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ON VIABLE THERAPY STRATEGY FOR A MATHEMATICAL SPATIAL CANCER MODEL DESCRIBING THE DYNAMICS OF MALIGNANT AND HEALTHY CELLS

Alexander S. Bratus

Moscow State University
GSP-1, Leninskie Gory, Moscow, Russia

Svetlana Yu. Kovalenko

Federal Science and Clinical Center of the Federal Medical and Biological Agency
28 Orehovuy boulevard, Moscow, 115682, Russia

Elena Fimmel†

Mannheim University of Applied Sciences
Paul-Wittsack-Str. 10, 68163 Mannheim, Germany

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Abstract. A mathematical spatial cancer model of the interaction between a drug and both malignant and healthy cells is considered. It is assumed that the drug influences negative malignant cells as well as healthy ones. The mathematical model considered consists of three nonlinear parabolic partial differential equations which describe spatial dynamics of malignant cells as well as healthy ones, and of the concentration of the drug. Additionally, we assume some phase constraints for the number of the malignant and the healthy cells and for the total dose of the drug during the whole treatment process.

We search through all the courses of treatment switching between an application of the drug with the maximum intensity (intensive therapy phase) and discontinuing administering of the drug (relaxation phase) with the objective of achieving the maximum possible therapy (survival) time. We will call the therapy a viable treatment strategy.

1. **Introduction.** Glioma is one of the most widespread and dangerous kinds of brain tumors. Almost half of initially diagnosed brain tumors are gliomas. There exist different methods of treatment: chemotherapy, radiotherapy and surgical resection.

One of the distinctive features of glioma is its extremely invasive character and fast penetration into surrounding tissues. Thus, it is often impossible to separate malignant and healthy areas of brain. In addition, during the chemotherapy process some of the malignant cells gain drug resistant properties.

One of the first attempts to formulate a searching strategy for glioma therapy was made in ([26], [31]). The problem of searching an optimal therapy strategy in mathematical models of leukemia based on Pontryagin's maximal principle was

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† Corresponding author.

investigated in ([1], [2]). An analogous approach was applied in many other mathematical models of avascular tumor ([20],[21], [9], [4], [34]).

Usually the aim of optimization is minimization of the number of malignant cells at the end of the therapy process or minimization of integral functional which represents the average integral value of the number of malignant cells during the whole process period ([7], [27], [26]),([32], [33]). As a rule, the dynamics of the chemotherapeutic agent and the drug effect described in the model presented in this paper with help of including the control function into the equation of population for malignant cells are not considered in the most models.

The problem of searching the optimal feedback control is more complicated from a mathematical point of view since it leads to a necessary consideration of PDE (Hamilton-Jacobi-Bellman equation) ([12], [5], [6], [8]).

It should be noted that, in general, the solution of an optimal control problem for nonlinear systems presents a sufficiently difficult mathematical problem. An analytical solution can be obtained in relatively simple mathematical models of small dimensions only. The condition becomes more complicated in the case of spatial (distributed) nonlinear mathematical models of optimal control since these models are not assigned to investigated problems ([15], [22], [28]).

Nevertheless the practical significance of the problem does not permit to wait when mathematics can provide an exhaustive solution of such problems.

Today, there is a sufficiently large experimental and theoretical base of information on various characteristics of glioma such as proliferation velocity and velocity of front profile ([32], [33], [26]), value of diffusion coefficient ([16], [11]) and its dependence on white and grey matter of brain ([16], [11]). A plethora of information is contained in the special database BrainWeb and the program EMMA (Extensible MATLAB Medical Analysis) is based on experimental patient data ([32]) and ([26]).

In the present article we consider a spatial (distributed) mathematical model of glioma that consists of three nonlinear PDE of parabolic type which describe the dynamics of malignant and normal cells and the concentration of chemotherapeutic agent during the therapy process. Chemotherapeutic agent kills not only malignant cells but damages some healthy cells, too.

At every moment in time the restriction on the total number of malignant cells (upper limit) and the restriction on the total number of normal cells (lower limit) is introduced. In addition, we introduce the restriction on the total amount of chemotherapeutic agent during the therapy process. Thus, for every moment in time these restrictions form in the phase space some domain Ω. A violation of the boundary of the domain Ω by phase variable means in reality the death of a patient. At the same time a change of phase variables inside of the domain Ω means in reality to secure the life of a patient. Below we refer to the domain Ω as a viable domain.

For the sake of simplicity we will consider the set of so called simple therapy strategies that consists of alternating periods: active treatment and relaxation.

Among such strategies we will search for a strategy which provides the maximal viable time without violating the restrictions described above and the boundary of the viable domain Ω.

In this work we will pay special attention to cyclic and quasi cyclic therapy strategies, i.e. such strategies for which, as a result of its application, the phase variables form cyclic or quasi cyclic trajectories which are entirely contained in the viable domain Ω . Existence of such cycles means a potential possibility of

transforming the illness to a chronic phase where the illness can be controlled with the help of regular treatment therapy.

2. Statement of the problem.

2.1. **Description of the model.** Let $D \subset \mathbb{R}^m$ $(m = 2, 3)$ be a bounded domain of area (or volume) S with a smooth boundary Γ, ν be the outer normal unit vector to Γ.

Let $c(x,t)$ and $n(x,t)$ be the density of tumor and normal cells, respectively, and $h(x,t)$ the amount of chemotherapeutic agent at the moment t in $x \in D$.

We will consider the following mathematical model which describes the process of growth and spread of malignant and normal cells under the influence of chemotherapy:

$$\left\{\begin{array}{lcl} \frac{\partial c(x,t)}{\partial t} & = & f_1(c(x,t)) + \nabla\left(d_c(x)\nabla c(x,t)\right) - k_1 c(x,t) g(h), \\ \frac{\partial n(x,t)}{\partial t} & = & f_2(n(x,t)) + d_n \Delta n(x,t) - k_2 n(x,t) g(h) - \alpha\varphi(c,n), \\ \frac{\partial h(x,t)}{\partial t} & = & -\gamma_h h(x,t) + d_h \Delta h(x,t) + u(x,t). \end{array}\right. \tag{2.1}$$

with the following initial and boundary conditions:

$$\begin{array}{c} c(x,0) = c_0(x) > 0,\ n(x,0) = n_0(x),\ h(x,0) = h_0(x); \\ \left.\frac{\partial c(x,t)}{\partial \nu}\right|_\Gamma = 0,\ \left.\frac{\partial n(x,t)}{\partial \nu}\right|_\Gamma = 0,\ \left.\frac{\partial h(x,t)}{\partial \nu}\right|_\Gamma = 0; \end{array} \tag{2.2}$$

Here ∇ denotes taking gradient, Δ the Laplace-operator, $k_1, k_2, d_n, d_h, \gamma_h, \alpha \in \mathbb{R}^{>0}$ are positive constants.

The positive coefficient k_1 expresses the intensity of the therapy for cancer cells, k_2 the intensity of the damage to normal cells, the positive parameter α the competition effect, d_n is the diffusion coefficient for normal cells. Positive constants γ_h and d_h describe a dissipation rate and the diffusion coefficient of the medicine.

Taking into account the nonhomogenous property of the matter, we suppose for the diffusion coefficient for tumor cells $d_c(x)$ that

$$d_c(x) = \left\{\begin{array}{ll} d_g, & \text{if } x \text{ belongs to grey matter,} \\ d_w, & \text{if } x \text{ belongs to white matter} \end{array}\right.$$

with $d_g, d_w \in \mathbb{R}^{>0}$. The values of the constants used for our numerical simulations are taken from the literature and given in the Table 1 in the section 5.

The functions f_i $(i = 1, 2)$ describe in the model proliferation laws for malignant and normal cells, respectively. In the literature (see for example [29],[18], [14],[24]) the Gompertzian (logarithmic) law

$$f_i(v) = \rho_i v(1 - \beta_i \ln v),\ v \geqslant 0,$$

or the logistic law

$$f_i(v) = \rho_i v(1 - \beta_i v),\ v \geqslant 0,\ \rho_i,\ \beta_i > 0,\ v \geqslant 0,$$

are frequently chosen for the description.

Both laws have a similar qualitative property of saturation if $v \to \infty$. They differ in their behavior for small values of v. For the Gompertz law the velocity of growth at $v = 0$ is infinite, at the same time for logistic law this velocity is restricted. Note that from our point of view the Gompertz law is more suitable for describing such invasive kind of tumor as glioma.

The function $g(h)$ describes the influence of the chemotherapy on the process of proliferation: both cell kinds will be damaged under influence of chemotherapy. So

we can call $g(h)$ 'therapy function' considering its effect on the malignant cells and 'damage function' in the case of the normal cells. In this paper we will model this function as an increasing concave function of the form:

$$g(h) = \frac{h}{a_0 + h},\ a_0 > 0.$$

The function $\varphi(c, n)$ describes how the malignant cells influence the population of the normal cells (the competition effect):

$$\varphi(c, n) = \frac{c(x,t)n(x,t)}{b_0 + c(x,t)},\ b_0 > 0.$$

The control function $u(x, t)$ denotes the quantity of the chemotherapeutic agent applied to a patient at time t in $x \in D$.

We assume that for all $x \in D$ and all $t \geq 0$ the following inequality holds

$$0 \leqslant u(x,t) \leqslant q,\ q > 0. \tag{2.3}$$

2.2. **The actual optimization problem.** The aim of the present work is to identify a therapy strategy which provides the maximal viable time for the patient. To implement the results of the mathematical modelling to the existent medical practice we will consider a set of the so called simple therapy strategies which consist of alternating periods of active treatment and relaxation.

Definition 2.1. Let $D_0 \subseteq D, q > 0, \tau_1 > 0, \tau_2 > 0$. We will call the set of control functions (compare 2.3) of the form

$$u(x,t) = \chi_{D_0}(x)u_0(t), \tag{2.4}$$

where

$$u_0(t) = \begin{cases} q, & 0 \leqslant t \leqslant \tau_1; \\ 0, & \tau_1 \leqslant t \leqslant \tau_1 + \tau_2; \end{cases}$$

$$\chi_{D_0}(x) = \begin{cases} 1, & x \in D_0; \\ 0, & x \notin D_0; \end{cases}$$

the class of simple therapy strategies and denote it as Σ.

Note that each function from the class Σ can be uniquely defined given a subset $D_0 \subseteq D$ and three parameters: the intensity of therapy q, the time of active therapy τ_1 and the time of relaxation τ_2. In the case $D_0 \equiv D$ the control function depends only on time. In the case when the domain D_0 coincides with a single point $x_0 \in D$ the control function has the form $u(x,t) = \delta(x - x_0)u_0(t)$ where δ is the Dirac delta function.

Let us introduce the following notations for the average integral logarithmic numbers of the normal and malignant cells, respectively:

$$\overline{n(t)} = \int_D \ln n(x,t)\,dx,\ \overline{c(t)} = \int_D \ln c(x,t)\,dx. \tag{2.5}$$

The positive constant c^* denotes in the further considerations the restriction on the total number of malignant cells (upper limit), n^* the restriction on the total number of normal cells (lower limit). Now we can give the definition of the viable domain:

Definition 2.2. If the solutions $n(x,t)$, $c(x,t)$ of the problem (2.1), (2.2) for all t satisfy the following integral inequalities:

$$\overline{n(t)} \geqslant n^*,\ \overline{c(t)} \leqslant c^*. \tag{2.6}$$

then we say that the numbers of malignant and normal cells are in the viable domain Ω bounded by the parameters n^* and c^*.

The inequality (2.6) means that the average integral number of normal cells could not be smaller then the lower limit n^* and the average integral number of malignant cells have to be smaller then the critical value c^*. The values n^* and c^* are determined from conditions of safe survival of a patient.

Without loss of generality we suppose here and further that $c(x,t) \geqslant 1$, $n(x,t) \geqslant 1$, $x \in D,\ t \geqslant 0$.

Now we can **formulate the control problem**.

To find the control function $u(x,t)$ in the class of simple tharapy strategies such that response time T in the viable domain Ω bounded by the parameters n^* and c^* (survival time) will be maximal under the restriction on cumulative amount of chemotherapeutic agent during the whole therapy process:

$$\int_0^T \int_D h(x,t)\,dx \leqslant Q. \tag{2.7}$$

Here Q is a given positive constant.

As mentioned before, of special interest is the problem of identifying a periodical strategy of therapy in the set of Σ for which, as a result of its application, the phase variables form cyclic or quasi cyclic trajectories which entirely fit into the viable domain of Ω. In theory, such a strategy allows the patient to stay alive during an unlimited time period.

Note also that the proposed model (2.1), (2.2) can be applied for the description of therapy processes for various kinds of tumours.

3. **Estimate for the average integral values.** Let us divide the first and the second equation of system (2.1) by the function $c(x,t)$ and $n(x,t)$ respectively and integrate the result in domain D.

Using the notations:

$$\overline{c(t)} = \int_D \ln c(x,t)\,dx,\ \overline{n(t)} = \int_D \ln n(x,t)\,dx,$$

$$\overline{h(t)} = \int_D h(x,t)\,dx,\ \overline{u(t)} = \int_D u(x,t)\,dx,$$

we obtain the following ODE system

$$\begin{cases} \frac{d\overline{c(t)}}{dt} &= \rho_1(S - \beta_1\overline{c(t)}) + A_1(c) - k_1\overline{g(h)}, \\ \frac{d\overline{n(t)}}{dt} &= \rho_2(S - \beta_2\overline{n(t)}) + A_2(n) - k_2\overline{g(h)} - \alpha L(c), \\ \frac{d\overline{h(t)}}{dt} &= -\gamma_h\overline{h(t)} + \overline{u(x,t)}. \end{cases} \tag{3.1}$$

Here

$$\begin{aligned} A_1(c) &= \int_D \tfrac{1}{c(x,t)}\nabla\left(d_c(x)\nabla c(x,t)\right)\,dx,\ A_2(n) = d_n\int_D \tfrac{1}{n(x,t)}\Delta n(x,t)\,dx \\ \overline{g(h)} &= \int_D \tfrac{h(x,t)}{a_0+h(x,t)}\,dx,\ L(c) = \int_D \tfrac{c(x,t)}{b_0+c(x,t)}\,dx. \end{aligned} \tag{3.2}$$

Lemma 3.1. *Let*

$$c(x,t) \geqslant 1,\ n(x,t) \geqslant 1 \text{ for } x \in D,\ t > 0,$$

$$\ln c(x,t) \in W_2^1(D),\ \ln n(x,t) \in W_2^1 \text{ for } t \geqslant 0.$$

Then the following inequalities hold

$$A_1(c) \geqslant 0,\ A_2(n) \geqslant 0 \tag{3.3}$$

where W_2^1 denotes the Sobolev space of functions which are squared integrable together with all derivatives.

Proof.

$$A_1(c) = \sum_{i=1}^{m} \int\limits_D \frac{1}{c(x,t)} \frac{\partial}{\partial x_i} \left(d \frac{\partial c(x,t)}{\partial x_i} \right) dx =$$

$$= \sum_{i=1}^{m} \int\limits_D \frac{\partial}{\partial x_i} \left(d \frac{1}{c(x,t)} \frac{\partial c(x,t)}{\partial x_i} \right) - \sum_{i=1}^{m} \int\limits_D \frac{\partial}{\partial x_i} \left(\frac{1}{c(x,t)} \right) \left(d \frac{\partial c(x,t)}{\partial x_i} \right) dx.$$

$m = 2, 3$.

Using the Gauss-Ostrogradsky equation we get

$$\sum_{i=1}^{m} \int\limits_{\mathbb{D}} \frac{\partial}{\partial x_i} \left(d_c(x) \frac{1}{c(x,t)}(x,t) \frac{\partial c(x,t)}{\partial x_i} \right) =$$

$$= \sum_{i=1}^{m} \int\limits_{\Gamma} d_c(x) \frac{1}{c(x,t)}(x,t) \frac{\partial c(x,t)}{\partial x_i} \cos(n, x_i)\, ds = 0$$

Therefore

$$A_1(c) = -\sum_{i=1}^{m} \int\limits_D \frac{\partial}{\partial x_i} \left(\frac{1}{c(x,t)} \right) \left(d \frac{\partial c(x,t)}{\partial x_i} \right) dx =$$

$$= \sum_{i=1}^{m} \int\limits_D d \left(\frac{1}{c(x,t)} \right)^2 \frac{\partial c(x,t)}{\partial x_i} \frac{\partial c(x,t)}{\partial x_i} dx =$$

$$= \sum_{i=1}^{m} \int\limits_D d \left(\frac{\partial \ln c(x,t)}{\partial x_i} \right)^2 dx \geqslant 0.$$

The proof of the inequality $A_2(n) \geqslant 0$ is similar. □

Lemma 3.2. *Let $h(x,t) \in L_1(D)$ be a solution of the third equation of the system (2.1), S the area of the domain D, S_{D_0} the area of the domain $D_0 \subset D$,*

$$\overline{h_0} = \int\limits_D h(x,0)\, dx = \int\limits_D h_0(x)\, dx; \quad u(x,t) \in \Sigma; \quad g(h) = \frac{h}{a_0 + h}.$$

Then the inequality

$$\overline{g(h)} = \int\limits_D \frac{h(x,t)}{a_0 + h(x,t)}\, dx \leqslant R \tag{3.4}$$

takes place where R is a positive constant which can be calculated as

$$\begin{aligned} R = &\quad Sg\left(\overline{h_0} + \tfrac{Sq}{\gamma_h}\right), &&\text{for } u(x,t) = u(t),\\ R = &\quad Sg\left(\overline{h_0} + \tfrac{S_{D_0}q}{\gamma_h}\right), &&\text{for } u(x,t) = \chi_{D_0}(x)u(t),\\ R = &\quad Sg\left(\overline{h_0} + \tfrac{q}{\gamma_h}\right), &&\text{for } u(x,t) = \delta(x-x_0)u(t),\ x_0 \in D. \end{aligned} \tag{3.5}$$

Proof. Integrating the third equation of (2.1) and using the Gauss-Ostrogradsky‘s formula we get

$$\frac{d\overline{h}}{dt}(t) = -\gamma_h\overline{h}(t) + \overline{u}(t),\ \overline{h}(0) = \overline{h_0}.$$

The soluton of the equation is

$$\overline{h}(t) = \overline{h_0}e^{-\gamma_h t} + \int_0^t e^{-\gamma_h(t-s)}\overline{u}(s)\,ds.$$

Evidently it holds for $u(x,t) \in \sum$

$$\begin{aligned} \overline{u}(t) \leqslant &\quad Sq, &&\text{if } u(x,t) = u(t),\\ \overline{u}(t) \leqslant &\quad S_{D_0}q, &&\text{if } u(x,t) = \chi_{D_0}(x)u(t),\\ \overline{u}(t) \leqslant &\quad q, &&\text{if } u(x,t) = \delta(x-x_0)u(t),\ x_0 \in D. \end{aligned} \tag{3.6}$$

and, consequently, we can estimate

$$\overline{h}(t) \leqslant \frac{q}{\gamma_h}\left(1 - e^{-\gamma_h t}\right) + h_0e^{-\gamma_h t} \leqslant \frac{q}{\gamma_h} + \overline{h_0},$$

if for example $\overline{u}(t) \leqslant q$.

For concave function $g(h)$ the Jensen inequality has the form

$$\int_D g(h(x))\lambda(x)\,dx \leqslant g\left(\int_D \lambda(x)h(x)\,dx\right),\ \lambda(x) > 0,\ \int_D \lambda(x)\,dx = 1.$$

Taking $\lambda(x) = \frac{1}{S}$ we obtain

$$g\left(\frac{\overline{h}}{S}\right) = g\left(\int_D \frac{1}{S}h(x)\,dx\right) \geqslant \int_D g(h(x,t))\frac{1}{S}\,dx = \frac{1}{S}\overline{g(h)}.$$

Using the fact that $g(h)$ is increasing and estimating $\overline{h}(t)$ with the help of (3.6) we obtain (3.4), (3.5). □

Theorem 3.1. *Let $C(t)$ and $N(t)$ be positive functions defined by*

$$C(t) := \frac{\sigma_c}{\rho_1\beta_1}\left(1 - e^{-\rho_1\beta_1 t}\right) + e^{-\rho_1\beta_1 t}\overline{c(0)}$$

$$N(t) := \frac{\sigma_n}{\rho_2\beta_2}\left(1 - e^{-\rho_2\beta_2 t}\right) + e^{-\rho_2\beta_2 t}\overline{n(0)}$$

where $\sigma_c := \rho_1 S - k_1 R$, $\sigma_n := \rho_2 S - k_2 R - \alpha S$, $\overline{c(0)} = \int_D \ln c_0(x)\,dx$, $\overline{n(0)} = \int_D \ln n_0(x)\,dx$, R is the maximal of constants from the lemma above, ρ_i, β_i denote parameters of Gompertz's Law for cancer ($i = 1$) and normal cells ($i = 2$), respectively, k_1 denotes the intensity of the therapy for cancer cells and k_2 the intensity of the damage to normal cells.

Then the following statements are true

- *If for* **some** $t \geqslant 0$ *and some* $c^* > 0$ *the inequality*
$$C(t) > c^*$$
takes place then there is **no treatment strategy** $u(x,t) \in \Sigma$ *that can supply the fulfillment of the viable restriction* $\overline{c(t)} \leqslant c^*$.
- *If for* **any** $t > 0$ *and some* $n^* > 0$ *the inequality*
$$N(t) > n^*$$
takes place then for **any treatment strategy** *from the set* Σ *the viable restriction* $\overline{n(t)} \geqslant n^*$ *is fulfilled.*

Proof. Using the estimates (3.3)-(3.5) and the inequality $L(c) \leqslant S$ we obtain the following system of differential inequalities

$$\begin{cases} \frac{d\overline{c}(t)}{dt} & \geqslant & \rho_1 S - k_1 R - \rho_1\beta_1\overline{c}(t) = \sigma_c - \rho_1\beta_1\overline{c}(t), \\ \frac{d\overline{n}(t)}{dt} & \geqslant & \rho_2 S - k_2 R - \alpha S - \rho_2\beta_2\overline{n}(t) = \sigma_n - \rho_2\beta_2\overline{n}(t). \end{cases}$$

Therefore

$$\begin{cases} \overline{c}(t) & \geqslant & \frac{\sigma_c}{\rho_1\beta_1}\left(1 - e^{-\rho_1\beta_1 t}\right) + e^{-\rho_1\beta_1 t}\overline{c(0)} = C(t), \\ \overline{n}(t) & \geqslant & \frac{\sigma_n}{\rho_2\beta_2}\left(1 - e^{-\rho_2\beta_2 t}\right) + e^{-\rho_2\beta_2 t}\overline{n(0)} = N(t). \end{cases}$$

The result of the theorem immediately follows from last inequalities. □

4. **Stability of the space homogenous steady state position.** Consider the dynamical system (2.1) without taking into account a space distribution

$$\begin{cases} \frac{dc(t)}{dt} & = & \rho_1 c(t)(1 - \beta_1 \ln c(t)) - k_1 c(t) g(h(t)), \\ \frac{dn(t)}{dt} & = & \rho_2 n(t)(1 - \beta_2 \ln n(t)) - k_2 n(t) g(h(t)) - \alpha\varphi(c(t), n(t)), \\ \frac{dh(t)}{dt} & = & -\gamma_h h(t) + u(t). \end{cases} \tag{4.1}$$

Denote by $\overline{c}(t) = \ln c(t)$, $\overline{n}(t) = \ln n(t)$.

For any $t \geqslant 0$ to determine the viable domain Ω bounded by the parameters n^* and c^* by the following inequalities:

$$\overline{n}(t) \geqslant n^*, \ \overline{c}(t) \leqslant c^*. \tag{4.2}$$

Let us consider now the control function $u(t) = u$ as a parameter of the system that does not depend on the variable t and satisfies the restriction $0 \leqslant u \leqslant q$.

Consider now the critical point of the dynamical system (4.1) which depends on the parameter u $A_u\,(\overline{c}_u, \overline{n}_u, h_u)$ where

$$\overline{c}_u = \frac{1}{\beta_1}(1 - \kappa_1 g(h_u)), \ \overline{n}_u = \frac{1}{\beta_2}(1 - \kappa_2 g(h_u)) - \frac{\alpha}{\beta_1\rho_2} l(\overline{c}_u), \ h_u = \frac{u}{\gamma} \tag{4.3}$$

Here

$$\kappa_i = \frac{k_i}{\rho_i} \ i = 1, 2, \quad g(h_u) = \frac{u}{a_0\gamma + u}, \quad l(\overline{c}_u) = \frac{e^{\overline{c}_u}}{1 + e^{\overline{c}_u}}.$$

Analyzing the eigenvalues of the Jacobi matrix at point A_u, we obtain that for any possible value of the parameter $0 \leqslant u \leqslant q$ the critical point A_u will be a stable knot. [1]

Aside from the point A_u the system (4.1) has another critical points. It can be shown that all these critical points are unstable (see Figure 1).

[1]Note that for sufficiently small values of the parameter α the characteristic of the critical point A_u does not change comparing with the case when $\alpha = 0$.

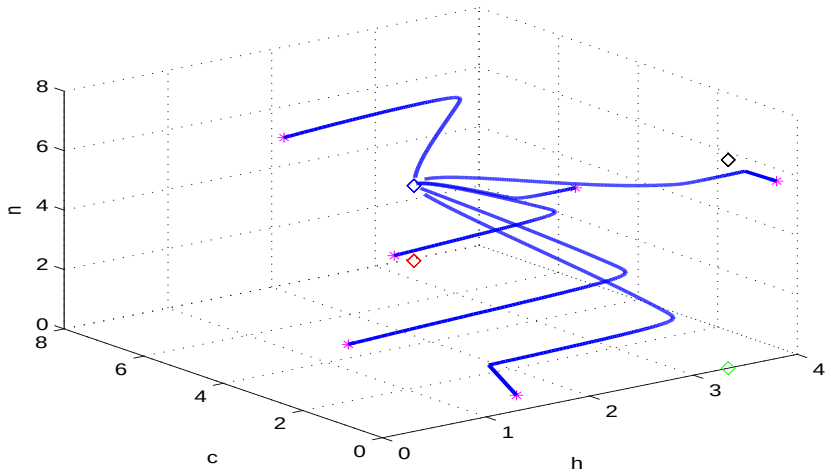

FIGURE 1. critical points of the system (4.1)

For $u = 0$ the critical point A_0 will be situated out of the viable domain Ω since in this case the density of tumour cells reaches its maximal value.

On the other hand, since the critical point A_u is asymptotically stable, then the phase orbits will be located in the viable domain Ω only if $A_u \in \Omega$ holds. Let us estimate the value of the parameter u that is supplied this location (for $\alpha = 0$).

If $A_u \in \Omega$ then

$$1 - \kappa_1 g(h_u) \leq \beta_1 c^*,\ 1 - \kappa_2 g(h_u) \geq \beta_2 n^*,\ \kappa_i = \frac{k_i}{\rho_i}, i = 1, 2,\ \kappa_1 > \kappa_2 > 1.$$

Therefore

$$\frac{a_0 \gamma_h r_1}{1 - r_1} \leq u \leq \frac{a_0 \gamma_h r_2}{1 - r_2}$$

where

$$r_1 := \frac{1}{\kappa_1}(1 - \beta_1 c^*),\ r_2 := \frac{1}{\kappa_2}(1 - \beta_2 n^*).$$

The critical point of the system (4.1) will be a space homogenous steady state position of the distributed system (2.1).

We introduce the following supposition:

1. The positive functions $c(x,t)$, $n(x,t)$, $h(x,t)$ are smooth functions of a real variable $t \geqslant 0$.
2. For any $t \geqslant 0$ the functions $c(x,t)$, $n(x,t)$, $h(x,t)$ belong to the Sobolev space $W_2^2(D)$ as functions of a variable $x \in D$.
3. $u(x,t) = u$ is a parameter with $0 \leqslant u \leqslant q$,
4. $d_c(x) = d \in \mathbb{R}^{>0}$ for all $x \in D$.

Note that from the embedding theorem (see, for instance, [23]) it follows that the functions from $W_2^2(D)$ coincide with continuous functions $C(D)$ everywhere, excluding maybe a set of measure zero.

Let us recall that a space homogenous equilibrium $v^0 = (c^0, n^0, h^0)$, with $c^0, n^0, h^0 > 0$ of the distributed system (2.1) is called Lyapunov stable if for any

$\varepsilon > 0$ we can find in the space $W_2^2(D)$ such neighborhood $U_{v^0}^{\delta}$ of the equilibrium v^0 that any initial data of the system (2.1) which belong to $U_{v^0}^{\delta}$ will fulfill the condition:

$$\|v(x,t) - v^0\|_{W_2^2(D)} < \varepsilon,\ t > 0$$

where $v(x,t) = (c(x,t),\, n(x,t),\, h(x,t))$ is a solution of the system (2.1) with initial data from the neighborhood $U_{v^0}^{\delta}$.

The equilibrium v^0 will be asymptotically stable if besides that

$$\lim_{t\to\infty} \|v(x,t) - v^0\|_{W_2^2(D)} = 0.$$

We consider the following auxiliary boundary eigenvalue problem for the Laplace equation

$$\Delta\psi(x) = -\lambda\psi(x),\ x \in D,\ \left(\frac{\partial\psi}{\partial\nu}\right)_{\Gamma} = 0 \tag{4.4}$$

The system of eigenfunctions of this problem $\psi_0(x) = 1$, $\{\psi_i(x)\}_{i=1}^{\infty}$ forms a complete system in the Sobolev space $W_2^2(D)$

$$\int_D \psi_i(x)\psi_j(x)\,dx = \delta_{i,j},\ i,j = 0,1,2\ldots \tag{4.5}$$

where $\delta_{i,j}$ is the Kronecker symbol ([23]). Here and further the parentheses $(\ ,\ )$ denote the scalar product in the space $L_2(D)$.

The corresponding eigenvalues of (4.4) satisfy the condition

$$\lambda_0 = 0 < \lambda_1 \leqslant \lambda_2 \ldots \leqslant \lambda_n \leqslant \ldots \lim_{n\to+\infty} \lambda_n = +\infty \tag{4.6}$$

Theorem 4.1. *Suppose that assumptions* $1-4$ *are fulfilled. Then the space homogenous steady state position (4.3) will be asymptotically stable in the space* $W_2^2(D)$ *for all values of the control parameters* $0 \leqslant u \leqslant q$.

Proof. Using (4.4-4.6) we seek the solution of the system (2.1) in the following form:

$$\begin{aligned}
c(x,t) &= \tilde{c} + \delta\left(c_0(t) + \sum_{s=1}^{\infty} c_s(t)\psi_s(x)\right) = \tilde{c} + \delta\Psi_c(x,t),\\
n(x,t) &= \tilde{n} + \delta\left(n_0(t) + \sum_{s=1}^{\infty} n_s(t)\psi_s(x)\right) = \tilde{n} + \delta\Psi_n(x,t),\\
h(x,t) &= \tilde{h} + \delta\left(h_0(t) + \sum_{s=1}^{\infty} h_s(t)\psi_s(x)\right) = \tilde{h} + \delta\Psi_h(x,t).
\end{aligned} \tag{4.7}$$

Here $\ln\tilde{c} = \overline{c_u}$, $\ln\tilde{n} = \overline{n_u}$, $\tilde{h} = \frac{u}{\gamma_h}$. The values $\overline{c_u}$ and $\overline{n_u}$ are defined by (4.4). δ is a sufficiently small value.

Note that expatiations (4.7) are possible since eigenfunctions $\{\psi_s(x)\}_{s=0}^{\infty}$ of the boundary problem (4.5) complete the full system in the space $W_2^2(D)$.

Substituting (4.7) into (2.1) and retaining in the usual way only linear terms with respect to $\Psi_c(x,t)$, $\Psi_n(x,t)$, $\Psi_h(x,t)$ we obtain the following linear system

$$\begin{aligned}
\tfrac{\partial\Psi_c(x,t)}{\partial t} &= \left(\rho_1(1-\beta_1\ln\tilde{c}) - \beta_1\rho_1 - k_1 g(\tilde{h})\right)\Psi_c(x,t) - k_1\tilde{c}g'(\tilde{h})\Psi_h(x,t) +\\
&\quad + d_c\Delta\Psi_c(x,t),\\
\tfrac{\partial\Psi_n(x,t)}{\partial t} &= \left(\rho_2(1-\beta_2\ln\tilde{n}) - \beta_2\rho_2 - k_2 g(\tilde{h}) - \alpha\tfrac{\partial\varphi(\tilde{c},\tilde{n})}{\partial n}\right)\Psi_n(x,t) -\\
&\quad - \alpha\tfrac{\partial\varphi(\tilde{c},\tilde{n})}{\partial c}\Psi_c(x,t) - k_2\tilde{c}g'(\tilde{h})\Psi_h(x,t) + d_n\Delta\Psi_n(x,t),\\
\tfrac{\partial\Psi_h(x,t)}{\partial t} &= -\gamma_h\Psi_h(x,t) + u + d_h\Delta\Psi_h(x,t).
\end{aligned} \tag{4.8}$$

From [17] it follows that sufficient investigate stability of the system (4.8).

Integrating (4.8) and using (4.6) we obtain an ODE system respective to the functions $c_0(t),\ n_0(t)$ and $h_0(t)$ from the expansion (4.7)

$$\begin{array}{rcl} \frac{dc_0(t)}{dt} & = & \left(\rho_1(1-\beta_1\ln\tilde{c})-\beta_1\rho_1-k_1g(\tilde{h})\right)c_0(t)-k_1\tilde{c}g'(\tilde{h})h_0(t), \\ \frac{dn_0(t)}{dt} & = & \left(\rho_2(1-\beta_2\ln\tilde{n})-\beta_2\rho_2-k_2g(\tilde{h})-\alpha\frac{\partial\varphi(\tilde{c},\tilde{n})}{\partial n}\right)n_0(x,t)- \\ & & -\alpha\frac{\partial\varphi(\tilde{c},\tilde{n})}{\partial c}c_0(x,t)-k_2\tilde{c}g'(\tilde{h})h_0(t), \\ \frac{dh_0(t)}{dt} & = & -\gamma_h h_0(t)+u. \end{array} \tag{4.9}$$

The Jacobi matrix of the system (4.9) at the critical point (4.3) coincides with the Jacobi matrix of the system (4.1). Therefore

$$\lim_{t\to\infty}c_0(t)=\lim_{t\to\infty}n_0(t)=\lim_{t\to\infty}h_0(t)=0.$$

Multiplying equations from (4.8) with the eigenfunctions $\psi_s(x),\ s=1,2,\dots$ and integrating the obtained equations over D we get a sequence of systems of ODE for $c_s(t),\ n_s(t)$ and $h_s(t),\ s=1,2,\dots$ This systems 'almost' coincide with the system (4.9) except that to each equation the terms $-\lambda_s d_c c_s(t),\ -\lambda_s d_n n_s(t),\ -\lambda_s d_h h_s(t)$, respectively, will be added.

Due to the facts that $\lambda_s>0$ for each $s=1,2,\dots$ and $\lambda_s\to+\infty$ if $s\to+\infty$, the presence of these terms does not change the signs of eigenvalues of corresponding Jacobi matrixes.

Therefore

$$\lim_{t\to\infty}c_s(t)=\lim_{t\to\infty}n_s(t)=\lim_{t\to\infty}h_s(t)=0,\ s=1,2\dots$$

This completes the proof of theorem 4.1. □

5. **Numerical simulation.** One of important aims of a therapy process is securing the life of a patient or in our terms keeping the phase orbit inside of the viable domain Ω. Therefore it is necessary to investigate the behavior of the system in the neighborhood of the boundary of the viable domain Ω.

The point is that the system (2.1) has the property of inertia when the control function switches from its maximal value $u=q$ to its minimal value $u=0$ and vice versa.

For a demonstration of this phenomenon we consider the following example:

Taking $h(t_0)=h_0\geq 0,\ \tau_1>0$ and

$$u(t)=\begin{cases} q, & t_0\leqslant t\leqslant t_0+\tau_1, \\ 0, & t>t_0+\tau_1, \end{cases}$$

we obtain the following solution of the third equation from (4.1)

$$h(t)=\begin{cases} h_0+\frac{q}{\gamma_h}\left(1-e^{-(t-t_0)}\right), & t_0\leqslant t\leqslant t_0+\tau_1, \\ h_0+\frac{q}{\gamma_h}\left(1-e^{-(t_0+\tau_1)}\right)e^{-\gamma_h(t-t_0-\tau_1)}, & t>t_0+\tau_1. \end{cases}$$

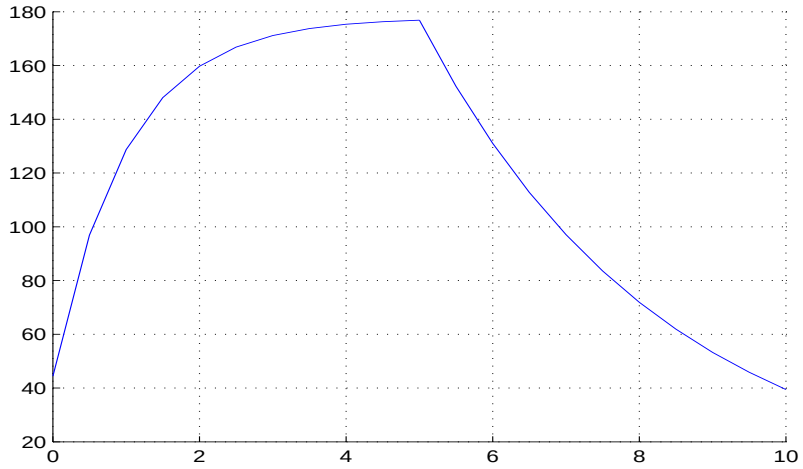

FIGURE 2. $h(t)$

Above we can see (Figure 2) that if the control function switches instantly the concentration of the chemotherapeutic agent stays a continuous function and approaches its limit value after some time only.

An analogous behavior takes places for $c(t)$, $n(t)$.

Therefore, to ensure that a phase orbit does not leave the viable domain Ω it is necessary to increase the dosage of the chemoterapeutic agent some time before this orbit reaches the boundary of Ω.

Consider the null-isocline of variables $\overline{c}(t)$, $\overline{n}(t)$ in the planes $(h, \overline{c})$ and $(h, \overline{n})$ (compare 4.3) respectively:

$$\overline{c} = \beta_1^{-1}\left(1 - \frac{\kappa_1 h}{a_0 + h}\right) = \varphi_{\overline{c}}(h),\ \overline{n} = \beta_2^{-1}\left(1 - \frac{\kappa_2 h}{a_0 + h}\right) = \varphi_{\overline{n}}(h). \tag{5.1}$$

These isoclines divide the domain Ω into four subdomains:

$$D^+_{\overline{c}} = \{(\overline{c}, \overline{n}, h) \in \Omega :\ \overline{c} > \varphi_{\overline{c}}(h)\}$$
$$D^-_{\overline{c}} = \{(\overline{c}, \overline{n}, h) \in \Omega :\ \overline{c} < \varphi_{\overline{c}}(h)\}$$
$$D^+_{\overline{n}} = \{(\overline{c}, \overline{n}, h) \in \Omega :\ \overline{n} > \varphi_{\overline{n}}(h)\}$$
$$D^+_{\overline{n}} = \{(\overline{c}, \overline{n}, h) \in \Omega :\ \overline{n} < \varphi_{\overline{n}}(h)\}$$

If the phase orbit belongs to the domain $\Omega_1 = D^-_{\overline{c}} \cap D^+_{\overline{n}}$, then for any choice of control function from the set Σ the restrictions $\overline{c} \leqslant c^*$, $\overline{n} \geqslant n^*$ will be always fulfilled.

If a phase orbit gets into the domain $\Omega_2 = D^+_{\overline{c}} \cap D^+_{\overline{n}}$, then the restriction $\overline{c} \leqslant c^*$, can be violated. Note that at the same time the restriction $\overline{n} \geqslant n^*$ will be fulfilled for any control function from the set Σ.

Leave out the orbits of the system (4.1) in inverse time with control $u = q$ from each point of the set $\overline{c} = \varphi_{\overline{c}}(h)$. The calculation shows that orbits do not leave the domain Ω_2 except the orbits are situated below the orbit which goes from the point $\varphi_{\overline{c}}(h) = c^*$. Therefore the restriction $\overline{c} \leqslant c^*$ will be violated if the phase points belong to this area (see Fig. 3).

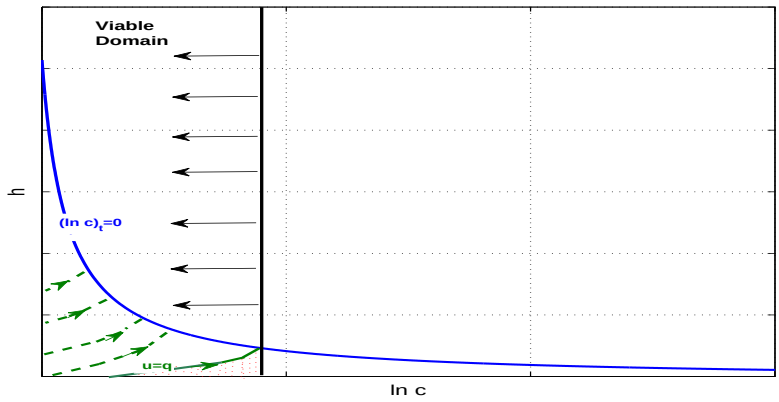

FIGURE 3. The viable domain is located on the left. Shaded area $B_{\overline{c}}$ is bounded by the viable domain and the new surface produced from the orbits in inverse time with control $u = q$ from each point of the set $\varphi_{\overline{c}}(h) = c^*$. Here $k_1 > \rho_1$.

If a phase orbit gets into the domain $\Omega_3 = D^-_{\overline{c}} \cap D^-_{\overline{n}}$ then the restriction $\overline{n} \geqslant n^*$ can be violated while the restriction $\overline{c} \leqslant c^*$ is fulfilled for any control function from the set Σ.

Leave out the orbits of the system (4.1) in inverse time with control $u = 0$ from each point of the set $\overline{n} = \varphi_{\overline{n}}(h)$. The calculation shows that the orbits do not leave the domain Ω_4 except the orbits are situated above the orbit which goes from the point $\varphi_{\overline{n}}(h) = n^*$. Thus, the restriction $\overline{n} \geqslant n^*$ is violated if the phase points belong to this area (see Fig. 4).

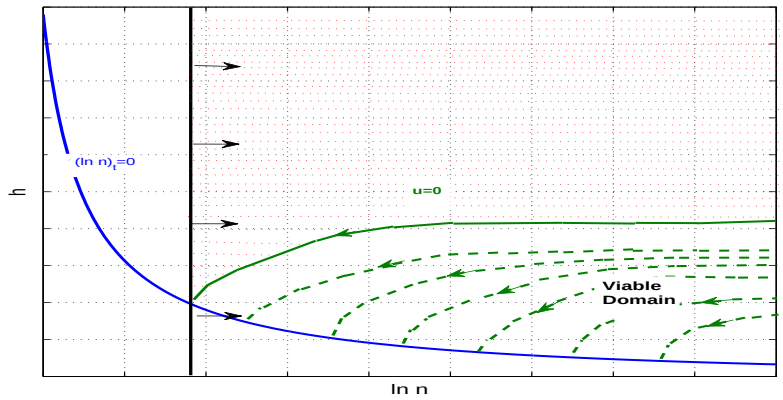

FIGURE 4. The viable domain is located on the right. Shaded area $B_{\overline{n}}$ is bounded by the viable domain and the new surface produced from the orbits in inverse time with control $u = 0$ from each point of the set $\varphi_{\overline{n}}(h) = n^*$. Here $k_2 > \rho_2$.

If a phase orbit gets into the domain $\Omega_4 = D_{\overline{c}}^{+} \cap D_{\overline{n}}^{-}$ then both restrictions on the numbers of healthy and malignant cells can be violated.

Note that if we suppose that $\overline{c} > c^*$ then the domains $D_{\overline{c}}^{+}$ and $D_{\overline{n}}^{-}$ are mutually disjoint.

One of the important problems of searching the optimal strategy from the set Σ is the choice of the relation

$$p = \frac{\tau_2}{\tau_1}$$

between the time of relaxation ($\tau_2,\ u = 0$) and the time of active control ($\tau_1,\ u = q$).

For chosing the optimal response time T in the viable domain Ω as a function of the parameter p, we assume the following restriction on the total value of the chemotherapeutic agent

$$Q = 500[\text{gm}],\ c^* = 250,\ n^* = 350.$$

Let D be a square of an area 25 cm^2. The remaining values of parameters of the system (2.1) (see [10], [11], [26], [33]) are presented in the table below:

TABLE 1. Parameters of the system (2.1)

parameter	**notation**	**value**
diffusion of cancer cells	d_g	1.3×10^{-3} cm^2/day
diffusion of cancer cells	d_w	5×10^{-3} cm^2/day
diffusion of drug	d_h	0.386×10^{-2} cm^2/day
diffusion of normal cells	d_n	1.0×10^{-3} cm^2/day
drug dissipation	γ_h	0.0347
proliferation of cancer cells	ρ_1	0.012 day^{-1}
saturation of cancer cells	β_1	0.0819
proliferation of normal cells	ρ_2	0.006 day^{-1}
saturation of normal cells	β_2	0.0869
cancer domain area	S_D	5×5 cm^2

For our numerical simulation we choose the control function $u(x,t) = u_0(t)$ (for the case $D_0 \equiv D$). The values of the parameter k_1, k_2 and q as well as the corresponding value of the parameter p will be presented separately in each case.

Our calculation shows that increasing the value of the parameter $p = \frac{\tau_2}{\tau_1}$ leads to a violation of the restriction $\overline{c} \leqslant c^*$. On the other hand decreasing the value of the parameter p leads to a violation of the restriction $\overline{n} \geqslant n^*$. The explanation of this phenomenon is very simple. In the first case the population of malignant cells have a plethora of time for restoration after applying drugs. In contrast, in the second case the population of normal cells have not enough time for restoration since the schedule of applying drugs is very intensive.

The projections of trajectories $((\overline{c}(t), \overline{n}(t)))$ of the system (2.1) on the plane $((\overline{c} \times \overline{n}))$

$$\overline{c}(t) = \int\limits_D \ln c(x,t)\,dx,\ \overline{n}(t) = \int\limits_D \ln n(x,t)\,dx$$

are presented in the Fig. 5.

Three cases are presented: $p = 4,\ p = 3,\ p = 1$. The number of cycles of control function from the set Σ is denoted by m. The amount of the chemotherapeutic agent which was spent during one cycle is denoted by H [gm].

The time in the viable domain is denoted by T [day] and the total value of the chemotherapeutic agent applied in this time is denoted by Q_T.

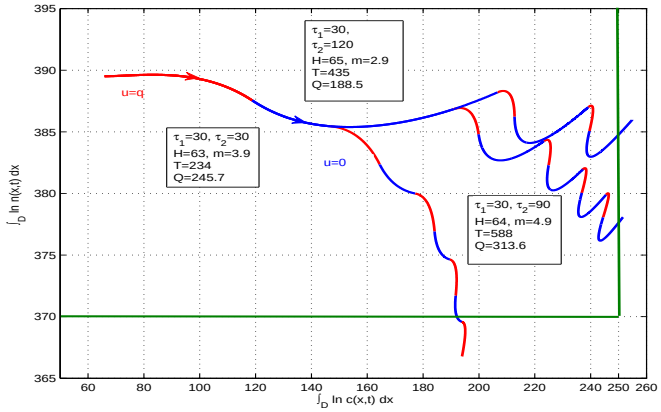

FIGURE 5. $\frac{k_2}{k_1} = 0.5,\ \alpha = 0,\ q = 0.002.$

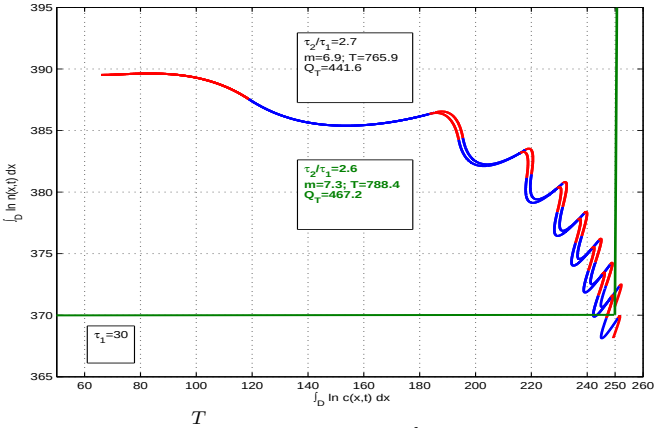

FIGURE 6. $Q = \int\limits_D \int\limits_0^T h(x,t)\,dx \leqslant 500;\ \frac{k_2}{k_1} = 0.5,\ \alpha = 0,\ q = 0.002.$
The best strategy: $\tau_1 = 30,\ \tau_2 = 78.$

In all cases after several cycles the trajectory leaves the viable domain. Nevertheless, the second case ($p = 3$) supplies the maximal survival time T.

From analysis of graphs of the fig. 5 it is possible to drow the conclusion that an optimal strategy of control from the set Σ has to provide almost simultaneous violation of both restrictions on numbers of malignant and normal cells. This strategy is realized when $p = 2.6$ and $Q_T = 470$[gm]. Fig. 6 demonstrates the behavior of trajectories $\overline{c}(t)$ and $\overline{n}(t)$ when $p = 2.6$ and $p = 2.7$.

Note that this strategy will be optimal only if it is possible to use a sufficiently large quantity of drugs, and cannot be optimal if, for example, $Q < 470$[gm] (compare 2.7).

Analysis of the behavior of trajectories $\overline{c}(t)$ and $\overline{n}(t)$ which correspond to the relations $\frac{k_2}{k_1}$ and α are demonstrated in Fig. 7 and Fig. 8, respectively.

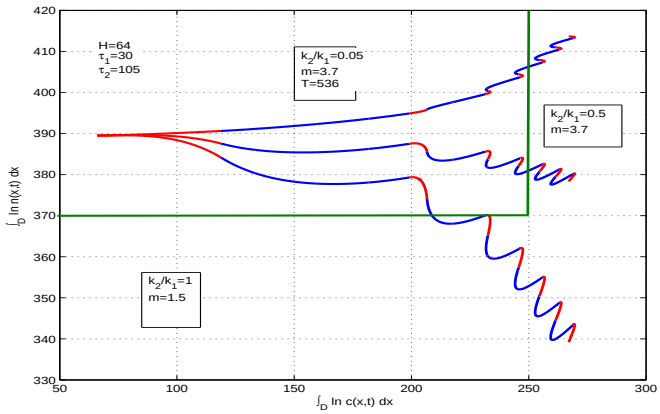

FIGURE 7. $\tau_1 = 30$, $\alpha = 0$, $q = 0.002$.

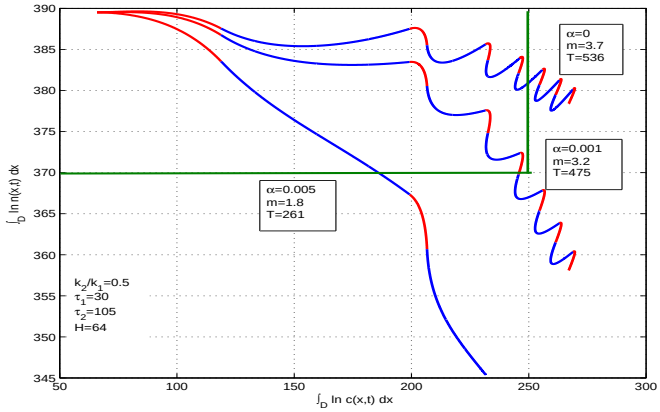

FIGURE 8. $\frac{k_2}{k_1} = 0.5$, $q = 0.002$.

In both cases there exist threshold values of parameters $\frac{k_2}{k_1} = 0.5$ and $\alpha = 0.001$ after that the survival time T rapidly decreases.

In Fig. 9 the numerical results for the case if the time of active control is decreasing while the ratio of the time of active control to the relaxation time stays equal to 2.6 are presented. The results obtained show that a consequence of decreasing the active control time is an increase of the total survival time, which reaches its maximal value at $\tau_1 = 3$ (Fig. 10).

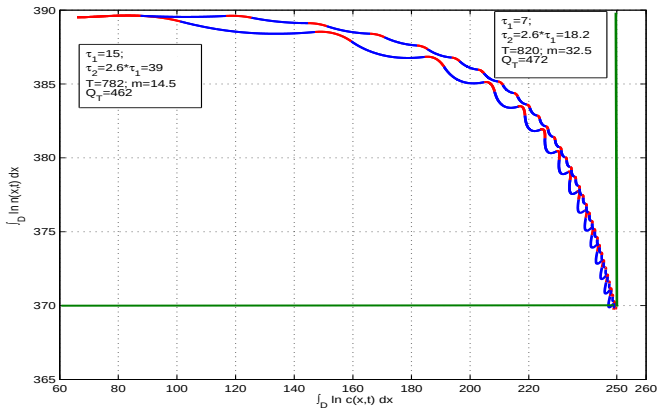

FIGURE 9. $\frac{k_2}{k_1} = 0.5,\ p = 2.6,\ q = 0.002.$

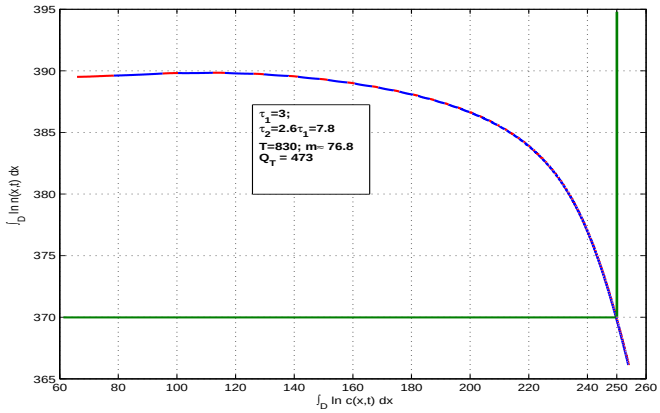

FIGURE 10. $\frac{k_2}{k_1} = 0.5,\ p = 2.6,\ q = 0.002.$

In Fig. 11 the dependence of the total viable time on the parameter q if the value of the parameter p is constant and equal to 2.6 is shown. The results obtained show that in the case of the increasing dose of drug the total survival time does not increase.

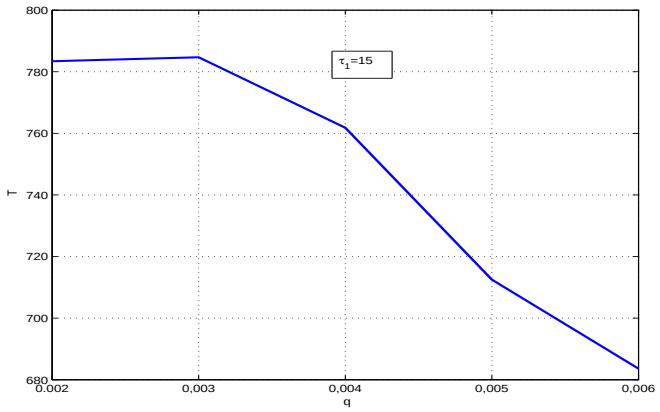

FIGURE 11. $\frac{k_2}{k_1} = 0.5,\ p = 2.6$

In Fig. 12 the dependence of the value of the parameter p on the parameter q, which guarantee the maximal survival time is shown. The results obtained show that the dependence p on q is almost linear. For instance for $q = 0.005$ the corresponding optimal value p is 8.

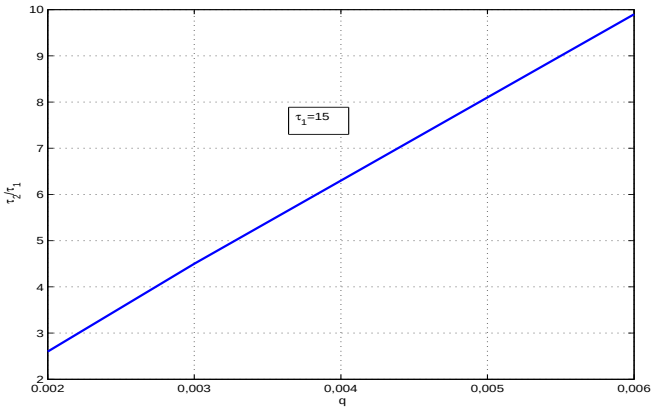

FIGURE 12. $\frac{k_2}{k_1} = 0.5,\ p = 2.6$

Obtained numerical results do not give an answer on the question of the possibility of realizing a strategy from the set Σ which supplies presence in the viable domain for a desired time. Moreover these results show the impossibility of existence of such a strategy for given values of parameters. Note also the latter fact agrees with medical practice.

Nevertheless, if we suppose that it is possible to increase the value of the parameter q and that a patient can sustain a sufficiently large dose of chemotherapeutic agent without any harm to their health then we have a stabilizing strategy of treatment. An example of this strategy is given in Fig. 13 which shows the projection of the trajectory of a solution of (2.1) on a plane $\overline{c}$, $\overline{n}$.

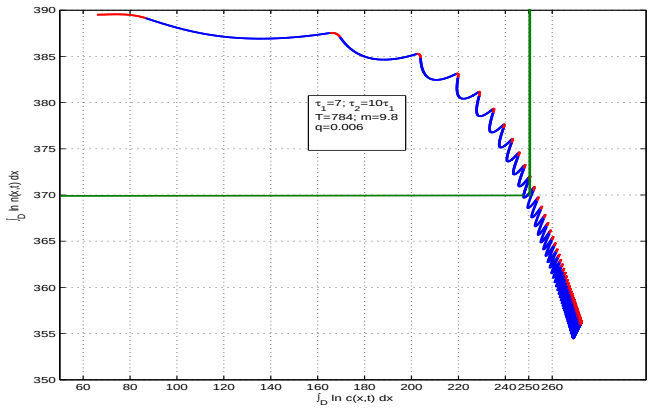

FIGURE 13. $\frac{k_2}{k_1} = 0.5,\ p = 10$

In this case the time of relaxation is 10 times more then the time of active control. The position of the trajectory stabilizes outside of the viable domain.

6. **Conclusions.** In the present work a mathematical spatial cancer model of interaction between a drug and both malignant and healthy cells is considered. It is assumed that the drug influences negative malignant cells as well as healthy ones. The mathematical model under consideration consists of three non-linear parabolic partial differential equations that describe spatial dynamics of malignant cells, that of healthy ones, and of the concentration of drug (pharma-kinetic equation), respectively. Additionally, we assume there are phase constraints for the total quantity of the drug during the whole treatment process. In contrast to most works on therapy optimization with the aim to minimize the number of malignant cells, the aim of the present work is to find a therapy strategy which maximizes the survival time of the patient.

The qualitative implications of our analysis of the task considered can be summarized as follows:

The ratio of the time of the active control to the relaxation time influences the viable time essentially. The optimal value of this parameter depends on the intensity of application of the therapeutic agent. Therefore, stronger administration of drug requires a longer period of relaxation. In our opinion, this fact has very important implications for a real therapy process.

Based on the analysis of the task considered, we can argue that there exists a threshold value for the time of active control: The viable time increases if the time of active control decreases to this threshold value, if the time of active control is below this threshold value the viable time decreases again.

As expected, the restriction on the cumulative amount of the chemotherapeutic agent is the strongest factor which hinders a periodic therapy strategy. This implies a need to decrease the total admissible dosis of drugs and emphasises the need for further medical investigations.

At the same time, when it comes to the intensity of the damage to normal cells and the efficiency of the therapy for cancer cells, their ratio does not lead to significant effects when it is smaller than some threshold value, while increasing the competition parameter has essential influence on the value of viable time.

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E-mail address: e.fimmel@hs-mannheim.de
E-mail address: applmath1miit@yandex.ru
E-mail address: zaylanka@gmail.com