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An optimal strategy for leukemia therapy: a multi-objective approach

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Abstract — In this work we introduce a multi-objective optimization problem using the example of a leukemia treatment model. We believe that treatment affects not only leukemia cells, but also the healthy cells. The treatment effect is modelled as a therapy function. The optimization problem consists of two objective functions that are in conflict: on the one hand, minimizing the leukemia cells and on the other hand, maximizing the number of healthy cells. We reduce this multi-objective problem by using the ε-constraint method. With the aid of Pontryagin's Maximum Principle we give an analytical solution to this reduced problem. In order to solve the problem using the epsilon-constraint-method, the restriction of a threshold value for the number of healthy cells is separately considered as an optimization problem with a new extended objective function. For the most relevant parameters the maximum dose of chemotherapeutics should be administered as long as the predetermined restrictions are not violated. Furthermore, the case in which singular control may occur during the therapy process is analysed. In this case, the optimal control is also determined.

1. Statement of the problem

Numerous mathematical studies pay tribute to the importance of cancer research ([28, 6]), in particular, to the research of leukemia. We base our work on the model of Afenya and Calderón [2],which describes the dynamics of normal N and leukemic L cells under the assumption that both cell types follow the Gompertzian growth and develop this model further introducing therapy effects. The model of Afenya and Calderón is a further development of earlier models by Clarkson [5], Rubinow and Lebowitz [27], and Djulbegovic and Svetina [8] and is defined as follows:

$$\begin{aligned} \frac{\mathrm{d}L(t)}{\mathrm{d}t} &= r_l L(t) \ln\left(\frac{A_l}{L(t)}\right) - \gamma_l L(t) \\ \frac{\mathrm{d}N(t)}{\mathrm{d}t} &= r_n N(t) \ln\left(\frac{A_n}{N(t)}\right) - \gamma_n N(t) - cN(t)L(t) \end{aligned} \tag{1.1}$$

where $r_l, r_n, \gamma_l, \gamma_n, c, A_l, A_n \in \mathbb{R}_+$. The constants r_l and r_n represent the replication rate of leukemic and normal cells, respectively γ_l, γ_n denote the mortality rates of

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both cell types, respectively, and c is the mutation rate, which presents the strength of interaction between leukemic and normal cells. A_l and A_n are the asymptotic bounds of both cell populations.

In [1], model (1.1) is extended and takes into account the therapy effect on both cell types. The therapy effect was modelled by subtracting $ku(t)$ from the first and $lu(t)$ from the second differential equation of (1.1), where k, $l \in \mathbb{R}_+$ are the strengths of the therapeutic agent $u(t)$ on the leukemic and normal cells, respectively. Paper [20] proposes a strategy, in which an adaptive model predictive control is used to personalize chemotherapeutic dosing for the treatment of acute childhood lymphoblastic leukemia.

Papers [3, 24] consider the synthesis of optimal control aiming to minimize the number of virulent cells growing according to logistic and Gompertzian laws. They take into consideration monotonic and non-monotonic therapy functions for only one type of tumor cell. Paper [10] deals with four models of chemotherapy regarding the optimal control. A problem of optimal therapy control presented in [4] considers tumor cells sensitive and non-sensitive to chemotherapeutic agents. In [12] dynamical analysis of a cancer model during radiotherapy is considered with the aim of investigating whether a cancer cell-free steady state exists. Paper [21] presents an optimal control problem of tumor treatment by angiogenic inhibitors in combination with chemotherapeutic agents.

There are many approaches in the area of multi-objective optimization. Compared to the traditional optimization methods, multi-objective optimization provides a set of optimal solutions, i.e., Pareto optimal solution, which is a subset of the set of all possible (feasible) solutions [16]. The Pareto optimal solutions are not necessarily better than all feasible solutions, but no better feasible solutions exist. The ideal point is usually infeasible, especially when the objective functions are in conflict. For this reason, one or more decision makers are necessary, who have to choose one control quantity from the Pareto optimal set at each point of time t_i, $i = \{0, 1, \ldots, n\}$, $t_n = T$. In these approaches, it is not possible to pass from t_i through t_{i+1} without a decision maker. The aggregation approaches in multi-criteria optimization, which transform multiple objectives into a single one, are the weighted-sum-method, the ε-constraint method, and the goal-programming method [19]. Additionally there are more modern interactive methods, where the decision maker gets an overall picture of the problem and its development when arriving at a certain decision [15]. Another approach is based on genetic (evolutionary) algorithms [7].

Papers [9] and [26] present multicriteria optimization problems for planning radiation therapy. In [13] a multi-criteria optimization strategy based on the lexicographic method has been implemented and evaluated using two clinical cases for IMRT (Intensity-Modulated Radiation Therapy) planning. Papers [22] and [23] use genetic algorithms to find the optimal chemotherapeutic treatment as a multi-objective problem. In [11] a multi-objective optimization problem for cancer therapy is presented. There, the multi-objective structure is transformed into a single-objective format through goal programming.

In this work we suggest, as announced above, a model based on (1.1) for the

population dynamics of normal N and leukemic cells L under the influence of a therapeutic agent h, assuming the growth process of normal and leukemic cells follows the Gompertzian law:

$$\begin{aligned}
\frac{\mathrm{d}L(t)}{\mathrm{d}t} &= r_l L(t)\ln\left(\frac{L_a}{L(t)}\right) - \gamma_l L(t) - f_l(h)L(t)\\
\frac{\mathrm{d}N(t)}{\mathrm{d}t} &= r_n N(t)\ln\left(\frac{N_a}{N(t)}\right) - \gamma_n N(t) - cN(t)L(t) - f_n(h)N(t)\\
\frac{\mathrm{d}h(t)}{\mathrm{d}t} &= -\gamma_h h(t) + u(t), \quad 0 < t \leqslant T
\end{aligned} \tag{1.2}$$

with $L(0) = L_0$, $N(0) = N_0$, $h(0) = 0$, where L_a, N_a, r_l, r_n, γ_l, γ_n, and c are constants, L_a and N_a denote the limit of the number of leukemic and normal cells, respectively, in the equation above. γ_l and γ_n represent the mortality rates of both cell types. The impact of leukemic cells on the growth and evolution of normal cells is also included in the model by the term $cN(t)L(t)$. The constant c has to be interpreted as a mutation rate. The last equation in (1.1) represents the dynamics of the therapeutic agent with dissipation rate γ_h and the amount of the administered therapeutic agent $u(t) \in L_\infty[0,T]$ at the time t that we hereinafter call the control function. The influence of the therapeutic agent on normal and leukemic cells has been considered in the model with the therapy functions $f_l(h)$ and $f_n(h)$, assuming that the therapy affects the leukemic cells more strongly than normal cells. In this work two types of therapy functions are considered, as indicated later.

Furthermore, we introduce the following constraints for the maximal quantity of the chemotherapeutic at each moment t and a limitation of the cumulative quantity of the chemotherapeutic during the overall-therapy process:

$$\begin{aligned}
&0 \leqslant u(t) \leqslant R\\
&\int_0^T h(t)\mathrm{d}t \leqslant Q
\end{aligned} \tag{1.3}$$

with the constant parameters $R, Q \in \mathbb{R}_+$.

We describe a multi-objective optimization problem as follows:

$$\text{minimize the functions } L(t) \text{ and } -N(t) \text{ subject to} (1.2). \tag{1.4}$$

In this article we use the ε-constraint method, which reduces problem (1.3) as follows

$$\text{minimize } L(t) \text{ subject to } (1.2) \text{ and } N(t) > \varepsilon = N_{\min}, \quad N_{\min} \in \mathbb{R}^{>0} \tag{1.5}$$

The ε-constraint method simplifies the optimization problem, in which we set a restriction for the state variable $N(t)$. This restriction describes the fact that the number of healthy cells during the therapy process is not allowed to fall below a minimal limit $N_{\min}$, which is necessary for the patient's vitality.

Now we have to deal with only one objective function. For the solution of the problem we use Pontryagin's maximum principle [25], which gives an analytical solution of the optimal control problem.

2. General case of optimal control

In order to simplify the system, we substitute

$$l(t) = \ln \frac{L_a}{L(t)}, \quad n(t) = \ln \frac{N_a}{N(t)} \tag{2.1}$$

where L_a and N_a are the maximal possible amounts of leukemic and normal cells, respectively.

Thereafter, the system has the form:

$$\begin{aligned} \frac{\mathrm{d}l(t)}{\mathrm{d}t} &= -r_l l(t) + \gamma_l + f_l(h) \\ \frac{\mathrm{d}n(t)}{\mathrm{d}t} &= -r_n n(t) + \gamma_n + c_a \mathrm{e}^{-l(t)} + f_n(h) \\ \frac{\mathrm{d}h(t)}{\mathrm{d}t} &= -\gamma_h h(t) + u(t) \\ l(0) = \ln \frac{L_a}{L_0}, &\quad n(0) = \ln \frac{N_a}{N_0}, \quad h(0) = 0. \end{aligned} \tag{2.2}$$

Solving differential equations (2.2), we obtain the time response of the system

$$\begin{aligned} l(t) &= l_0 \mathrm{e}^{-r_l t} + \frac{\gamma_l}{r_l}(1 - \mathrm{e}^{-r_l t}) + \int_0^t \mathrm{e}^{-r_l(t-s)} f_l(h(s))\mathrm{d}s \\ n(t) &= n_0 \mathrm{e}^{-r_n t} + \frac{\gamma_n}{r_n}(1 - \mathrm{e}^{-r_n t}) + \int_0^t \mathrm{e}^{-r_n(t-s)} f_n(h(s))\mathrm{d}s + c_a \int_0^t \mathrm{e}^{-r_n(t-s)-l(s)}\mathrm{d}s \\ h(t) &= \int_0^t \mathrm{e}^{-\gamma_h(t-s)} u(s)\mathrm{d}s \end{aligned} \tag{2.3}$$

with $c_a = cL_a$.

The objective function and the constraints with the new variables have the following form:

$$\begin{gathered} \Phi(l(T)) = L_a \mathrm{e}^{-l(T)} \\ n(t) \leqslant \ln \frac{N_a}{N_{\min}} \\ 0 < u(t) \leqslant R \\ \int_0^T h(t)\mathrm{d}t \leqslant Q. \end{gathered} \tag{2.4}$$

In order to find the optimal control, the Hamiltonian [14] of the system (2.2) is considered:

$$H = \psi_1(-r_l l + \gamma_l + f_l) + \psi_2(-r_n n + \gamma_n + c_a \mathrm{e}^{-l} + f_n) + \psi_3(-\gamma_h h + u). \tag{2.5}$$

According to Pontryagin's Maximum Principle, the co-states of the system are defined as follows

$$\begin{aligned}
\frac{\mathrm{d}\psi_1(t)}{\mathrm{d}t} &= r_l\,\psi_1(t) + \psi_2(t) c_a \mathrm{e}^{-l(t)} \\
\frac{\mathrm{d}\psi_2(t)}{\mathrm{d}t} &= r_n \psi_2(t) \\
\frac{\mathrm{d}\psi_3(t)}{\mathrm{d}t} &= -\psi_1(t)\frac{\mathrm{d}f_l(h(t))}{\mathrm{d}h(t)} - \psi_2(t)\frac{\mathrm{d}f_n(h(t))}{\mathrm{d}h(t)} + \gamma_h\,\psi_3(t)
\end{aligned} \tag{2.6}$$

with the terminal conditions:

$$\psi_1(T) = L_a \mathrm{e}^{-l(T)}, \quad \psi_2(T) = 0, \quad \psi_3(T) = 0. \tag{2.7}$$

Solving differential equations (2.6), we obtain the time response of the co-states:

$$\begin{aligned}
\psi_1(t) &= \psi_{10}\mathrm{e}^{r_l t} + c_a \int_0^t \mathrm{e}^{r_l(t-s)-l(s)}\,\psi_2(s)\mathrm{d}s \\
\psi_2(t) &= \psi_{20}\mathrm{e}^{r_n t} \\
\psi_3(t) &= \psi_{30}\mathrm{e}^{\gamma_h t} - \int_0^t \mathrm{e}^{\gamma_h(t-s)} \Big(\psi_1(s)\,\frac{\mathrm{d}f_l(h(s))}{\mathrm{d}h(s)} + \psi_2(s)\,\frac{\mathrm{d}f_n(h(s))}{\mathrm{d}h(s)}\Big)\mathrm{d}s.
\end{aligned} \tag{2.8}$$

Using the Pontryagin's Maximum Principle we choose for each fixed time $t \in [0,T)$, u^* to be the value of u that maximizes the Hamiltonian $H = H(u)$. Since H is linear in u, it follows that the maximum occurs in the case of $\psi_3 \neq 0$ at one of the endpoints $u = 0$ or $u = R$. More precisely,

$$u^*(t) = \begin{cases} R, & \psi_3(t) > 0 \\ 0, & \psi_3(t) < 0 \\ \text{unknown}, & \psi_3(t) = 0. \end{cases} \tag{2.9}$$

For the case of $\psi_3(t) = 0$ we have a singular control law.

In order to determine the optimal control law, we should analyse the zeroes of ψ_3.

Lemma 2.1. *It holds* $\psi_2(t) = 0$ *and* $\psi_1(t) = \psi_{10}\mathrm{e}^{r_l t}$ *with* $\psi_{10} > 0$ *for all* $t \in [0,T]$.

Proof. From $\psi_2(T) = 0$ we obtain $\psi_2(T) = \psi_{20}\mathrm{e}^{r_n T} = 0$. Therefore, $\psi_{20} = 0$ and $\psi_2(t) = 0$ for $t \in [0,T]$ holds, respectively. Furthermore, from the first equation of (2.8) we obtain $\psi_1(t) = \psi_{10}\mathrm{e}^{r_l t}$. Due to $\psi_{10}\mathrm{e}^{r_l T} = L_a \mathrm{e}^{-l(T)} > 0$, we obtain $\psi_{10} > 0$. Thus, $\psi_1(t)$ is a strictly increasing function in $[0,T]$.

Remark 2.1. It immediately follows from the third equation of (2.3) and the last constraint of (2.4) that the parameters R, γ_h, T, Q are not arbitrary and so they satisfy the following inequality:

$$\frac{R}{\gamma_h^2}(T\gamma_h + \mathrm{e}^{-\gamma_h T} - 1) \leqslant Q.$$

It shows that the maximal therapy time T depends on the model parameters in a plausible manner.

2.1. The case of a monotonic therapy function

Let us consider a monotonic therapy function, i.e. $f'(h) > 0$ for all $h \geqslant 0$. For example, it could be the following monotonic therapy function:

$$f(h) = \frac{\lambda h}{h+1}$$

which describes an interaction according to Michaelis–Menten law or:

$$f(h) = \lambda h, \quad \lambda \in \mathbb{R}^{>0}$$

which describes models of the Lotka–Volterra type.

Theorem 2.1. *Function $\psi_3(t)$ has only one zero point on $[0,T]$ (at T) in the case of a monotonic therapy function f_l and the optimal control function is given by $u(t) = R$ for all $t \in [0,T]$.*

Proof. Due to the terminal condition $\psi_3(T) = 0$ and Lemma 1, we get the following result:

$$\psi_{30} = \mathrm{e}^{-\gamma_h T} \int_0^T \mathrm{e}^{\gamma_h (T-s)}\, \psi_1(s)\, \frac{\mathrm{d}f_l(h(s))}{\mathrm{d}h(s)} \mathrm{d}s = \int_0^T \mathrm{e}^{-\gamma_h s}\, \psi_1(s)\, \frac{\mathrm{d}f_l(h(s))}{\mathrm{d}h(s)} \mathrm{d}s.$$

Note that because of $\mathrm{e}^{-\gamma_h s} > 0$, $\psi_1(s) > 0$, and $\mathrm{d}f_l(h(s))/\mathrm{d}h(s) > 0$ for all $s \in [0,T]$, it implies $\psi_{30} > 0$. Now we can rewrite the equation for $\psi_3(t)$ as follows:

$$\begin{aligned}\psi_3(t) &= \int_0^T \mathrm{e}^{\gamma_h (t-s)}\, \psi_1(s)\, \frac{\mathrm{d}f_l(h(s))}{\mathrm{d}h(s)} \mathrm{d}s - \int_0^t \mathrm{e}^{\gamma_h (t-s)}\, \psi_1(s)\, \frac{\mathrm{d}f_l(h(s))}{\mathrm{d}h(s)} \mathrm{d}s \\ &= \int_t^T \mathrm{e}^{\gamma_h (t-s)}\, \psi_1(s)\, \frac{\mathrm{d}f_l(h(s))}{\mathrm{d}h(s)} \mathrm{d}s.\end{aligned}$$

Due to the strict positivity of the function under the integral, we obtain the proposition: ψ_3 has only one root on $[0,T]$ (at $t = T$).

The proposition $u(t) = R$ for all $t \in [0,T]$ immediately follows from (2.9).

2.2. The case of a non-monotonic therapy function

Let us consider a non-monotonic therapy function that has a threshold effect. The therapy effect grows till a certain moment of time at which $h(t) = h_m$ and then decreases for $h > h_m$. Thus, the maximum value of the therapy function is reached at $h(t) = h_m$. The value of h_m can be interpreted as the maximal acceptable amount of medicine for patients without doing harm to their health. Precisely, let $f(h)$ be a differentiable function with a continuous derivative with $f'(h) > 0$ for $h \in [0, h_m)$, $f'(h_m) = 0$, and $f'(h) < 0$ for $h > h_m$, e.g.,

$$f(h) = ah\,\mathrm{e}^{-bh}, \quad a, b \in \mathbb{R}^{>0}$$

with

$$f'(h) = \frac{\mathrm{d}(ah\,\mathrm{e}^{-bh})}{dh} = a\mathrm{e}^{-bh}(1-bh), \quad h_m = \frac{1}{b}.$$

Since $\psi_{20} = 0$, we can rewrite the equation for $\psi_3(t)$ as follows:

$$\psi_3(t) = \psi_{30}\mathrm{e}^{\gamma_h t} - \int_0^t \mathrm{e}^{\gamma_h(t-s)}\,\psi_1(s)\,\frac{\mathrm{d}f_l(h(s))}{\mathrm{d}h(s)}\mathrm{d}s.$$

We consider the following function $\tilde{\psi}_3(t)$ with $\tilde{\psi}_3(t) = \mathrm{e}^{-\gamma_h t}\psi_3(t)$ which has the same roots as ψ_3 and the same sign as ψ_3 for all $t \in [0, T]$:

$$\tilde{\psi}_3(t) = \psi_{30} - \psi_{10}\int_0^t \mathrm{e}^{(r_l-\gamma_h)s}\,\frac{\mathrm{d}f_l(h(s))}{\mathrm{d}h(s)}\mathrm{d}s.$$

The first derivative of this function is given by

$$\tilde{\psi}_3'(t) = -\psi_{10}\mathrm{e}^{(r_l-\gamma_h)t}\,\frac{\mathrm{d}f_l(h(t))}{\mathrm{d}h(t)}$$

$$\mathrm{sign}\,(\tilde{\psi}_3'(t)) = -\mathrm{sign}\left(\frac{\mathrm{d}f_l(h(t))}{\mathrm{d}h(t)}\right)$$

i.e. $\tilde{\psi}_3(t)$ is strictly increasing (decreasing, respectively), if and only if, $\mathrm{d}f_l(h(t))/\mathrm{d}h(t)$ is strictly decreasing (increasing, respectively).

Lemma 2.2. *The inequality $\psi_3(0) = \psi_{30} > 0$ holds in the case of a non-monotonic therapy function f_l.*

Proof. Set $t_x = \inf\{t \in [0, T] | h(t) = h_m\}$. By default, $t_x = T$ if $h(t) < h_m$ for all $t \in [0, T]$. Note that $t_x > 0$.

Suppose that $\psi_{30} \leqslant 0$. By definition of t_x, we have $h(t) < h_m$ (i.e. $\mathrm{d}f_l(h(t))/\mathrm{d}h(t) > 0$) for $t \in [0, t_x)$ and

$$\tilde{\psi}_3(t) = \psi_{30} - \psi_{10}\int_0^t \mathrm{e}^{(r_l-\gamma_h)s}\,\frac{\mathrm{d}f_l(h(s))}{\mathrm{d}h(s)}\mathrm{d}s < 0$$

and strictly decreasing on $(0,t_x)$. It follows that $\tilde{\psi}_3(t) < 0$ for $t \in (0,t_x)$ and $u(t) = 0$ for all $t \in [0,t_x)$, respectively (see (2.10)). We obtain $h(t) = 0$ for all $t \in [0,t_x)$ due to $h(0) = 0$ and $h(t) = \int_0^t \mathrm{e}^{-\gamma_h(t-s)}u(s)\mathrm{d}s$. By continuity, $h(t_x) = 0$. If $t_x \in (0,T)$ we get a contradiction to $h(t_x) = h_m > 0$. It follows that $t_x = T$ and $h \equiv 0$ on $[0,T]$.

It implies that $\tilde{\psi}_3$ is negative and strictly decreasing on $(0,T]$. This contradicts the condition $\tilde{\psi}_3(T) = 0$. Therefore, the inequality $\psi_{30} > 0$ takes place.

Theorem 2.2. *Let f_l be a non-monotonic therapy function, $h_m > 0$ with $f_l'(h_m) = 0$ and*

$$t_0 = \begin{cases} \min\Big\{ -\dfrac{1}{\gamma_h}\ln\Big(1 - \dfrac{\gamma_h h_m}{R}\Big), T\Big\}, & h_m < \dfrac{R}{\gamma_h} \\ T, & h_m \geqslant \dfrac{R}{\gamma_h}. \end{cases}$$

Then

(1) $\psi_3(t) > 0$ *for all* $t \in [0,t_0)$ *and* $u(t) = R$ *for all* $t \in [0,t_0)$, *respectively;*
(2) $\psi_3'(t_0) = 0$, *if* $t_0 < T$ *holds,* $\psi_3(t) = 0$ *and* $u(t) = \gamma_h h_m$ *for all* $t \in [t_0,T]$.

Proof. Set $t_0 = \inf\{t \in [0,T] | \psi_3(t_0) = \tilde{\psi}_3(t_0) = 0\}$. Since $\tilde{\psi}_3(0) = \psi_{30} > 0$ (see Lemma 2.2) then $t_0 > 0$. Suppose that $t_0 < T$.

Due to Lemma 2.2 and the definition of t_0, the inequality $\tilde{\psi}_3(t) > 0$ holds for all $t \in [0,t_0)$ and

$$\tilde{\psi}_3'(t_0) \leqslant 0$$

that is, $h(t_0) \leqslant h_m$.

It follows from (2.10) that $u(t) = R$ for all $t \in [0,t_0)$ and consequently

$$h(t) = \frac{R}{\gamma_h}(1 - \mathrm{e}^{-\gamma_h t})$$

is strictly increasing for $t \in [0,t_0)$.

We have $\tilde{\psi}_3(t_0) = \tilde{\psi}_3(T) = 0$. If $\tilde{\psi}_3(t)$ is not identically trivial on $[t_0,T]$, then either

$$m = \min_{t\in[t_0,T]} \tilde{\psi}_3(t) < 0 \quad \text{or} \quad M = \max_{t\in[t_0,T]} \tilde{\psi}_3(t) > 0.$$

Case (1). Let $m = \min\limits_{t\in[t_0,T]} \tilde{\psi}_3(t) < 0$ and $\tilde{\psi}_3(t_1) = m$, where $t_0 < t_1 < T$. Then $\tilde{\psi}_3'(t_1) = 0$, $h(t_1) = h_m$ and there exists such $\delta > 0$ that $\tilde{\psi}_3(t) < 0$ in $(t_1, t_1+\delta)$. By (2.10) we have $u(t) = 0$ in this interval and, by (2.2), $\mathrm{d}h/\mathrm{d}t = -\gamma_h h(t) < 0$. It follows that $h(t)$ decreases on $(t_1, t_1+\delta)$ and $h(t) < h(t_1) = h_m$ in this interval. Hence $\mathrm{d}f_l(h(t))/\mathrm{d}h(t) > 0$ on $(t_1, t_1+\delta)$ and for $t \in (t_1, t_1+\delta)$ we have

$$\begin{aligned} \tilde{\psi}_3(t) &= \psi_{30} - \psi_{10}\int_0^{t_1} \mathrm{e}^{(r_l-\gamma_h)s}\frac{\mathrm{d}f_l(h(s))}{\mathrm{d}h(s)}\mathrm{d}s - \psi_{10}\int_{t_1}^{t} \mathrm{e}^{(r_l-\gamma_h)s}\frac{\mathrm{d}f_l(h(s))}{\mathrm{d}h(s)}\mathrm{d}s \\ &< \tilde{\psi}_3(t_1) = m. \end{aligned}$$

We get a contradiction with the definition of m.

Note that case (1) includes the case when $\tilde{\psi}_3'(t_0) < 0$. Consequently, $\tilde{\psi}_3'(t_0) = 0$, $h(t_0) = h_m$.

Now we can express t_0 from $h_m = R/\gamma_h(1 - \mathrm{e}^{-\gamma_h t_0})$ as follows:

$$t_0 = -\frac{1}{\gamma_h} \ln\left(1 - \frac{\gamma_h h_m}{R}\right)$$

i.e., in particular, $h_m - R/\gamma_h < 0$.

Case (2). Let $M = \max_{t\in[t_0,T]} \tilde{\psi}_3(t) > 0$ and $\tilde{\psi}_3(t_2) = M$, where $t_0 < t_2 < T$. Then again $\tilde{\psi}_3'(t_2) = 0$, $h(t_2) = h_m$, and there exists such $\delta > 0$ that $\tilde{\psi}_3(t) > 0$ in $(t_2, t_2 + \delta)$. By (2.10) we have $u(t) = R$ in this interval and by (2.2) $\mathrm{d}h/\mathrm{d}t = -\gamma_h h(t) + R > 0$, since $R > \gamma_h h_m$. It follows that $h(t)$ increases in $(t_2, t_2 + \delta)$ and $h(t) > h(t_2) = h_m$ in this interval. Hence $\mathrm{d}f_l(h(t))/\mathrm{d}h(t) < 0$ in $(t_2, t_2 + \delta)$ and for $t \in (t_2, t_2 + \delta)$, we have

$$\begin{aligned}\tilde{\psi}_3(t) &= \psi_{30} - \psi_{10}\int_0^{t_2} \mathrm{e}^{(r_l-\gamma_h)s} \frac{\mathrm{d}f_l(h(s))}{\mathrm{d}h(s)}\mathrm{d}s - \psi_{10}\int_{t_2}^{t} \mathrm{e}^{(r_l-\gamma_h)s} \frac{\mathrm{d}f_l(h(s))}{\mathrm{d}h(s)}\mathrm{d}s \\ &> \tilde{\psi}_3(t_2) = M.\end{aligned}$$

We get a contradiction with the definition of M. Consequently, $\tilde{\psi}_3(t) \equiv 0$ and $\psi_3(t) \equiv 0$ in $[t_0, T]$.

Since $\psi_3(t) = 0$ in $[t_0, T]$, then the control $u(t)$ is singular on this segment. The last equation of (2.2) implies that

$$0 = -\gamma_h h_m + u(t), \quad t \in [t_0, T].$$

Hence, the constant value of singular control is

$$u(t) = \gamma_h h_m, \quad t \in [t_0, T].$$

3. Optimal control with phase constraints

Now we additionally consider the limitation of the minimal necessary amount of normal cells and the cumulated chemotherapeutic agent during the therapy process:

$$\int_0^t h(s)\mathrm{d}s \leqslant Q, \qquad n(t) \leqslant \ln\frac{N_a}{N_{\min}}.$$

From the equation for $n(t)$ we get the following equivalent restriction:

$$\int_0^t \mathrm{e}^{r_n s} f_n(h(s))\mathrm{d}s \leqslant \mathrm{e}^{r_n t}\left(\ln\frac{N_a}{N_{\min}} - n_0\mathrm{e}^{-r_n t} - \frac{\gamma_n}{r_n}(1 - \mathrm{e}^{-r_n t}) - c_a\int_0^t \mathrm{e}^{-r_n(t-s)-l(s)}\mathrm{d}s\right).$$

The aim of the task is to expand the system so that the therapy is terminated by exceeding the cumulative amount of the therapeutic agent or continues under the

minimum number of healthy cells, i.e. the switching function $\psi_3(t)$ in these cases is negative. Different approaches to the penalty function are presented in [18].

In order to impute the constraints of the system (1.11) in the optimal control problem, we introduce the function $g(t)$ and $w(t)$ with

$$g(t) = \int_0^t h(s)\mathrm{d}s$$
$$w(t) = \int_0^t \mathrm{e}^{r_n S} f_n(h(s))\mathrm{d}s.$$

Now we have the following system:

$$\begin{aligned}
&\frac{\mathrm{d}l(t)}{\mathrm{d}t} = -r_l l(t) + \gamma_l + f_l(h)\\
&\frac{\mathrm{d}n(t)}{\mathrm{d}t} = -r_n n(t) + \gamma_n - c_a \mathrm{e}^{-l(t)} + f_n(h)\\
&\frac{\mathrm{d}h(t)}{\mathrm{d}t} = -\gamma_h h(t) + u(t)\\
&\frac{\mathrm{d}g(t)}{\mathrm{d}t} = h(t)\\
&\frac{\mathrm{d}w(t)}{\mathrm{d}t} = \mathrm{e}^{r_n t} f_n(h(t))\\
&l(0) = \ln\frac{L_a}{L_0}, \quad n(0) = \ln\frac{N_a}{N_0}, \quad h(0) = 0, \quad g(0) = 0, \quad w(0) = 0.
\end{aligned} \tag{3.1}$$

We define the penalty functions:

$$\phi_1(g(t)) = \begin{cases} 0, & g(t) \leqslant Q \\ \lambda_1 g(t), & \text{otherwise}, \end{cases} \qquad \phi_2(w(t)) = \begin{cases} 0, & n(t) \leqslant \ln\dfrac{N_a}{N_{\min}} \\ \lambda_2 w(t), & \text{otherwise} \end{cases} \tag{3.2}$$

with large positive numbers λ_1, λ_2.

Thus, the objective function is extended by two additional terms in order to consider the restrictions.

$$\Phi_c(T) = L_a \mathrm{e}^{-l(T)} + \phi_1(g(T)) + \phi_2(w(T)). \tag{3.3}$$

If any of the restrictions is violated, the objective function sharply increases, i.e. its minimization can only be performed by terminating the therapy.

We construct the Hamiltonian and the corresponding adjoint system:

$$\begin{aligned}
H = {} & \psi_1(-r_l l + \gamma_l + f_l) + \psi_2(-r_n n + \gamma_n + c_a \mathrm{e}^{-l} + f_n)\\
& + \psi_3(-\gamma_h h + u) + \psi_4 h + \psi_5 \mathrm{e}^{r_n t} f_n(h(t)).
\end{aligned}$$

For the adjoint variables we obtain the following system of differential equations:

$$\begin{aligned}
\frac{\mathrm{d}\psi_1(t)}{\mathrm{d}t} &= r_l\,\psi_1(t) + \psi_2(t) c_a \mathrm{e}^{-l(t)} \\
\frac{\mathrm{d}\psi_2(t)}{\mathrm{d}t} &= r_n \psi_2(t) \\
\frac{\mathrm{d}\psi_3(t)}{\mathrm{d}t} &= -\psi_1(t) f_l'(h(t)) - \psi_2(t) f_n'(h(t)) + \gamma_h\,\psi_3(t) - \psi_4(t) \\
&\quad -\psi_5(t)\mathrm{e}^{r_n t} f_n'(h(t)) \\
\frac{\mathrm{d}\psi_4(t)}{\mathrm{d}t} &= 0 \\
\frac{\mathrm{d}\psi_5(t)}{\mathrm{d}t} &= 0
\end{aligned} \tag{3.4}$$

with the terminal conditions:

$$\psi_1(T) = L_a \mathrm{e}^{-l(T)}, \quad \psi_2(T) = 0, \quad \psi_3(T) = 0$$

$$\psi_4(T) = \begin{cases} 0, & g(T) \leqslant Q \\ -\lambda_1, & \text{otherwise}, \end{cases} \qquad \psi_5(T) = \begin{cases} 0, & n(T) \leqslant \ln \dfrac{N_a}{N_{\min}} \\ -\lambda_2, & \text{otherwise}. \end{cases}$$

From the two last terminal conditions, $\psi_4(t)$ and $\psi_5(t)$ are determined as follows:

$$\psi_4(t) = \begin{cases} 0, & g(T) \leqslant Q \\ -\lambda_1, & \text{otherwise}, \end{cases} \qquad \psi_5(t) = \begin{cases} 0, & n(T) \leqslant \ln \dfrac{N_a}{N_{\min}} \\ -\lambda_2, & \text{otherwise}. \end{cases} \tag{3.5}$$

The optimal control function $u^*(t)$ can still be calculated according to (2.9), where the restrictions are taken into account.

4. Numerical results

In this section we present some numerical results concerning the optimal treatment of leukemia for the cases of monotonic and non-monotonic therapy functions. All results are obtained for the same model parameters and constraints: $r_l = 0.25$, $r_n = 0.38$,$\gamma_l = 0.01$, $\gamma_n = 0.01$, $\gamma_h = 0.5$, $c_a = 3.7 \times 10^{-5}$, $\lambda_l = 4.5$, $\lambda_n = 4.0$, $a_1 = 8.0$, $a_2 = 4.5$, $b_1 = 0.7$, $b_2 = 0.5$, $Q = 100$, $L_a = 10^{10}$, $N_a = 10^{10}$. The initial values $N(0) = 10^8$, $L(0) = 5 \times 10^7$ and $N_{\min} = 2 \times 10^7$ are chosen for all numerical calculations. The maximal amount of the chemotherapeutic agent $R = 1$ was chosen for the general control situation and $R = 2$ for the presentation of the singular control.

Figures 1–6 show that the therapy is terminated because of $N(t) = N_{\min}$. The same behaviour is obtained if $\int_0^t h(s)\mathrm{d}s = Q$ occurs.

5. Conclusions

The mathematical modelling of leukemia therapy considering the effect of the chemotherapeutic agent is a complex problem for optimal control. The number of

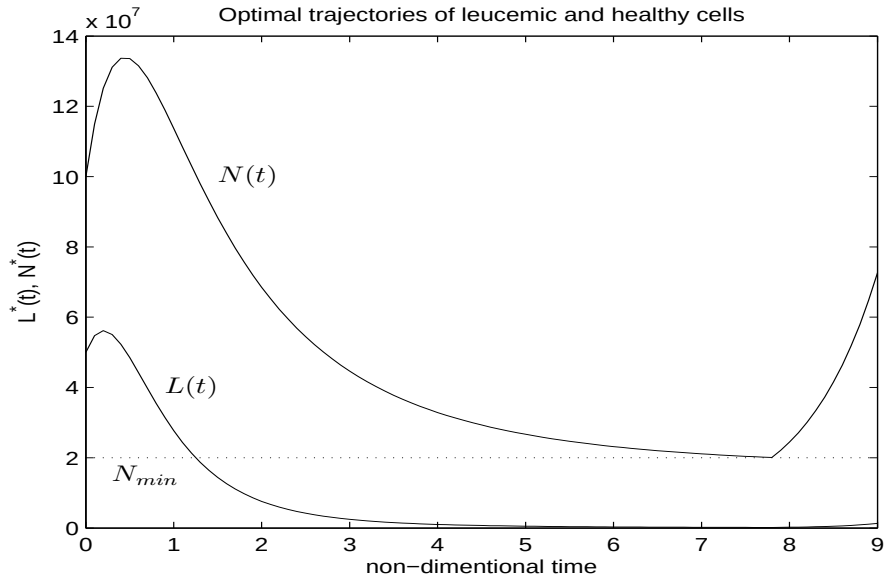

Figure 1. Optimal control with phase constraints using the monotonic therapy function. Time response of $L(t)$ and $N(t)$. Calculated terminal states: $N(T^*) = 2 \times 10^7$, $L(T^*) = 2.43 \times 10^6$.

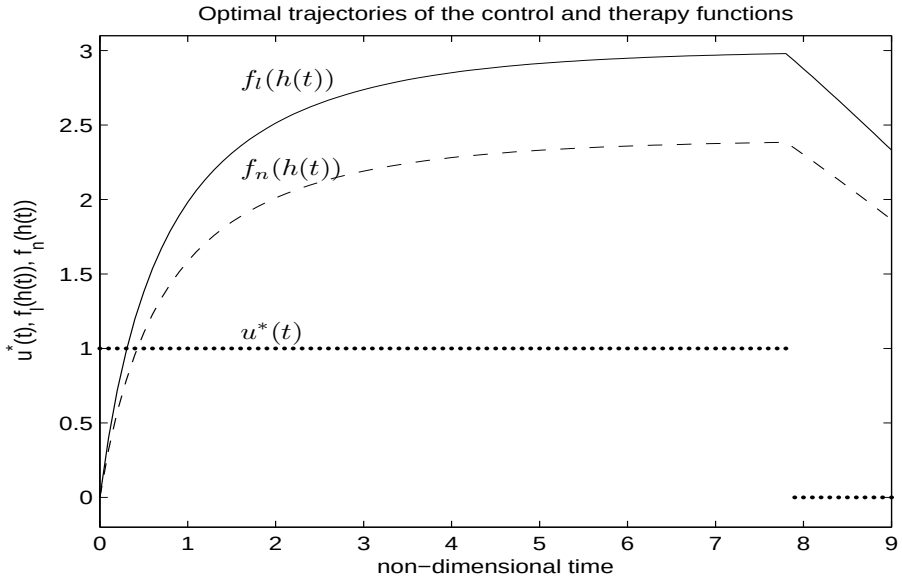

Figure 2. Optimal control with phase constraints: $u^*(t)$ and optimal trajectories of the monotonic therapy functions $f_l(h(t))$ and $f_n(h(t))$. Calculated optimal switching time $T^* = 7.8$.

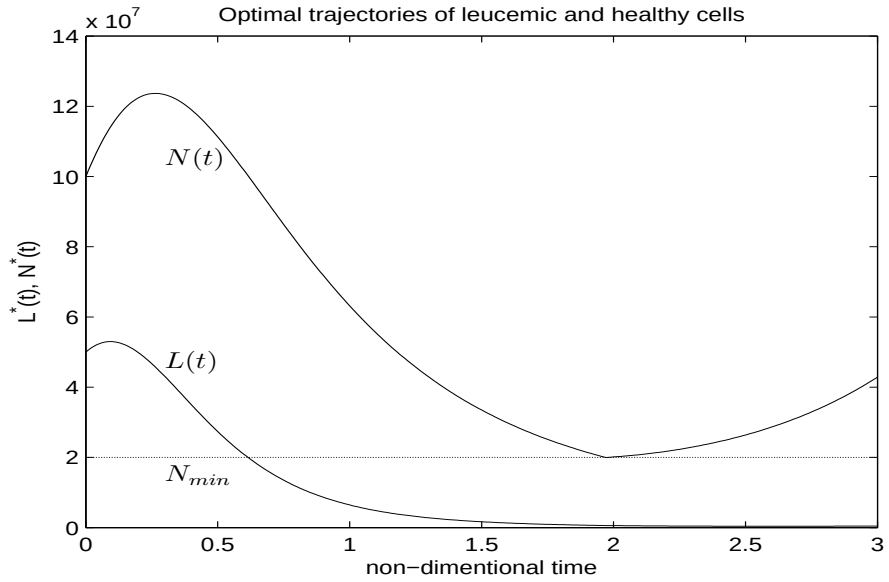

Figure 3. Optimal control with phase constraints using the non-monotonic therapy function. Time response of $L(t)$ and $N(t)$. Calculated terminal states: $N(T^*) = 2 \times 10^7$, $L(T^*) = 5.66 \times 10^5$.

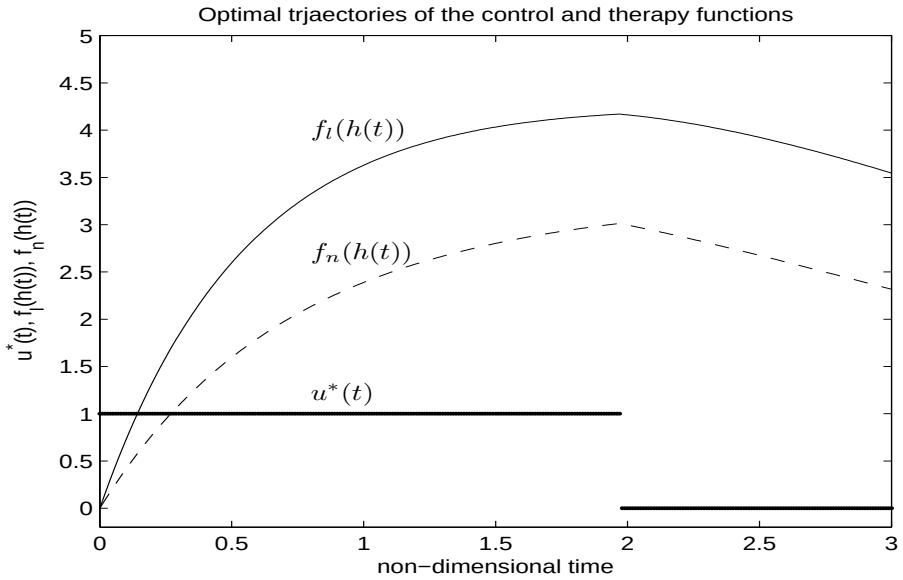

Figure 4. Optimal control with phase constraints: $u^*(t)$ and optimal trajectories of the non-monotonic therapy functions $f_l(h(t))$ and $f_n(h(t))$. Calculated optimal switching time $T^* = 1.97$.

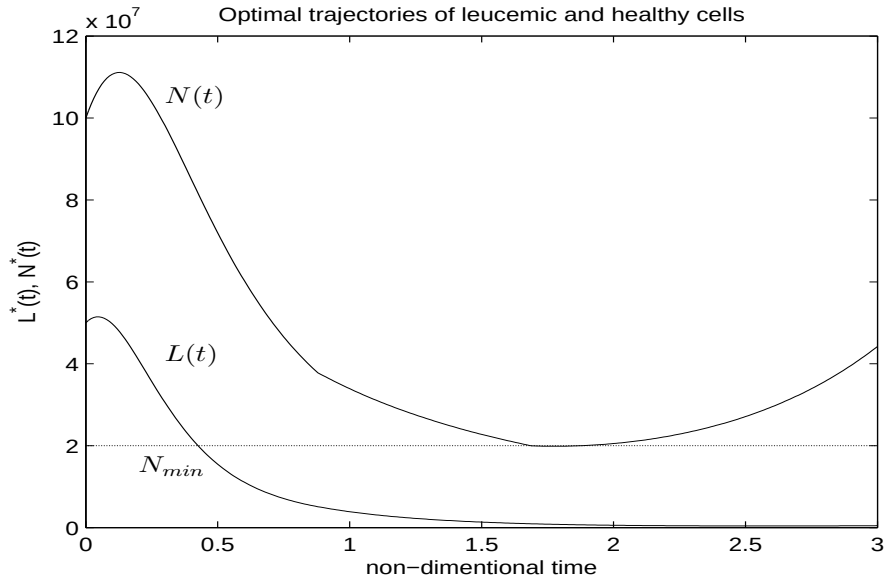

Figure 5. Singular optimal control with phase constraints using the non-monotonic therapy function. Time response of $L(t)$ and $N(t)$. Calculated terminal states: $N(T^*) = 2 \times 10^7$, $L(T^*) = 9.14 \times 10^5$.

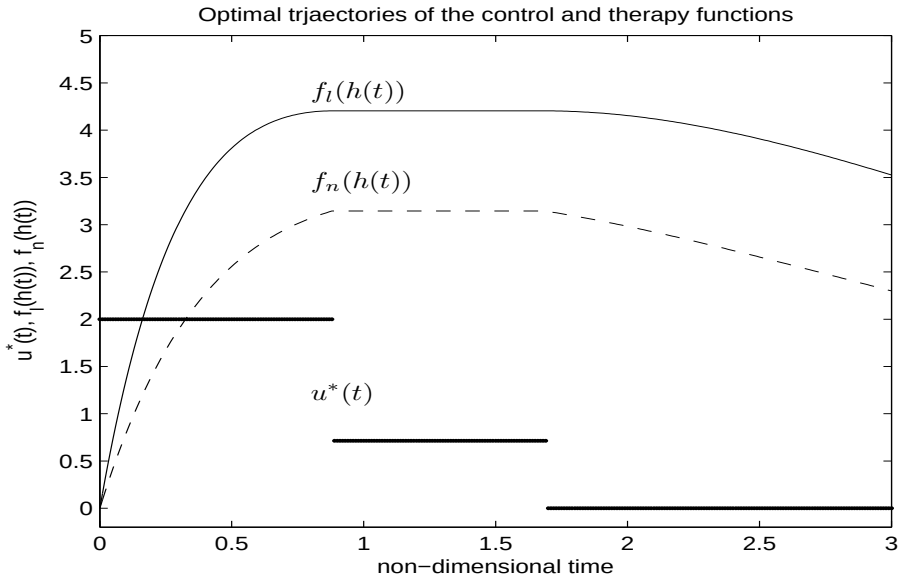

Figure 6. Singular optimal control with phase constraints: $u^*(t)$ and optimal trajectories of the non-monotonic therapy functions $f_l(h(t))$ and $f_n(h(t))$. Calculated optimal switching time $T^* = 1.7$.

cells and the interaction between the cells and the chemotherapeutic agent are determined by certain non-linear laws. The cumulative amount of a chemotherapeutic agent which can be applied during the therapy, as well as the intensity of this application, should be restricted by some prescribed values. The corresponding optimization problem becomes more complicated as a consequence of the fact that chemotherapy destroys not only leukemic cells, but normal cells too. Thus, we simultaneously have two opposite objectives: to destroy leukemic cells without the normal cells falling below a minimum acceptable quantity.

The authors have considered two kinds of therapy functions: strictly increasing therapy functions and non-monotonic therapy functions with a threshold effect. In the first case the therapy effect grows with the increasing amount of chemotherapeutic agent. In the second case the therapy effect grows to a specific moment in time and then decreases. The second case is more realistic.

The results of this study have shown that in the case of a monotonic therapy function the maximum admissible amount of the chemotherapeutic agent must be administered until one of the admissible boundary values of the constraints is obtained and then therapy must be immediately stopped. In the case of a non-monotonic therapy function the optimal control strategy is to give the patient the maximal admissible quantity of the chemotherapeutic agent up to the moment in which the maximum therapy effect is reached, then to hold the maximum effect until one of the admissible boundary values of the constraints is obtained and then to stop the therapy. The moment of the maximal effect of the therapy can be calculated based on the model parameters.

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