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ON OPTIMAL AND SUBOPTIMAL TREATMENT STRATEGIES FOR A MATHEMATICAL MODEL OF LEUKEMIA

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Abstract. In this work an optimization problem for a leukemia treatment model based on the Gompertzian law of cell growth is considered. The quantities of the leukemic and of the healthy cells at the end of the therapy are chosen as the criterion of the treatment quality. In the case where the number of healthy cells at the end of the therapy is higher than a chosen desired number, an analytical solution of the optimization problem for a wide class of therapy processes is given. If this is not the case, a control strategy called *alternative* is suggested.

1. **Introduction.** The nature of the interaction between the size of the tumor and the prescribed treatment is still unclear.

At the beginning of the 1960s, Skipper et al. examined the L1210 murine leukemia model and formulated some principles of tumor cell kill [26], namely, that a given dose of a drug kills a constant fraction of cells and not a constant number, and that there is a relationship between the dosage of a drug and the percentage of the leukemic cells killed.

Norton and Simon ([22], [23]) hypothesized in the 1970s that the cell-kill is proportional to the growth law of tumor cells.

In the 1980s Holford and Sheiner ([17], [27]) proposed that cell-kill is described in terms of a saturable function of Michaelis-Menten form with the supremum E_{max}, and that is why this hypothesis is also called the E_{max} model.

It is a natural approach to consider the cancer treatment models from the point of view of the optimization theory (see, for instance, [28], [19], [20], [13], [12], [6]).

In [12] an optimal control problem for optimal treatment strategies for three different cell-kill models is considered: Skipper's percentage-kill hypothesis, Norton-Simon hypothesis, and, Holford and Sheiner E_{max} hypothesis. In [12] Fister and Panetta analyzed the existence and uniqueness of the solutions for two optimal control problems in each of the three cases mentioned above. In the first problem the objective is for the tumor density to be as close as possible to the desired tumor density and the toxicity to be minimized. The objective of the second problem implies that the tumor density and the toxicity at the end of the treatment are to be minimized.

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The leukemia treatment model considered in this paper was suggested in [7], [29] and is based on the Afenya's model [4], which is a further development of earlier models by Clarkson [8], Rubinow and Lebowitz [25] and Djulbegovic and Svetina [9]. It is assumed that the chemotherapeutic agent kills leukemic cells as well as normal ones. In [20] Ledzewicz and Schättler suggest and analyze an alternative mathematical model for the bone marrow proliferation under chemotherapy treatment, taking into account the side-effects of the drugs. This model is based on the two-compartment growth model (differentiating between the proliferating and quiescent cell mass) for tissue suggested by Panetta in [24] and analyzed in [13] from the point of view of the optimal control theory. The therapy then affects only the proliferating cell mass. This model does not contain a description of the dynamics of the healthy cells during the therapy. The side-effects of the drugs were taken into account using the definition of the objective function. In the model considered in this work the number of leukemic cells can be understood as the sum of the numbers of the proliferating and quiescent cells. The dynamics of the healthy cells and of the amount of the chemotherapeutic agent are parts of the model.

Any optimization problem becomes more complicated since the chemotherapy destroys not only the leukemic cells but the normal cells too. Thus we have simultaneously two opposite objectives: to destroy leukemic cells and not to let the number of normal cells fall below some minimal acceptable value.

In [7] a classical optimization problem for the model studied in the present article with one objective function for strictly increasing cell-kill strategies and cell-kill strategies with a threshold effect is considered. In the present work we consider a different objective function. The reasons for this change are explained in Section 1. In [29] a multi-objective approach was applied to the same model in order to minimize the number of leukemic and at the same time to maximize the number of healthy cells. The results of this article generalize the results of both articles [7] and [29].

In Section 2 will be shown that the optimal control function is a bang-bang control function with the number of switching points depending on the number of zeroes of the derivatives of the treatment processes if the cell-kill velocities for leukemic and healthy cells are proportional.

If the number of the healthy cells at the end of the therapy process is higher than a prescribed value, the optimal control function can be determined in a purely analytical way for a wide class of therapy functions as is shown in Section 2. The optimal control strategy involves giving the patient the maximal admissible quantity of the chemotherapeutic agent up to the moment when the maximal therapy effect is reached. Then the maximal effect should be maintained until one of the admissible boundary values of the constraints is achieved. After this the therapy needs to stop. The moment of the maximal effect of the therapy can be calculated on the basis of the model parameters. If the side-effects of the therapy cannot be disregarded, that is, if the number of the healthy cells falls at the end of the therapy below a prescribed value, a suboptimal control function called alternative control function is suggested in Section 3.

In Section 4 we consider some examples and present numerical results for the optimal and alternative treatment therapy. The comparison of these two kinds of strategies shows a relatively small difference in treatment quality. Thus, the alternative strategy should be viewed as an effective one too.

2. **Model formulation and the optimization problem.** Let $N(t)$ be the number of healthy cells, $L(t)$ the number of leukemic cells and $h(t)$ the amount of the chemotherapeutic agent at the moment t. In [7] the following mathematical model for leukemia therapy based on the Gompertzian cell growth law was proposed:

$$\begin{aligned}
&\frac{dL(t)}{dt} = r_l L(t) \ln \frac{L_a}{L(t)} - \gamma_l L(t) - f_l(h(t))L(t) \\
&\frac{dN(t)}{dt} = r_n N(t) \ln \frac{N_a}{N(t)} - \gamma_n N(t) - cN(t) \cdot L(t) - f_n(h(t))N(t) \\
&\frac{dh(t)}{dt} = -\gamma_h h(t) + u(t), \quad 0 < t \le T\,;
\end{aligned} \tag{1.1}$$

$$L(0) = L_0,\ N(0) = N_0,\ h(0) = 0\,. \tag{1.2}$$

Here L_a, N_a, r_l, r_n, γ_l, γ_n, γ_h, $c \in \mathbb{R}^{>0}$ are some constants. L_a and N_a denote in (1.1) the limit numbers of the leukemic and normal cells, respectively, r_l, r_n and γ_l, γ_n present the growth and mortality rates of both cell types, respectively, $f_l(h)$ and $f_n(h)$ describe the influence of the chemotherapy on the cells (called *therapy functions*). We assume that $f_l(h) > f_n(h)$ for all $h > 0$, since although drugs affect all cells in an organism, a lot of useful treatment is most effective against rapidly growing cells.

The parameter c is the interaction rate while γ_h is the dissipation rate. The quantity of the chemotherapeutic agent applied to a patient at the moment t is the control function $u(t) \in L_\infty[0,T]$.

Let $u(t)$ satisfy the constraint

$$0 \le u(t) \le R \tag{1.3}$$

with a parameter $R \in \mathbb{R}_+$.

We obtain the following solution of the third differential equation of (1.1)

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

Thus we have the following condition for the amount of the drug at any point of time $t \in [0,T]$:

$$h(t) < \frac{R}{\gamma_h}.$$

In some cases for the optimal treatment strategy $h(t)$ is automatically bounded by the value h_M at which the maximum value of the therapy function is reached (see Section 2).

It is reasonable to require the following constraint for the cumulative quantity of the chemotherapeutic agent during the overall therapy process:

$$\int_0^T h(t)dt \le Q, \quad \text{where, obviously,} \quad 0 < Q \le \frac{TR}{\gamma_h}. \tag{1.4}$$

We consider the following optimal control problem. We need to find the time $T \in (0,\infty)$ and the control function $u(t) \in L_\infty[0,T]$ satisfying (1.3)-(1.4) and providing the lower boundary to the cost function:

$$\Phi(L(T),N(T)) = \begin{cases} L^2(T), & N(T) \ge N_d \\ L^2(T) + \alpha(N(T) - N_d)^2, & N(T) < N_d \end{cases} \tag{1.5}$$

Here $N_d > 0$ and $\alpha > 0$ are two parameters, N_d is the desired number of the normal cells at the end of the therapy process, α is a preference indicator. For $\alpha > 1$ the preference is to make the number of normal cells close to N_d; for $\alpha < 1$ it is to minimize the number of leukemic cells. We consider the quadratic terms for the following reasons: the difference $N(T)-N_d$ can become negative and thus violate the lower bound of the cost function. Further, it is mathematically easier to work with quadratical terms than, for instance, with the absolute value of $N(T) - N_d$ which would deliver the same biological effect. $L(T)$ is minimized if $L^2(T)$ is minimized. The term $L^2(T)$ is chosen for the case $N(T) \geq N_d$ for the reason of the compatibility with the second part of the objective function.

In [7] a slightly different objective function was considered, namely,

$$\Phi(L(T), N(T)) = L^2(T) + \alpha(N(T) - N_d)^2 \,.$$

The reason for changing the objective function is the following: if the number of healthy cells at the end of the therapy process is high enough (that is $N(T) \geq N_d$), it is not necessary and may even be harmful[1] to make it as close as possible to N_d. In the other case we want to get $N(T)$ as close as possible to N_d and $L(T)$ as close as possible to zero in both cases.

3. **An extension of a class of therapy possibilities.** In this section we will extend the class of therapy functions considered and generalize the analytical results of [7] and [29]. Let us consider first the situation when the derivatives of both therapy functions are proportional. It is a quite natural assumption and it means that the leukemic and healthy cells are being destroyed by the drug with proportional velocities. For instance, it takes place for both pairs of therapy functions considered in [7]:

$$f_i(h) = \lambda_i h e^{-bh} \;\text{ or }\; f_i(h) = \frac{\lambda_i h}{1+h}, \quad i \in \{l, n\}\,, \;\; \lambda_i, b \in \mathbb{R}.$$

Our aim is now to show that for the relevant values of model parameters in this case the optimal control function is a bang-bang function with the maximum number of switching points depending on the number of zeroes of the functions $f_l'(h(t))$ and $f_n'(h(t))$ (see Theorem 2.1 below).

It was proved in [7] using the Pontryagin's maximum principle that for the optimal control function u^* the following conditions hold:

$$u^*(t) = \begin{cases} R\,, & \psi_3(t) > 0 \\ 0\,, & \psi_3(t) < 0 \\ \mathit{unknown}\,, & \psi_3(t) = 0\,. \end{cases} \tag{2.1}$$

where

$$\begin{aligned} \psi_3(t) &= \psi_{30} e^{\gamma_h t} - \int_0^t e^{\gamma_h (t-s)} \left(\psi_1(s) \cdot \frac{df_l(h(s))}{dh(s)} + \psi_2(s) \cdot \frac{df_n(h(s))}{dh(s)} \right) ds \\ \psi_1(t) &= \psi_{10} e^{r_l t} + c_a \int_0^t e^{r_l (t-s) - l(s)} \cdot \psi_2(s) ds \\ \psi_2(t) &= \psi_{20} e^{r_n t}. \end{aligned} \tag{2.2}$$

with $\psi_{30},\ \psi_{10},\ \psi_{20} \in \mathbb{R}$, $c_a := cL_a$, $l_0 := \ln \dfrac{L_a}{L_0}$, $n(T) := \ln \dfrac{N_a}{N(T)}$, $e^{-n_d} := \dfrac{N_d}{N_a}$

[1] In this case $N(T)$ can become smaller and $L(T)$ bigger at the end of the therapy.

and

$$l(t) = l_0 e^{-r_l t} + \frac{\gamma_l}{r_l}(1 - e^{-r_l t}) + \int_0^t e^{-r_l(t-s)} f_l(h(s))ds \,,$$
$$n(t) = n_0 e^{-r_n t} + \frac{\gamma_n}{r_n}(1 - e^{-r_n t}) + \int_0^t e^{-r_n(t-s)} f_n(h(s))ds + c_a \int_0^t e^{-r_n(t-s)-l(s)} ds \,,$$
$$h(t) = e^{-\gamma_h t} \int_0^t e^{\gamma_h s} u(s)ds \,.$$

Additionally, we have the following terminal conditions

$$\psi_1(T) = 2L^2(T),\ \psi_2(T) = \begin{cases} 0, & N(T) \geq N_d \\ 2\alpha N(T)(N(T) - N_d), & N(T) < N_d \end{cases}, \psi_3(T) = 0.$$

Note that the terminal condition for ψ_2 here differs from the corresponding terminal condition in [7] due to the change of the objective function.

Theorem 3.1. *Let $f_l(h), f_n(h)$ be therapy functions with*

$$\frac{df_l(h(t))}{dh(t)} = \beta \frac{df_n(h(t))}{dh(t)} \quad \textit{for all } t \in [0, T), \quad \beta > 0,$$

and $f_n'(h(t))$ has $k \in \mathbb{N}_0$ zeroes on the interval $[0; T)$. Then the optimal control function $u^*(t)$ is a bang-bang control with

- *at most k switching points provided $N(T) \geq N_d$ and*
- *at most $k+1$ switching points $t_i \in [0, T), i \in \{1, \ldots, k+1\}$, in which the value of $u^*(t)$ switches between R and 0 provided $N(T) < N_d$ and* **the following inequality**

$$-c_a \beta e^{-l_{min}} \leq r_n - r_l \leq -c_a \beta e^{-l_{max}}$$

does not hold. *Here* $l_{max} = \max\limits_{t\in[0,T]} \ln \dfrac{L_a}{L(t)}$, $l_{min} = \min\limits_{t\in[0,T]} \ln \dfrac{L_a}{L(t)}$, $c_a = cL_a$.

Proof. Let $\tilde{\psi}_1(t) = \psi_1(t)e^{-r_l t}$, $\tilde{\psi}_3(t) = \psi_3(t)e^{-\gamma_h t}$. Evidently, $\tilde{\psi}_3(t)$ has the same zeroes as $\psi_3(t)$.

It follows from (2.2) that the zeroes of $\dfrac{d\tilde{\psi}_3(t)}{dt}$ are exactly the solutions of the equation

$$\tilde{\psi}_1(t) \cdot \frac{df_l(h(t))}{dh(t)} = -\psi_{20} e^{(r_n - r_l)t} \cdot \frac{df_n(h(t))}{dh(t)}$$

or, equivalently, they are k zero points of $f_n'(h(t))$ and the solutions of the equation

$$\delta(t) = 0 \,, \tag{2.3}$$

where $\delta(t) \equiv \beta\tilde{\psi}_1(t) + \psi_{20} e^{(r_n - r_l)t}$. The derivative of $\delta(t)$ is (see again (2.2))

$$\delta'(t) = \beta\tilde{\psi}_1'(t) + \psi_{20}(r_n - r_l)e^{(r_n - r_l)t} = \psi_{20} e^{(r_n - r_l)t}(\beta c_a e^{-l(t)} + (r_n - r_l)) \,.$$

If $\psi_{20} = 0$ (that is $N(T) \geq N_d$) the condition $\tilde{\psi}_1(t) \equiv \psi_{10} = 2L^2(T) > 0$ holds, the equation (2.3) has no solution and, hence, the equation $\dfrac{d\tilde{\psi}_3(t)}{dt} = 0$ has k roots.

For $\psi_{20} \neq 0$ (that is $N(T) < N_d$) and

$$\text{either} \quad r_n - r_l > -c_a \beta e^{-l_{max}} \quad \text{or} \quad r_n - r_l < -c_a \beta e^{-l_{min}}$$

with

$$l_{max} = \max_{t\in[0,T]} l(t), \quad l_{min} = \min_{t\in[0,T]} l(t)$$

(both exist since l is continuous on the segment $[0,T]$) δ is either a strictly increasing or a strictly decreasing function.

In both cases there is at most one root of the equation (2.3) on $[0,T)$ and, consequently, at most $k+1$ roots of the equation $\dfrac{d\tilde{\psi}_3(t)}{dt}=0$.

It is well known that between two zeroes of a differentiable function there is a zero of its derivative. Hence, $\tilde{\psi}_3(t)$ and, consequently, $\psi_3(t)$ has at most k zeroes provided $N(T)\geq N_d$, and $k+1$ zeroes on $[0,T)$ provided $N(T)<N_d$ and

$$\text{either} \quad r_n-r_l>-c_a\beta e^{-l_{max}} \quad \text{or} \quad r_n-r_l<-c_a\beta e^{-l_{min}}\,,$$

since $\psi_3(T)=\tilde{\psi}_3(T)=0$. □

Remark 1. The case $\beta\leq 0$ is practically unrealistic. For $\beta<0$ we can derive that the therapy at the same time either destroys the leukemic cells and increases the number of healthy cells, or vice versa. If $\beta=0$ holds, it means that $f_l\equiv const$ and, consequently, the effect of the therapy does not depend on the dosage of the drug.

Remark 2. It follows immediately from Theorem 2.1 that in the case of strictly increasing therapy functions with proportional derivatives the optimal control function has no switching points, that is the entire therapy process takes place with the maximum amount of chemotherapeutic agents as long as none of the constraints is violated, if the number of the healthy cells at the end of the therapy is high enough[2] and has at most one switching point if the number of the healthy cells at the end of the therapy is smaller than N_d.

Of course, it is important to know how big the range r_n-r_l is where we do not know anything about the behaviour of the optimal control function. The following lemma will be very useful in understanding this:

Lemma 3.2. *In previous notation the following inequality holds for all $t\in[0,T]$:*

$$0\leq l_{min}\leq l(t)\leq l_{max}\leq \max\left(l_0,\frac{\gamma_l}{r_l}\right)+\frac{1}{r_l}\max_{s\in[0,T]}f_l(h(s))\,.$$

Proof. Recall that

$$l(t)=l_0e^{-r_lt}+\frac{\gamma_l}{r_l}(1-e^{-r_lt})+\int_0^t e^{-r_l(t-s)}f_l(h(s))ds$$

for all $t\in[0,T]$. Since $l(t)\geq 0$ then $l_{min}=\min\limits_{t\in[0,T]}l(t)\geq 0$. An upper boundary for $l_{max}=\max\limits_{t\in[0,T]}l(t)$ can be obtained as follows. For all $t\in[0,T]$ we have

$$l(t)\leq\frac{\gamma_l}{r_l}+\left(l_0-\frac{\gamma_l}{r_l}\right)e^{-r_lt}+\max_{s\in[0,T]}f_l(h(s))\int_0^t e^{r_l(s-t)}ds\leq$$

$$\leq\max\left(l_0,\frac{\gamma_l}{r_l}\right)+\frac{\max\limits_{s\in[0,T]}f_l(h(s))}{r_l}(1-e^{-r_lt})\leq\max\left(l_0,\frac{\gamma_l}{r_l}\right)+\frac{1}{r_l}\max_{s\in[0,T]}f_l(h(s))\,.$$

Thus, $l_{max}\leq\max\left(l_0,\dfrac{\gamma_l}{r_l}\right)+\dfrac{1}{r_l}\max\limits_{s\in[0,T]}f_l(h(s))$. □

[2]The results of Theorem 2.3 show that the influence of the chemotherapeutic agent applied on the healthy cells can be completely disregarded in this case.

Example 1. Let us consider a numerical example to show that the difference between growth rates r_l and r_n for which the Theorem 2.1 is not valid is very small.

Let us consider for $\lambda_i, b \in \mathbb{R}_+,\ i \in \{l, n\}$, two pairs of therapy functions:

$$f_i(h) = \frac{\lambda_i h}{1+h} \quad \text{(monotonic therapy functions)}$$

and

$$f_i(h) = \lambda_i h e^{-bh} \quad \text{(non-monotonic therapy functions)}$$

with the following values of parameters

$$\lambda_l = 3, \lambda_n = 1.8, c_a = 3.7 \cdot 10^{-5}, l_0 = 4, \gamma_l = 0.01, r_l = 0.25, b = 0.01$$

(chosen as in the numerical examples in [7]). In this case

$$\beta = \frac{\lambda_l}{\lambda_n} = \frac{5}{3}, \quad \max\left(l_0, \frac{\gamma_l}{r_l}\right) = l_0 = 4.$$

It is still unknown in the monotonic case whether the optimal control function u^* has at most one switching point only for the range

$$r_n - r_l \in \left[-6.1(6) \cdot 10^{-5}, -6.1(6) \cdot 10^{-5} \cdot e^{-16}\right]$$

and in the non-monotonic case only for the range

$$r_n - r_l \in \left[-6.1(6) \cdot 10^{-5}, -6.1(6) \cdot 10^{-5} \cdot e^{-4-1200/e}\right].$$

The length of the interval in both cases is less than $6.1(6) \cdot 10^{-5}$. In simulations we did not encounter problems when r_l was close or equal to r_n. The condition on the interval above seems to be technical.

However, $f'(h(t))$ can have an infinite number of zeroes in the interval $[0; T)$ even if $f'(h)$ has only one zero in $\left[0, \frac{R}{\gamma_h}\right]$. Such a situation occurs in the case $N(T) \geq N_d$, that is when we minimize the number of leukemic cells.

Theorem 3.3. *Let* $N(T) \geq N_d,\ f_l(h) \in C^{(1)}\left[0, \frac{R}{\gamma_h}\right],\ f_l'(h) \geq 0$ *for* $h \in [0; h_M]$ *with*

$$h_M := \min_{0 \leq h \leq \frac{R}{\gamma_h}} \{h \mid f_l(h) = M\}, \quad \textit{where} \quad M = \max_{0 \leq h \leq \frac{R}{\gamma_h}} f_l(h)\,,$$

and

$$t_0 := \begin{cases} -\frac{1}{\gamma_h} \ln(1 - \frac{\gamma_h h_M}{R}), & h_M < \frac{R}{\gamma_h}, \\ T, & h_M = \frac{R}{\gamma_h}. \end{cases}$$

Then the optimal control function is given by

$$u^*(t) = \begin{cases} R, & 0 \leq t < t_0, \\ \gamma_h h_M, & t_0 \leq t \leq T. \end{cases}$$

Proof. It is easy to see that the given control function $u^*(t)$ yields

$$h^*(t) = \begin{cases} \frac{R}{\gamma_h}(1 - e^{-\gamma_h t}), & 0 \leq t < t_0, \\ h_M, & t_0 \leq t \leq T. \end{cases}$$

If $N \geq N_d$ we minimize $L(T)$ or, equivalently, maximize $l(T) = \ln \dfrac{L_a}{L(T)}$. We will show now that for every admissible control function $u(t)$ for all $t \in [0, T]$ the inequality

$$l(t) \leq l^*(t) := l_0 e^{-r_l t} + \frac{\gamma_l}{r_l}(1 - e^{-r_l t}) + \int_0^t e^{-r_l(t-s)} f_l(h^*(s))ds$$

holds. Thus $u^*(t)$ is the optimal treatment strategy at each moment t and not only at the end T of the therapy process. Consider

$$l^*(t) - l(t) = \int_0^t e^{-r_l(t-s)}(f_l(h^*(s)) - f_l(h(s))ds.$$

Since $u(s) \leq R$ for $0 \leq s \leq t_0$, then $h(s) \leq h^*(s) \leq h_M$ for $0 \leq s \leq t_0$. It follows from the definition that the function $f_l(h)$ is not decreasing in the segment $[0, h_M]$. Hence, $f_l(h^*(s)) - f_l(h(s)) \geq 0$ when $s \in [0, t_0]$. If $s > t_0$ then $f_l(h^*(s)) \equiv M$ and $f_l(h^*(s)) - f_l(h(s)) = M - f_l(h(s)) \geq 0$.

Hence $f_l(h^*(s)) \geq f_l(h(s))$ for all $s \in [0, T]$. Consequently, $l^*(t) \geq l(t)$ for all $t \in [0, T]$, and, in particular, for $t = T$. □

Remark 3. Thus, the following assertion in the notations of Theorem 2.3 is valid: we have $f_l'(h^*(t)) \equiv 0$ for all $t \in [t_0, T]$ even if $f'(h)$ has only one zero in $\left[0, \dfrac{R}{\gamma_h}\right]$.

4. **Alternative control strategy.** For the case $N(T) < N_d$ we cannot present a concrete optimal control function $u^*(t)$ for the considered optimization problem. We can only say for most values of the model parameters how many switching points at most it has but we cannot calculate them exactly. Calculations show that the value of the cost function is sensitive to the position of the switching points.

Our aim is now to construct an admissible control function $u(t)$, termed 'an alternative strategy' such that the difference between the corresponding values of the cost function on the *optimal* control function obtained with the help of the Pontryagin Maximum Principle and on the *alternative* control function is sufficiently small.

The dynamic analysis of (1.1) yields a unique critical point:

$$\overline{L} = L_a e^{-\frac{\gamma_l + f_l(\overline{h})}{r_l}},\ \overline{N} = N_a e^{-\frac{\gamma_n + c\overline{L} + f_n(\overline{h})}{r_n}},\ \overline{h} = \frac{u}{\gamma_h}.$$

It is not hard to prove that the all eigenvalues of the Jacobian matrix of the system at the critical point are negative. Therefore, the steady-state of the system is stable. The position of this unique stable critical point depends on u.

Consider $\overline{L}$, $\overline{N}$ and, consequently,

$$\tilde{\Phi}(u) = \overline{L}(u)^2 + \alpha(\overline{N}(u) - N_d)^2$$

as functions depending on $u \in [0, R]$.

Let $u = R_a$, $0 \leq R_a \leq R$ be the value of u that minimizes the function $\tilde{\Phi}$

$$\tilde{\Phi}(R_a) = \min_{0 \leq u \leq R} \{\tilde{\Phi}(u)\}.$$

According to the Weierstrass's theorem a solution always exists.

We define the alternative control as follows:

$$\widetilde{u}(t) = \begin{cases} R, & 0 \le t \le t_0, \\ R_a, & t_0 < t \le T, \end{cases} \quad \text{where} \quad t_0 = -\frac{1}{\gamma_h} \ln\left(1 - \frac{R_a}{R}\right).$$

In the case when h does not reach the value $\dfrac{R_a}{\gamma_h}$, that is, when $t_0 > T$ or $R_a = R$, we consider

$$\widetilde{u}(t) = R \quad \text{for all} \quad t \in [0, T].$$

It means that for the amount of the drug h we have:

$$h(t) = \begin{cases} \dfrac{R}{\gamma_h}(1 - e^{-\gamma_h t}), & 0 \le t \le t_0, \\ \dfrac{R_a}{\gamma_h}, & t_0 < t \le T, \end{cases}$$

Thus, the alternative control $\tilde{u} = R$ increases the amount of drug up to the level at which $\tilde{\Phi}(u)$ reaches the minimum. Then the required level of drug should be maintained with $\tilde{u} = R_a$.

5. **Numerical results.** In this section we present some results obtained with the help of the computer system MAPLE.

Let the therapy functions be

$$f_i(h) = \lambda_i h e^{1-h}, \quad i \in \{l, n\}.$$

According to [7] the following values of mostly non-dimensional parameters were chosen:

$$\lambda_l = 3, \lambda_n = 1.8,\ c_a = 3.7 \cdot 10^{-5},\ \gamma_l = \gamma_n = 0.01\, day^{-1},$$

$$r_l = 0.25\, day^{-1},\ r_n = 0.38\, day^{-1}, L(0) = 5 \cdot 10^7 cells,\ N(0) = 10^8 cells,$$

$$L_a = N_a = 10^{10} cells,\ R = 1,\ \gamma_h = 0.5,\ \alpha = 1\,. \tag{4.1}$$

First of all, let us consider the value $N_d = 0.9 \cdot N(0) = 9 \cdot 10^7$ (that is $\mathbf{N(T) < N_d}$).

We have obtained the optimal therapy time $T = 47.0$ and the following optimal control function (having two switch points):

$$u(t) = \begin{cases} 1, & 0 \le t \le t_0 = 1.38629, \\ 0.5, & t_0 < t \le t_1 = 46.0382, \\ 0, & t_1 < t \le T = 47.0\,. \end{cases}$$

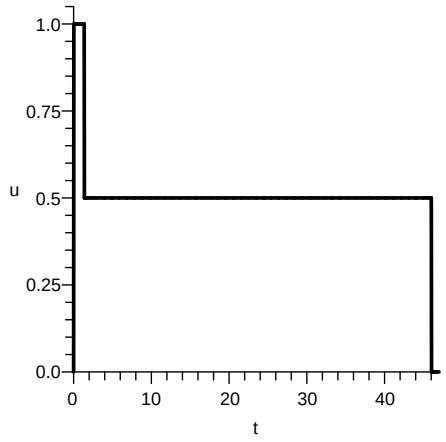

FIGURE 1. Optimal control function.

At the end of the therapy process we have got the following values:

$$L(T) = 64625\,, \quad N(T) = 8.999995 \cdot 10^7 < N_d\,, \quad \Phi(T) = 4.1763 \cdot 10^9\,.$$

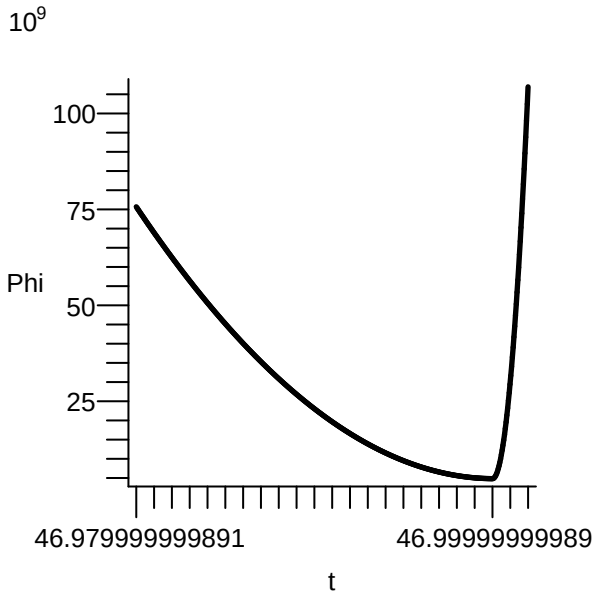

FIGURE 2. Cost function $\Phi(t)$ for the optimal control near $T = 47.0$.

Let us compare the optimal control with the alternative control. The following alternative control function was considered (in fact, we had two possibilities to choose from, $R_a = 0.428936$ and $R_a = 0.57851$, see Note below):

$$\widetilde{u}(t) = \begin{cases} 1, & 0 \le t \le t_0 = 1.120508, \\ R_a = 0.428936, & t_0 < t \le T = 47.0\ . \end{cases}$$

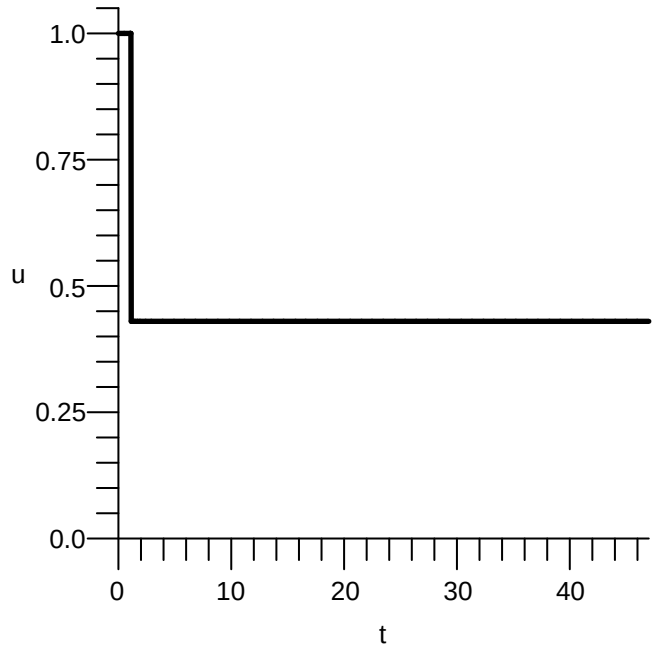

FIGURE 3. Alternative control function.

At the end of the alternative therapy process the following values were obtained: $\widetilde{L}(T) = 67452\,, \quad \widetilde{N}(T) = 9.000000096 \cdot 10^7 > N_d\,, \quad \widetilde{\Phi}(T) = 4.5498 \cdot 10^9$.

The ratio $\widetilde{\Phi}(T)/\Phi(T) = 1.0894$. Compare the numbers $L(T) = 64625$ and $\widetilde{L}(T) = 67452$ of leukemic cells at the end of the optimal and the alternative therapy process, respectively, with the asymptotic value $L_{min} = 59033$ when $\alpha = 0$ and $T \to \infty$. Recall that the initial value $L_0 = 50\,000\,000$. Thus, the optimal and the alternative control are quite effective in this case.

Remark 4. The control function

$$u(t) = \begin{cases} 1, & 0 \le t \le t_0 = 1.38629, \\ 0.5, & t_0 < t \le t_1 = 43.83421, \\ 1, & t_1 < t \le T = 45.0 \end{cases}$$

is "almost optimal". The therapy time is a little bit shorter but the number of the remaining leukemic cells is greater than for the optimal control: $L(T) = 64677\,,\ N(T) = 8.99999 \cdot 10^7 < N_d\,,\quad \Phi(T) = 4.1831 \cdot 10^9\,.$

Let the therapy functions be the same as above as well as the parameters and the therapy time be $T = 47.0$.

Let us consider now the value $N_d = 0.8 \cdot N(0) = 8 \cdot 10^7$ (that is $\mathbf{N(T) > N_d}$).

In accordance with Theorem 2.3 the optimal control function $u(t)$ coincides with the alternative control function. We have $R_a = 0.5$ and

$$u(t) = \begin{cases} 1, & 0 \le t \le t_0, \\ 0.5, & t_0 < t \le T, \end{cases} \quad \text{where} \quad t_0 = -\frac{1}{\gamma_h} \ln\left(1 - \frac{R_a}{R}\right) = 1.38629\,.$$

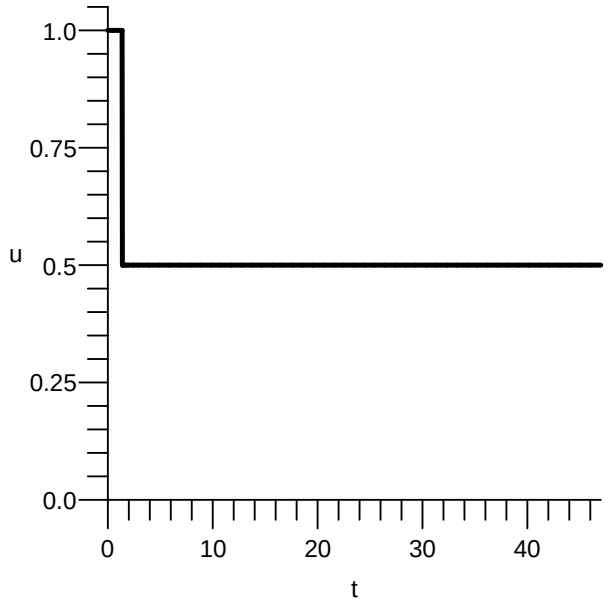

FIGURE 4. Optimal control function coinciding with the alternative control function

At the end of the therapy process we have obtained the following values:

$$L(T) = 59037\,,\quad N(T) = 8.53860 \cdot 10^7 > N_d\,,\quad \Phi(T) = 3.485 \cdot 10^9\,.$$

It should be mentioned that $L(T) \to L_{min} = 59033$, $N(T) \to N_{min} = 8.53860 \cdot 10^7$ and $\Phi(T) \to 3.485 \cdot 10^9$ as $T \to \infty$. The corresponding cost function is decreasing, that is, the best result of the therapy will be obtained for $T = \infty$. Of course, the therapy time is restricted in reality.

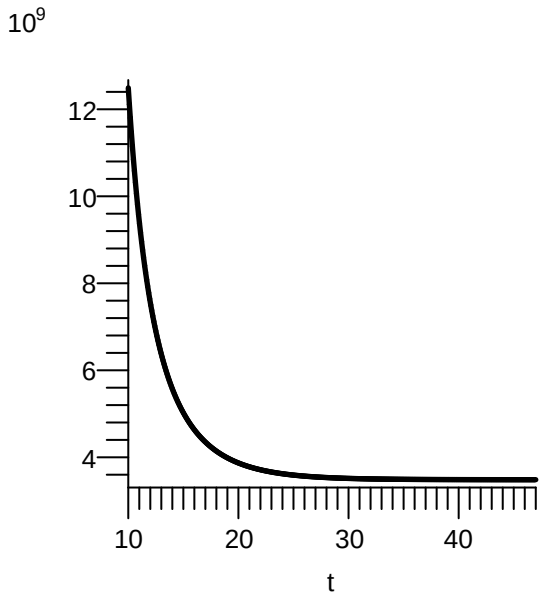

FIGURE 5. Cost function $\Phi(t)$ tends to its infimum as $T \to \infty$.

6. **Conclusion.** In the paper we investigate a classical optimization problem. The relevant objective function acquires two different forms, depending on either the number of the healthy cells at the end of the treatment process exceeds a given threshold value or this number is below of that value.

When the number of healthy cells is sufficiently high at the end of the therapy, we present an optimal treatment strategy for a wide class of therapy processes. In this case the side-effects of the therapy can be disregarded. The amount of the drug administered should start with the maximal dosage and should be maintained at this level until the maximal therapy effect is reached. Then the level of drug should be kept up to the end of the therapy process. The switching point can be calculated if we know three numbers: the maximum admissible dose, the dissipation rate and the amount of the applied chemotherapeutic agent creating the maximal therapy effect. The suggested treatment strategy provides the best possible therapy effect not only at the end of the therapy process but at each moment of that process.

When the side-effects of the therapy cannot be disregarded, a control strategy called *alternative* is suggested. This strategy consists of increasing the amount of the chemotherapeutic agent up to a certain value within the shortest possible period of time, and maintaining this level till the end of the treatment. The comparison of the quality of optimal treatment strategy (simulated numerically) with the quality of the alternative treatment strategy shows that the difference between both of the treatment results is sufficiently small. From the mathematical point of view it is

much easier to obtain the alternative strategy than the optimal one. Consequently, the alternative strategy seems to be quite effective.

In addition we obtained another result which is complementary to the result discussed above. It concerns the treatment processes with proportional cell-kill velocities for leukemic and healthy cells. We prove for such treatment processes that the optimal therapy strategy is divided into stages. Namely, the chemotherapeutic agent is either alternately applied with maximal admissible intensity or discontinued. The number of such stages does not exceed the number of the zeroes of the derivatives of the treatment processes on the whole therapy interval provided the number of the healthy cells at the end of the therapy is high enough. When at the end of the therapy the number of healthy cells falls below some prescribed value, the optimal strategy could have one additional stage.

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