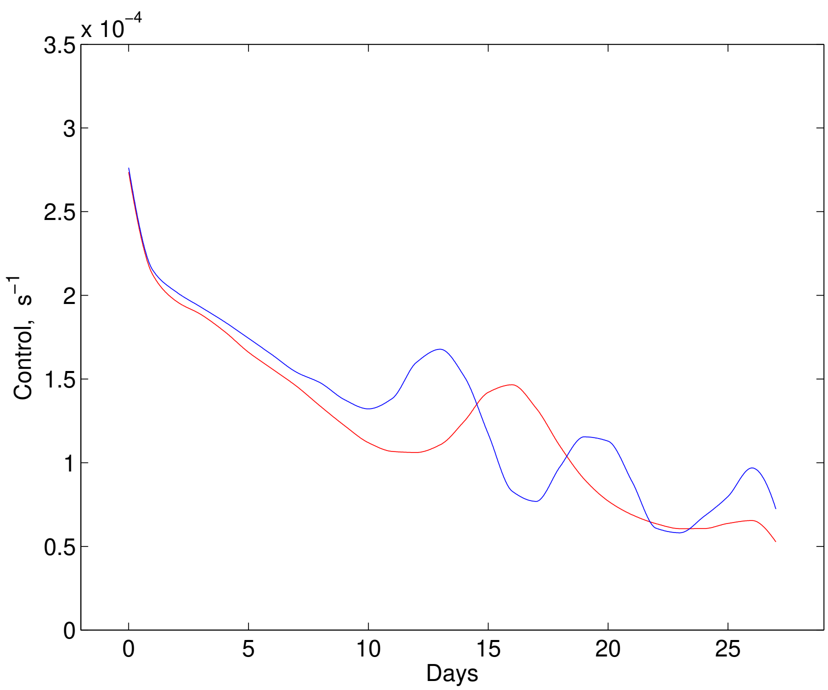

Figure 2: Control $u_\varepsilon(t)$ at the 6th iteration (red plot) and at the 10th iteration (blue plot).

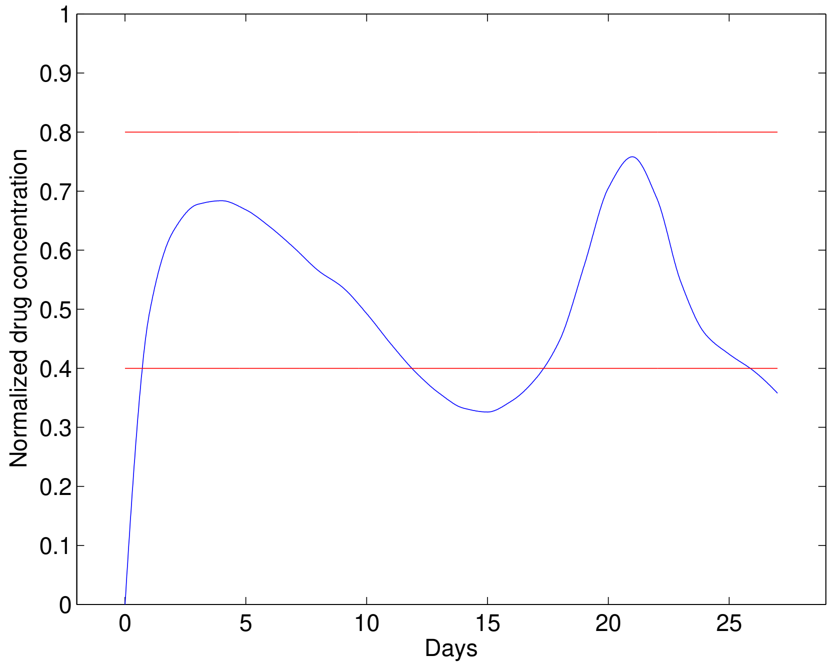

Figure 3: Drug concentration s_ε (blue plot) and limitations on drug concentration (red lines).

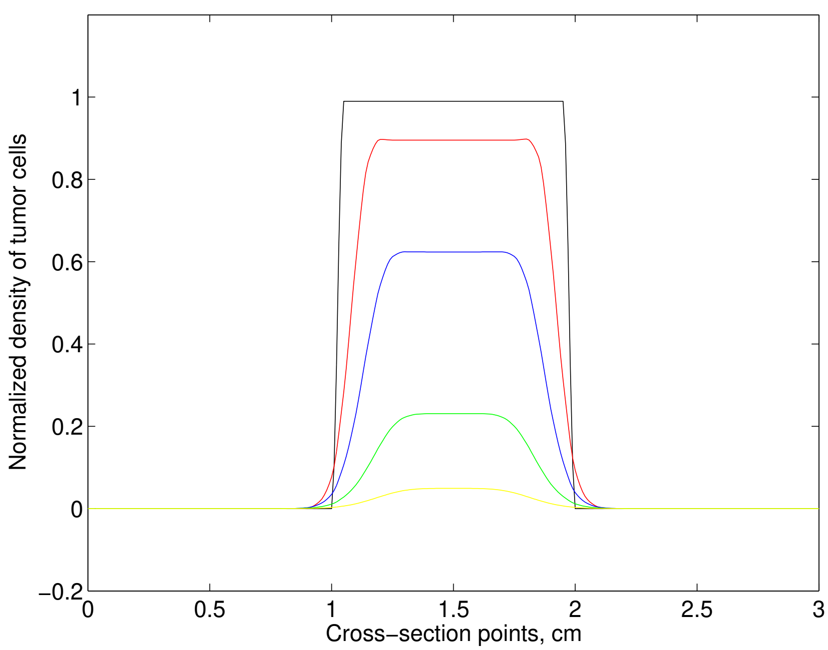

Figure 4: Normalized density of tumor cells y_ε in different time moments:
initial distribution (black), 1 week (red), 2 weeks (blue), 3 weeks (green), and 4 weeks (yellow).

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