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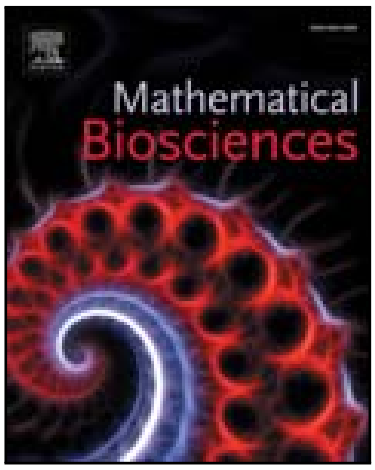

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Maximization of viability time in a mathematical model of cancer therapy

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Abstract

In this paper, we study a dynamic optimization problem for a general nonlinear mathematical model for therapy of a lethal form of cancer. The model describes how the populations of cancer and normal cells evolve under the influence of the concentrations of nutrients (oxygen, glucose, etc.) and the applied therapeutic agent (drug). Regulated intensity of the therapy is interpreted as a time-dependent control strategy. The therapy (control) goal is to maximize the viability time, i. e., the duration of staying in a so-called safety region (which specifies safe living conditions of a patient in terms of constraints on the amounts of cancer and normal cells), subject to limited resources of the therapeutic agent. In a specific benchmark case, a novel optimality principle for admissible therapy strategies is established. It states that the optimal trajectories should finally reach a certain corner of the safety region or at least the upper constraint on the quantity of cancer cells. The results of numerical simulations appear to be in good agreement with the proposed principle. Typical qualitative structures of optimal treatment strategies are also obtained. Furthermore, important characteristics of the model are the competition coefficient (describing the negative influence of cancer cells on normal cells), the upper bound in the drug integral constraint, and the ratio between the therapy and damage coefficients (i. e., the ratio between the positive primary and negative side effects of the therapy).

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1. Introduction

Since cancer is the second leading cause of death globally, dynamic modeling of cancer cells' evolution and therapy planning is a promising field of mathematical biology [1–4].

For instance, such categories of rapidly progressive cancer diseases as acute leukemia and glioma were modeled in [5, 6] and [7–9], respectively. Furthermore, a general mathematical model of tumor-immune interactions was first proposed in [10], and a detailed modern review of related models was given in [11].

Cancer progression and regression are assessed under various treatment techniques such as chemotherapy, immune therapy, radiotherapy, etc., while setting suitable dosages, durations, and frequencies. A catalogue of linear mathematical models of cell-cycle dependent chemotherapy was provided in [12, 13]. The works [7–9, 14–23] developed nonlinear mathematical models of chemotherapy against various cancer diseases. In particular, the works [19–21, 24, 25] considered chemotherapy processes in case of a heterogeneous tumor containing drug-resistant cells. Immunotherapy and combined treatment techniques were studied in [19, 26–34]. Besides, the monograph [35] presented a wide range of cancer therapy models involving target molecules, viruses, and Eigen quasispecies.

The works [14–19, 21, 23, 28–30, 36–40] considered unconstrained problems of constructing therapy strategies (treatment protocols) that are optimal with respect to certain scalar criteria written in terms of the state variables. In [14–18, 21, 23, 28–30], the optimal open-loop control laws were investigated by using Pontryagin's principle and corresponding numerical techniques. Moreover, the multi-objective approach of [22] was based on a specific reduction of the original unconstrained two-criteria problem to some constrained problem with a single criterion. In [19, 36–40], the closed-loop (feedback) representations of the optimal therapy strategies were obtained by coupling Pontryagin's principle (necessary optimality conditions) with dynamic programming arguments (sufficient optimality conditions).

Even though the derived optimal treatment protocols can give important qualitative information about the general orientation of efficient therapy, they may have shortcomings from the practical point of view. Despite modern medical achievements, the life expectancy of patients with certain particularly dangerous types of cancer (such as glioma, melanoma, acute leukemia, etc.) often does not exceed several years. Therefore, the related therapy planning should be focused on maximization of the time during which the patients are in safe living conditions. Therapy efficiency is restricted by the fact that the concentration of the therapeutic agent inside a patient is limited because of the negative influence not only on cancer cells but also on normal (healthy) cells. Thus, it is reasonable to consider the problem of seeking for a therapy strategy such

that, as long as possible, the amount of cancer cells would not exceed some predetermined number, while the amount of normal cells would not be less than another predetermined threshold value. Next, we will refer to the state-space subdomain specified by these constraints as the safety region. The thresholds are chosen in order to ensure the safe existence of a patient inside this region. The total amount of the available drug is also limited due to economic reasons.

If there exist admissible state trajectories that do not leave the safety region for a sufficiently long time, then there is the potential for the transition of the diseases to the chronic stages with maintaning the healthy conditions by periodic medication (like, for example, in case of diabetes mellitus treatment).

A similar problem statement was given in [41] (where a model with ordinary differential equations was considered in addition to a more general distributed model with partial differential equations) and inspired by the framework of viability theory [42]. It should be emphasized that the related problems appear to be essentially more complicated than unconstrained dynamic optimization problems.

Note also the paper [24] that formulated and investigated the viability-time maximization problem for a two-dimensional model describing the dynamics of drug-sensitive and drug-resistant cell populations (see [25] for a detailed biomedical discussion). The aim was to demonstrate that, if the tumor burden was controlled to minimize the rate of growth of the drug-resistant cells at all times, the related survival time could be maximized. For this purpose and for the sake of simplicity, the total tumor cell population was modeled as a control variable and could thereby be altered at will. The only constraint was imposed so that the size of the total tumor cell population should lie between the size of the drug-resistant population and a certain upper bound (survival threshold). Hence, the resulting optimal processes might substantially differ from practically realizable trajectories.

Conversely, the model of [41] focused on the influence of a therapeutic agent on two drug-sensitive populations of cancer and normal cells. The drug acted not directly but through its acquired concentration, so that a separate pharmacokinetic equation [15] was included in the model. Therefore, both constraints on the amounts of cancer and normal cells had the second order, leading to some inertia with respect to control switches on the constraint boundaries. Together with the high complexity and nonlinearity of the model, this would make it very difficult to use state-constrained versions of Pontryagin's principle as formulated in [43–46]. Examples of its successful applications to other nontrivial biomedical and aerospace models can be found in [47–49].

In this paper, we study a general nonlinear mathematical model for therapy of a lethal form of cancer. It extends the ODE model of [41] and describes how the populations of cancer and normal cells evolve under the influence of the concentrations of nutrients (oxygen, glucose, etc.) and the applied therapeutic agent. Regulated intensity of the therapy is interpreted as a time-dependent control strategy. The therapy (control) goal is to maximize the viability time, i. e., the duration of staying in the safety region of the state space, subject to limited resources of the therapeutic agent. In a specific benchmark case, we

establish a novel optimality principle for admissible therapy strategies. It states that the optimal trajectories should finally reach a certain corner of the safety region or at least the upper constraint on the quantity of cancer cells. We also conduct numerical simulations in order to test the proposed principle for realistic model parameters. The presented results are provided with biomedical interpretations.

2. Problem statement

Consider a general mathematical model that describes the dynamics of cancer and normal (healthy) cells affected by uptaken nutrients (oxygen, glucose, etc.) and some therapeutic agent (drug). Adopt the following basic assumptions:

1) the cell growth rates are determined by Gompertz law with the additional factor in the form of a nonlinear function of the nutrient concentration;

2) the therapeutic agent is spread out through blood vessels, and, therefore, the growth flux of its concentration is proportional to the nutrient concentration;

3) the negative influence of the therapeutic agent on the cell populations is specified by nonlinear functions, which we will refer to as the therapy and damage functions;

4) the cancer and normal cells compete each other for common resources of the patient's organism;

5) the rate of the incoming therapeutic agent is determined by a control function with values in a certain bounded interval;

6) the total amount of the therapeutic agent is limited.

Suppose that $t \geqslant 0$ is the time variable, $C = C(t)$ is the number of cancer cells of a certain type in some sample volume of the patient's organism, $N = N(t)$ is the number of related normal cells in this volume, $g = g(t)$ is the nutrient concentration, $h = h(t)$ is the concentration of the therapeutic agent, and $u = u(t)$ is a Lebesgue measurable control function taking values in the interval $[0, M]$ with $M = \text{const} > 0$. The corresponding dynamics is described

by the following system of ordinary differential equations:

$$\begin{cases} \dfrac{dC(t)}{dt} &= r_1 G(g(t))\big(\ln a_c - \ln C(t)\big)C(t) \;-\; \gamma_1 C(t) - \\ &\quad -\; k_1 f(h(t))C(t), \\ \dfrac{dN(t)}{dt} &= r_2 G(g(t))\big(\ln a_n - \ln N(t)\big)N(t) \;-\; \gamma_2 N(t) - \\ &\quad -\; k_2 f(h(t))N(t) \;-\; \beta N(t)C(t), \\ \dfrac{dg(t)}{dt} &= \alpha_g \;-\; \gamma_g g(t) \;-\; \big(\varepsilon_{gc}C(t) + \varepsilon_{gn}N(t)\big)\, g(t), \\ \dfrac{dh(t)}{dt} &= g(t)u(t) \;-\; \gamma_h h(t) \;-\; \big(\varepsilon_{hc}C(t) + \varepsilon_{hn}N(t)\big)\, h(t), \\ 0 \leqslant u(t) \leqslant M, \quad t \geqslant 0, \\ C(0) = C_0 > 0, \quad N(0) = N_0 > 0, \quad g(0) = g_0 > 0, \quad h(0) = h_0 \geqslant 0. \end{cases} \tag{1}$$

Here the constants $a_c, a_n > 0$ represent upper bounds on the numbers of cancer and normal cells, respectively. The cell growth coefficients are $r_1, r_2 > 0$, and the cell death rates are $\gamma_1, \gamma_2 \geqslant 0$. In principle, one can set $\gamma_1 = \gamma_2 = 0$ if it is adopted that the process of cell death is already taken into account in the saturating growth laws. The parameter $\alpha_g > 0$ is the incoming nutrient flux. The constants $\gamma_g, \gamma_h > 0$ are the dissipation rates of the nutrients and drug, respectively. The competition coefficient is $\beta \geqslant 0$. The parameters $\varepsilon_{gc}, \varepsilon_{gn}, \varepsilon_{hc}, \varepsilon_{hn} \geqslant 0$ characterize the uptaking of the nutrients and drug by the cancer and normal cells. The therapy and damage functions are $k_1 f(h)$ and $k_2 f(h)$, respectively, so that $k_1 > 0$ is the therapy coefficient, and $k_2 > 0$ is the damage coefficient. It is reasonable to assume that

$$r_1 \geqslant r_2, \quad k_1 > k_2.$$

Moreover, $G(g)$ determines the nutrient factor in the cell growth fluxes.

Let the functions $f(h)$ and $G(g)$ be strictly increasing and saturating, so that

$$f(0) = 0, \quad f'(h) > 0 \;\; \forall h \geqslant 0, \quad \exists \lim_{h \to +\infty} f(h) < +\infty,$$

$$G(0) = 0, \quad G'(g) > 0 \;\; \forall g \geqslant 0, \quad \exists \lim_{g \to +\infty} G(g) < +\infty.$$

For numerical simulations, we will use the particular forms of Michaelis–Menten law

$$f(h) \;=\; \frac{\mu_f h}{\nu_f + h}, \quad G(g) \;=\; \frac{\mu_g g}{\nu_g + g} \tag{2}$$

with positive constants $\mu_f, \nu_f, \mu_g, \nu_g$.

The general model (1) is inspired mainly by the models of glioma and acute leukemia therapies [7–9, 22, 23, 39], and, in addition to the dynamics of the three basic variables C, N, h, it takes the nutrient concentration g into account.

Let $\bar{C} \in (0, a_c)$ and $\bar{N} \in (0, a_n)$ be the constants specifying the safety region

$$\tilde{V} \;=\; \big\{(C,N) \,\in\, [0,+\infty) \times [0,+\infty) :\; C \leqslant \bar{C},\; N \geqslant \bar{N}\big\}. \tag{3}$$

The initial position (C_0, N_0) is supposed to lie inside $\tilde{V}$.

Let us consider the problem of maximizing the viability time T (i. e., the time of staying in the safety region (3)) over all state trajectories to the system (1) governed by Lebesgue measurable therapy strategies $u : [0,+\infty) \to [0,M]$, subject to the following integral constraint on the drug concentration:

$$\int\limits_0^T h(t)\,dt \;\leqslant\; Q, \quad Q = \mathrm{const} > 0. \tag{4}$$

Instead of (4), it is possible to impose the inequality

$$\int\limits_0^T u(t)\,dt \;\leqslant\; \tilde{Q}, \quad \tilde{Q} = \mathrm{const} > 0 \tag{5}$$

(written in terms of the control), and all subsequent analysis will remain similar. However, we prefer to consider namely the constraint (4), because, in addition to the primary economic interpretation (limited drug expenses), it can implicitly serve as one more reflection of the aim to avoid very high cumulative drug dosages, which are rather harmful to healthy cells.

By the variable changes

$$c(t) \,=\, \ln C(t), \quad n(t) \,=\, \ln N(t), \tag{6}$$

the system (1) transforms into

$$\begin{cases} \dfrac{dc(t)}{dt} \;=\; r_1 G(g(t))\big(\ln a_c - c(t)\big) \;-\; \gamma_1 \;-\; k_1 f(h(t)), \\ \dfrac{dn(t)}{dt} \;=\; r_2 G(g(t))\big(\ln a_n - n(t)\big) \;-\; \gamma_2 \;-\; k_2 f(h(t)) \;-\; \beta e^{c(t)}, \\ \dfrac{dg(t)}{dt} \;=\; \alpha_g \;-\; \big(\gamma_g + \varepsilon_{gc} e^{c(t)} + \varepsilon_{gn} e^{n(t)}\big)\, g(t), \\ \dfrac{dh(t)}{dt} \;=\; g(t)u(t) \;-\; \big(\gamma_h + \varepsilon_{hc} e^{c(t)} + \varepsilon_{hn} e^{n(t)}\big)\, h(t), \\ 0 \leqslant u(t) \leqslant M, \quad t \geqslant 0, \\ c(0) = c_0 = \ln C_0 < \ln \bar{C}, \quad n(0) = n_0 = \ln N_0 > \ln \bar{N}, \\ g(0) = g_0 > 0, \quad h(0) = h_0 \geqslant 0. \end{cases} \tag{7}$$

Then the safety region (3) is characterized by

$$V \;=\; \big\{(c,n) \in \mathbb{R}^2 :\; c \leqslant \bar{c} = \ln \bar{C},\; n \geqslant \bar{n} = \ln \bar{N}\big\}. \tag{8}$$

Next, it is convenient to represent the bounds $\bar{C}, \bar{N}$ as parts of the upper limits a_c, a_n:

$$\bar{C} = \delta_1 a_c, \quad \bar{N} = \delta_2 a_n, \quad 0 < \delta_i < 1, \quad i = 1, 2. \tag{9}$$

Hence,

$$\begin{cases} \bar{c} = \ln(\delta_1 a_c) = \ln a_c - \ln \delta_1^{-1}, \\ \bar{n} = \ln(\delta_2 a_n) = \ln a_n - \ln \delta_2^{-1}. \end{cases} \tag{10}$$

For numerical simulations, we will consider the case of glioma (brain cancer) therapy. Let us choose the values of the parameters $a_c, a_n, r_1, r_2, \gamma_1, \gamma_2$ as in [41] and measure time in years. Since [41] considers time in days, some parameter transformations have to be done here. For the sake of simplicity, suppose that 1 year consists of 365 days. Then we get

$$\ln a_c = 12.21, \quad \ln a_n = 11.51, \quad r_1 = 0.36, \quad r_2 = 0.19, \quad \gamma_1 = \gamma_2 = 0, \tag{11}$$

where measurement units are omitted for the sake of brevity. Also take

$$\begin{cases} M = 0.5, \quad \gamma_h = 3, \quad \alpha_g = 1, \quad \gamma_g = 1, \\ \mu_f = 1, \quad \nu_f = 0.5, \quad \mu_g = 2, \quad \nu_g = 1 \end{cases} \tag{12}$$

(note that the nutrient and drug concentrations can be measured in different units), and

$$\varepsilon_{gc} = \varepsilon_{gn} = \varepsilon_{hc} = \varepsilon_{hn} = 10^{-6}. \tag{13}$$

The remaining parameters and initial data will be specified in Section 5. In particular, the three different values

$$\beta = 10^{-6}, \quad \beta = 2 \cdot 10^{-6}, \quad \beta = 5 \cdot 10^{-6} \tag{14}$$

will be considered there.

3. Steady-state analysis and auxiliary parameter estimates

First, let $u \in [0, M]$ be a constant control and set

$$\varepsilon_{gc} = \varepsilon_{gn} = \varepsilon_{hc} = \varepsilon_{hn} = 0. \tag{15}$$

Then the system (7) has a unique steady state $P = (c^*, n^*, g^*, h^*)$, and

$$\begin{cases} g^* = \dfrac{\alpha_g}{\gamma_g}, \quad h^* = \dfrac{g^* u}{\gamma_h} = \dfrac{\alpha_g u}{\gamma_g \gamma_h}, \\ c^* = \ln a_c - \dfrac{\gamma_1 + k_1 f(h^*)}{r_1 G(g^*)}, \\ n^* = \ln a_n - \dfrac{\gamma_2 + k_2 f(h^*) + \beta e^{c^*}}{r_2 G(g^*)}. \end{cases} \tag{16}$$

The Jacobian matrix takes the form

$$J(c,n,g,h) \;=\; \begin{pmatrix} -r_1G(g) & 0 & r_1G'(g)(\ln a_c - c) & -k_1f'(h) \\ -\beta e^c & -r_2G(g) & r_2G'(g)(\ln a_n - n) & -k_2f'(h) \\ 0 & 0 & -\gamma_g & 0 \\ 0 & 0 & u & -\gamma_h \end{pmatrix},$$

and its eigenvalues are $-r_1G(g), -r_2G(g), -\gamma_g, -\gamma_h$. Hence, P is a stable node.

The representations (16) allow us to estimate the ratio k_1/k_2 between the therapy and damage coefficients in terms of the steady state P. Let

$$\begin{aligned} c^* \;&=\; \ln(\varkappa_1 a_c) \;=\; \ln a_c - \ln \varkappa_1^{-1}, \\ n^* \;&=\; \ln(\varkappa_2 a_n) \;=\; \ln a_n - \ln \varkappa_2^{-1}, \\ &0 < \varkappa_i < 1, \quad i = 1, 2. \end{aligned}$$

Then, by using (16), we obtain

$$\begin{aligned} \frac{f(h^*)}{G(g^*)} \;&=\; \frac{r_1}{k_1} \ln \varkappa_1^{-1} \;-\; \frac{\gamma_1}{k_1 G(g^*)} \;= \\ &=\; \frac{r_2}{k_2} \ln \varkappa_2^{-1} \;-\; \frac{\gamma_2 + \beta e^{c^*}}{k_2 G(g^*)}\,. \end{aligned} \tag{17}$$

If $\gamma_1 = \gamma_2 = 0$ and the number βe^{c^*} is relatively small, one can write

$$\frac{f(h^*)}{G(g^*)} \;=\; \frac{r_1}{k_1} \ln \varkappa_1^{-1} \;\approx\; \frac{r_2}{k_2} \ln \varkappa_2^{-1}$$

and, therefore,

$$\frac{k_1}{k_2} \;\approx\; \frac{r_1 \ln \varkappa_1^{-1}}{r_2 \ln \varkappa_2^{-1}}\,. \tag{18}$$

For the parameter values (11), this transforms into

$$\frac{k_1}{k_2} \;\approx\; 1.895 \cdot \frac{\ln \varkappa_1^{-1}}{\ln \varkappa_2^{-1}}\,. \tag{19}$$

For example, if $\varkappa_1 = 0.25$ and $\varkappa_2 = 0.5$, i. e., the steady-state amounts of cancer and normal cells constitute respectively 25% and 50% of the corresponding capacities, then (19) yields $k_1/k_2 \approx 3.79$. On the other hand, if we fix the ratio k_1/k_2 as, for instance, 2 and again take $\varkappa_1 = 0.25$, then (19) leads to $\varkappa_2 \approx 0.269$, i. e., a much smaller fraction of normal cells can now be saved.

If $(c^*, n^*) \notin V$, the safety region is eventually left by state trajectories attracted to the stable node (16). Even if $(c^*, n^*) \in V$, there can exist a subset of positive Lebesgue measure consisting of the initial positions such that some parts of the related trajectories do not lie in the safety region. Hence, the appearance of the stable steady state in the safety region does not guarantee that the viability constraints will always be satisfied. Fig. 1 shows some examples.

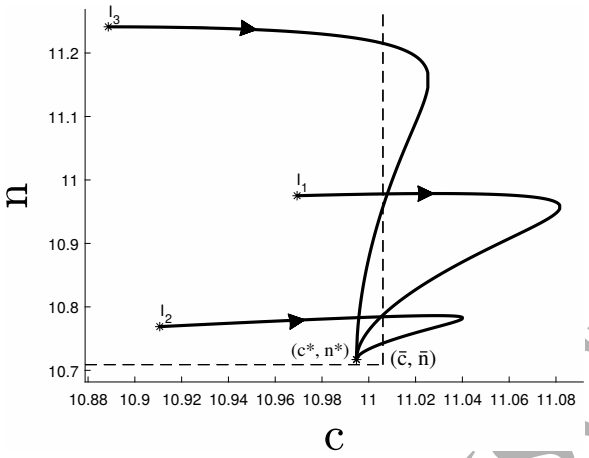

Figure 1: An illustration of the fact that, even if $(c^*, n^*) \in V$, the safety region can be left for some time. Here the parameters are taken as (11), (12), $\beta = 10^{-6}$, $k_1 = 7$, $k_2 = 1.45$, $\delta_1 = 0.3$, $\delta_2 = 0.45$, the constant control is $u = 0.1$, and three different initial coordinate pairs $(c_0, n_0) = I_1, I_2, I_3$ are considered with fixed $g_0 = 1$, $h_0 = 0$.

In case of nonzero but relatively small values of $\varepsilon_{gc}, \varepsilon_{gn}, \varepsilon_{hc}, \varepsilon_{hn}$ (for example, (13)), the qualitative features of the steady state and phase portrait remain similar.

By analyzing the signs of the right-hand sides of the differential equations in (7), one can directly establish the following sufficient condition for a trajectory of (7) to stay in the safety region till infinity.

Proposition. *Fix a time instant $t' \geqslant 0$. Let $(c(t'), n(t')) \in V$, $h(t') > 0$, and let $u : [0, +\infty) \to [0, M]$ be a Lebesgue measurable control function such that*

$$u(t) \geqslant m \quad \forall t \geqslant t' \tag{20}$$

for some constant $m \in (0, M)$. Also denote

$$\begin{cases} g_{\text{low}} \;=\; \min\left\{ g(t'),\, \dfrac{\alpha_g}{\gamma_g + \varepsilon_{gc} e^{\bar{c}} + \varepsilon_{gn} a_n} \right\}, \\ g_{\text{up}} \;=\; \max\left\{ g(t'),\, \dfrac{\alpha_g}{\gamma_g + \varepsilon_{gn} e^{\bar{n}}} \right\}, \\ h_{\text{low}} \;=\; \min\left\{ h(t'),\, \dfrac{g_{\text{low}} m}{\gamma_h + \varepsilon_{hc} e^{\bar{c}} + \varepsilon_{hn} a_n} \right\} \;>\; 0, \\ h_{\text{up}} \;=\; \max\left\{ h(t'),\, \dfrac{g_{\text{up}} M}{\gamma_h + \varepsilon_{hn} e^{\bar{n}}} \right\} \;>\; 0. \end{cases} \tag{21}$$

If

$$\begin{cases} k_1 > \dfrac{r_1 G(g_{\rm up})(\ln a_c - \bar{c}) - \gamma_1}{f(h_{\rm low})} = \dfrac{r_1 G(g_{\rm up}) \ln \delta_1^{-1} - \gamma_1}{f(h_{\rm low})}, \\ k_2 < \dfrac{r_2 G(g_{\rm low})(\ln a_n - \bar{n}) - \gamma_2 - \beta e^{\bar{c}}}{f(h_{\rm up})} = \\ \quad = \dfrac{r_2 G(g_{\rm low}) \ln \delta_2^{-1} - \gamma_2 - \beta e^{\bar{c}}}{f(h_{\rm up})}, \\ r_1 G(g_{\rm up}) \ln \delta_1^{-1} > \gamma_1, \\ r_2 G(g_{\rm low}) \ln \delta_2^{-1} > \gamma_2 + \beta e^{\bar{c}}, \end{cases} \tag{22}$$

then $(c(t), n(t)) \in V$ *for all* $t \geqslant t'$.

However, the conditions (22) on the therapy and damage coefficients turn out to be rather strict for a wide range of realistic parameter values (including the ones in (11)–(14)). Furthermore, the inequality (20) with a positive m leads to the violation of the integral constraint (4) (or (5)) after some finite time. Thus, it is relevant to consider the trajectories that eventually leave the safety region. The next section contains the derivation of a meaningful optimality principle for our problem of viability-time maximization under some simplification concerning several parameters.

4. Optimality principle

For the further analysis, the following simplification is needed.

Benchmark case. *The parameters* $\beta, \varepsilon_{gc}, \varepsilon_{gn}, \varepsilon_{hc}, \varepsilon_{hn}$ *vanish:*

$$\beta = 0, \quad \varepsilon_{gc} = \varepsilon_{gn} = \varepsilon_{hc} = \varepsilon_{hn} = 0. \tag{23}$$

The first equation in (7) originally does not contain n. We set $\beta = 0$ so as to make the second equation in (7) independent on c. Moreover, the condition (15) is imposed in order to make the third and fourth equations in (7) independent on c, n.

Even though the condition (23) is an idealization, we treat it as a benchmark case, because we expect a good agreement with the next property for relatively small values of $\beta, \varepsilon_{gc}, \varepsilon_{gn}, \varepsilon_{hc}, \varepsilon_{hn}$, such as taken in (13),(14) for the model of glioma therapy. The numerical simulation results in Section 5 will give an informal practical justification for our conjecture. Besides, the model of leukemia therapy from [22, 23, 39] was studied with relatively small β and vanishing analogs of $\varepsilon_{gc}, \varepsilon_{gn}, \varepsilon_{hc}, \varepsilon_{hn}$.

Optimality principle. *Let* $(u(\cdot), c(\cdot), n(\cdot), g(\cdot), h(\cdot))$ *be an optimal process in the formulated viability-time maximization problem for the dynamics (7), safety*

region (8), and integral constraint (4). Consider the benchmark case (23). Also suppose that the related viability time T is finite, $u(\cdot)$ is piecewise continuous, the Lebesgue measure of the set of time instants t where $u(t) \neq 0$ is positive, and the Lebesgue measure of the set of time instants t where $u(t) \neq M$ is also positive. Then the corresponding state trajectory satisfies either

$$(c(T),\, n(T)) \;=\; (\bar{c}, \bar{n}) \tag{24}$$

or

$$c(T) = \bar{c}, \quad n(T) > \bar{n}. \tag{25}$$

The second situtation is possible only when

$$\int_0^T h(t)\, dt \;=\; Q. \tag{26}$$

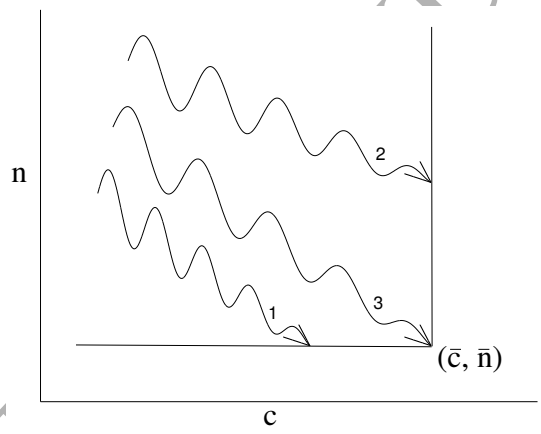

Figure 2: To the proof and discussion of the optimality principle.

Proof. First, consider the curve 1 in Fig. 2, which corresponds to the case

$$c(T) < \bar{c}, \quad n(T) = \bar{n}. \tag{27}$$

Then the negative influence of the drug on the normal cells is too large. By decreasing the control on some subset of $[0, T]$ with positive measure (for example, by increasing the total duration of the relaxation regime $u(t) = 0$), one can modify and shift the curve 1 to the right and up (lower drug amounts affect the cancer and normal cells less) so as to increase the viability time. This will also decrease the integral in the constraint (4). Hence, an optimal process cannot leave the safety region through the boundary part (27).

Now consider the curve 2 in Fig. 2, which corresponds to the case (25), and let the constraint (4) be satisfied as a strict inequality. By increasing the control on some subset of $[0, T]$ with positive measure, one can modify and shift the curve 2 to the left and down (higher drug amounts affect the cancer and normal cells more) so as to increase the viability time and also not to violate the constraint (4). Then the curve 2 cannot be optimal. □

The proposed principle yields that, under the mentioned conditions, an optimal trajectory should necessarily enter the right lower corner (24) if there are enough drug resources (see the curve 3 in Fig. 2). The boundary part (25) can be reached only if the integral constraint (4) on the drug concentration is satisfied in the equality form. The boundary part (27) cannot be reached by optimal trajectories.

Finally, note that the simplification (23) can be reasonable only for sufficiently small parameters $\beta, \varepsilon_{gc}, \varepsilon_{gn}, \varepsilon_{hc}, \varepsilon_{hn}$. In particular, the influence of the variable c on the equation for dn/dt should be weak enough. For example, the model of tumor-immune dynamics in [40] (inspired by the model of [10] and related modifications in [17, 18]) dealed with three state variables such as tumor volume x, immunocompetent cell density y, and drug concentration h, but the influence of y on dx/dt and also the influence of x on dy/dt appeared to be crucial and could not be neglected. For this kind of models, our approach is not applicable, and other techniques have to be developed.

5. Numerical simulations

For numerical simulations, we fix the parameter values (11)–(13) and

$$k_1 = 6.5, \quad k_2 = 1.5, \tag{28}$$

$$\begin{cases} \delta_1 = 0.15, \quad \bar{c} \;=\; \ln(\delta_1 a_c) \;\approx\; 10.313, \\ \delta_2 = 0.6, \quad \bar{n} \;=\; \ln(\delta_2 a_n) \;\approx\; 10.999 \end{cases} \tag{29}$$

(the upper constraint on the amount of cancer cells and the lower constraint on the amount of normal cells constitute respectively 15% and 60% of the related capacities), while the initial state is taken as

$$\begin{cases} c_0 \;=\; \ln(0.1 \cdot a_c) \;\approx\; 9.907, \quad n_0 \;=\; \ln(0.75 \cdot a_n) \;\approx\; 11.222, \\ g_0 = 1, \quad h_0 = 0 \end{cases} \tag{30}$$

(the initial amounts of cancer and normal cells constitute respectively 10% and 75% of the corresponding capacities). Then, for any constant control $u \in [0, M]$ and (14), the steady state is a stable node located outside the safety region (8).

Fig. 3–8 indicate the optimal processes approximated by using the software package BOCOP [50] in the following cases:

1) $\beta = 10^{-6}$, $Q = 0.14$;

2) $\beta = 10^{-6}$, $Q = 0.1$;

3) $\beta = 2 \cdot 10^{-6}$, $Q = 0.13$;

4) $\beta = 2 \cdot 10^{-6}$, $Q = 0.11$;

5) $\beta = 5 \cdot 10^{-6}$, $Q = 0.07$;

6) $\beta = 5 \cdot 10^{-6}$, $Q = 0.05$.

The corresponding maximum viability times are

$$T_1 \approx 2.734, \quad T_2 \approx 2.324, \quad T_3 \approx 2.219,$$
$$T_4 \approx 2.217, \quad T_5 \approx 1.494, \quad T_6 \approx 1.406,$$

respectively. A suitable computational accuracy has been achieved by choosing the implicit Gauss time discretization scheme that has the fourth order and two stages [50]. The boundary parts $c = \bar{c}$, $n = \bar{n}$ of the safety region are shown (as dashed lines) together with the state trajectories in Fig. 3–8.

In our model, control strategies can act on cancer and normal cells only through the drug concentration. Hence, the related inertial effects have to be taken into account when choosing the times to switch between different therapy regimes. In Fig. 3–8, the key switching points are marked on the state trajectories (together with the initial and final points).

The integral constraint (4) does not become active (i. e., holds as a strict inequality) in Fig. 3,5,7 (Cases 1,3,5), and it becomes active ((26) holds) in Fig. 4,6,8 (Cases 2,4,6). The safety region is left nearly through its right lower corner (24) in Fig. 3, 5–7, 8 and through the boundary part (25) in Fig. 4. Therefore, a good agreement with the optimality principle is achieved not only under the benchmark simplification (23) but also in more realistic situations.

In Fig. 3,4 (Cases 1,2 with a sufficiently small competition coefficient β), cancer growth is stabilized on the boundary $c = \bar{c}$, and the subsequent therapy regime with some intermediate intensity $u \in (0, M)$ tries to keep the quantity of cancer cells at this level as long as possible. A similar situation takes place in the benchmark case (23), which is therefore not illustrated for the sake of brevity. No therapy is performed at the very beginning. If there is a sufficient drug amount (Fig. 1), then the starting instant of the first therapy regime with the maximum intensity $u = M$ is chosen so that cancer growth is stopped exactly when reaching the boundary $c = \bar{c}$. If drug resources are not enough (Fig. 2), a therapy regime with a gradually increasing intensity appears instead of the regime with $u = M$.

Other structures of optimal processes can be seen in Fig. 5–8 (Cases 3–6), which correspond to greater values of β. The therapy regimes with $u = M$ start from the very beginning, which is more realistic from the practical point of view. Note that, in real medical practice, actual parameters of safety regions

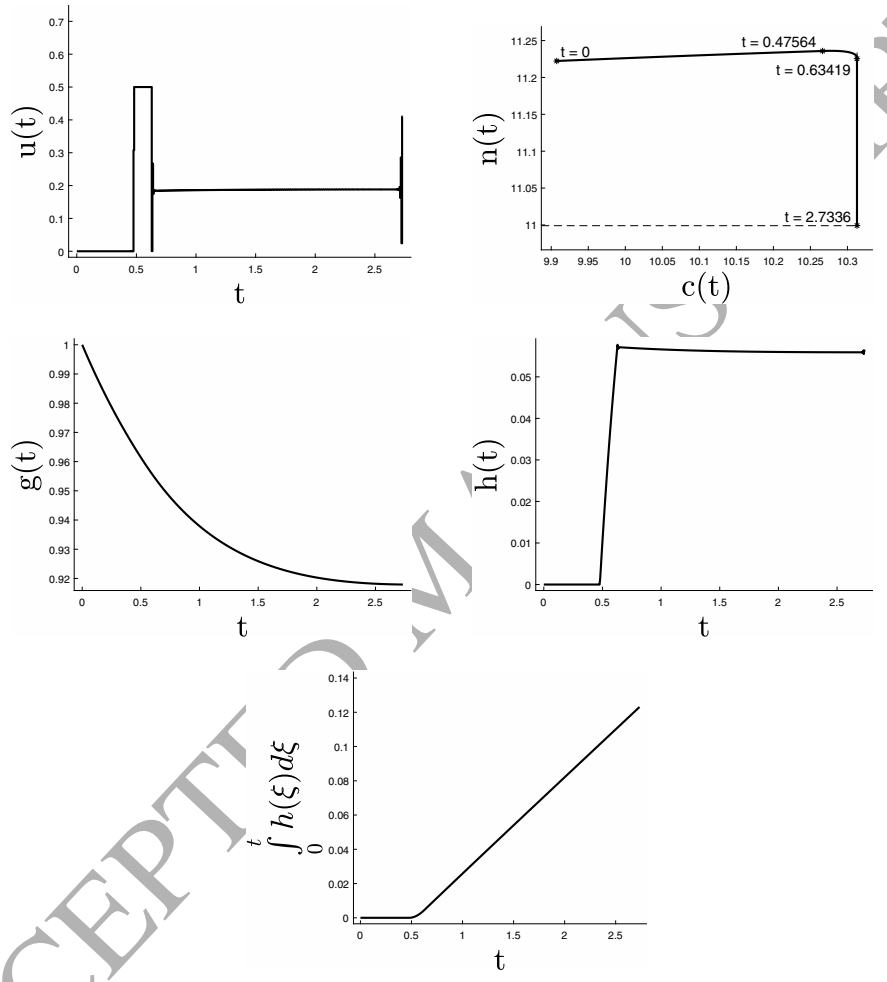

Figure 3: The optimal process approximated by using the software package BOCOP for the parameter values (11)–(13), (28), (29), $\beta = 10^{-6}$, $Q = 0.14$ and initial state (30) (Case 1). The maximum viability time is $T_1 \approx 2.734$. The integral constraint (4) does not become active.

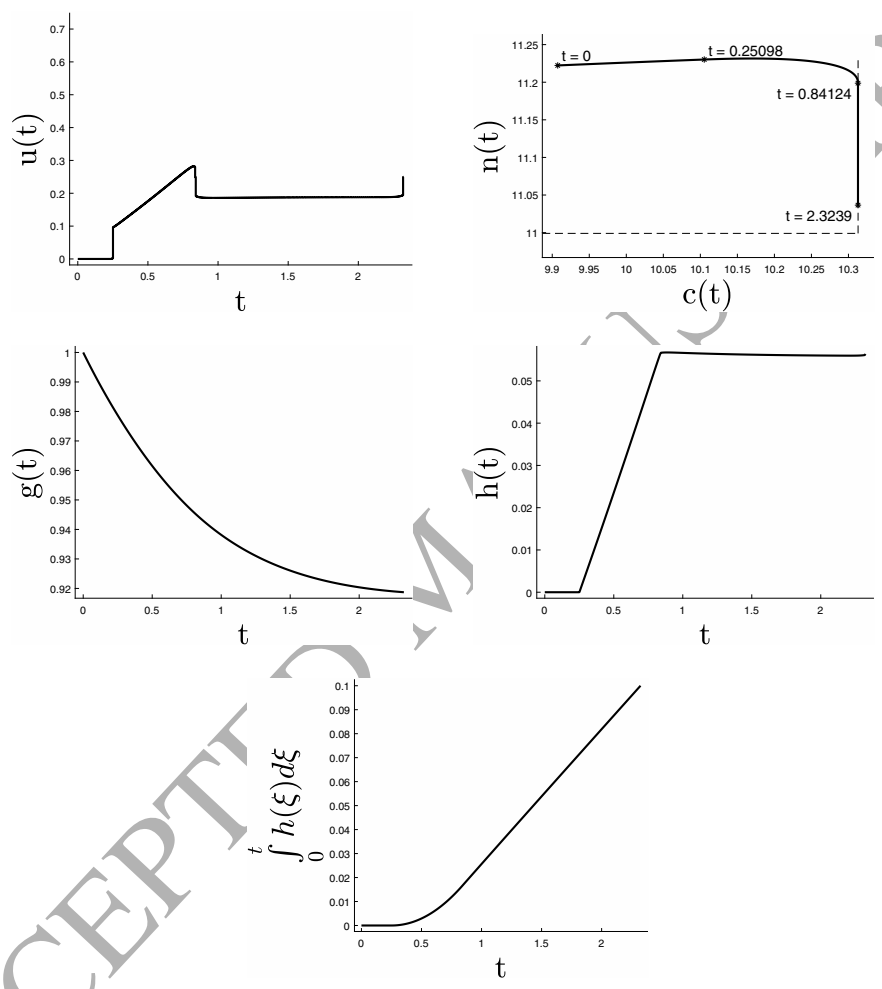

Figure 4: The optimal process approximated by using the software package BOCOP for the parameter values (11)–(13), (28), (29), $\beta = 10^{-6}$, $Q = 0.1$ and initial state (30) (Case 2). The maximum viability time is $T_2 \approx 2.324$. The integral constraint (4) becomes active.

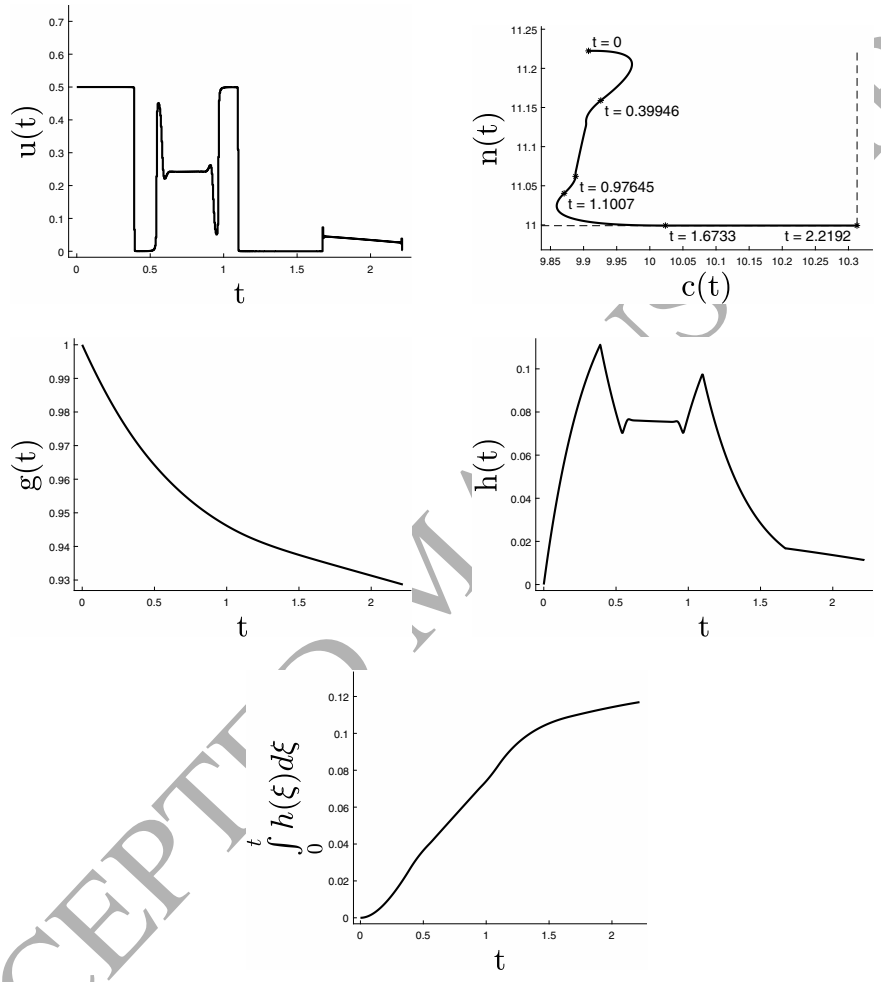

Figure 5: The optimal process approximated by using the software package BOCOP for the parameter values (11)–(13), (28), (29), $\beta = 2 \cdot 10^{-6}$, $Q = 0.13$ and initial state (30) (Case 3). The maximum viability time is $T_3 \approx 2.219$. The integral constraint (4) does not become active.

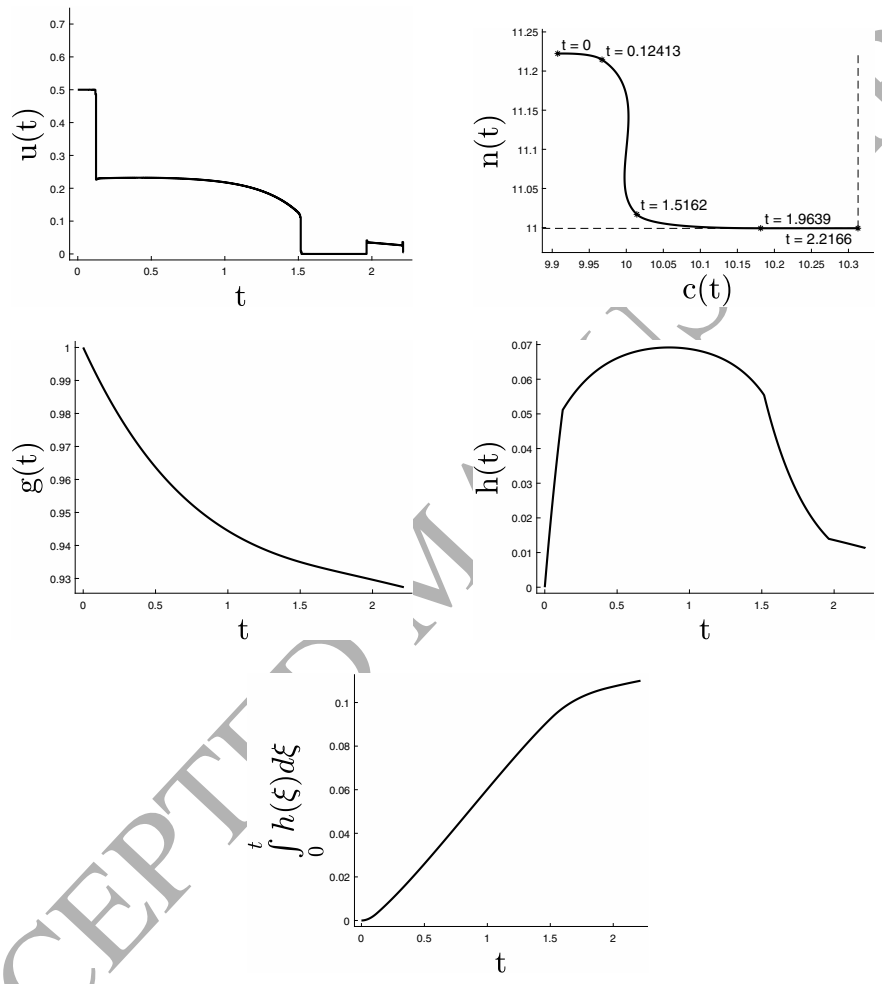

Figure 6: The optimal process approximated by using the software package BOCOP for the parameter values (11)–(13), (28), (29), $\beta = 2 \cdot 10^{-6}$, $Q = 0.11$ and initial state (30) (Case 4). The maximum viability time is $T_4 \approx 2.217$. The integral constraint (4) becomes active.

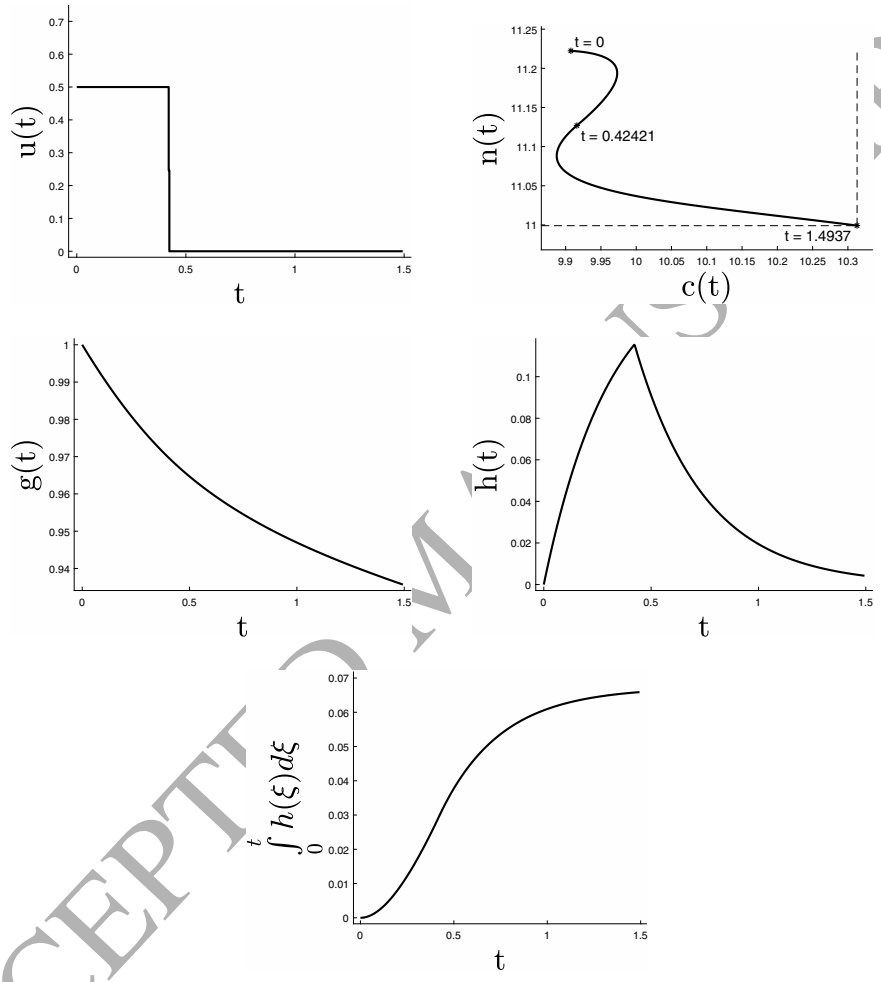

Figure 7: The optimal process approximated by using the software package BOCOP for the parameter values (11)–(13), (28), (29), $\beta = 5 \cdot 10^{-6}$, $Q = 0.07$ and initial state (30) (Case 5). The maximum viability time is $T_5 \approx 1.494$. The integral constraint (4) does not become active.

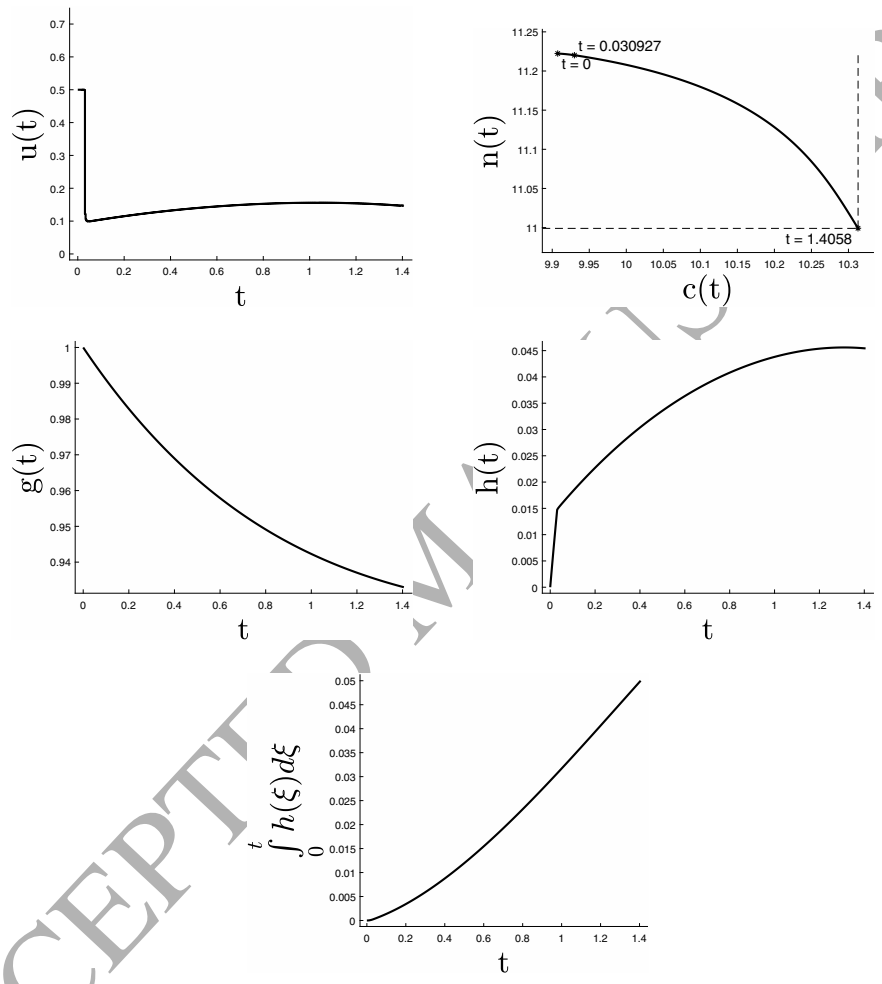

Figure 8: The optimal process approximated by using the software package BOCOP for the parameter values (11)–(13), (28), (29), $\beta = 5 \cdot 10^{-6}$, $Q = 0.05$ and initial state (30) (Case 6). The maximum viability time is $T_6 \approx 1.406$. The integral constraint (4) becomes active.

are not precisely known, and many important biological characteristics cannot be measured with high accuracy and frequency. These are particular reasons why cancer treatment is usually started as soon as possible.

For the process in Fig. 7, the negative influence of cancer cells on normal ones is so strong that the second and final control regime contains no therapy, i. e., subsequent treatment is inefficient. If the parameter Q is decreased so as to make the constraint (4) active, the starting regime with $u = M$ becomes shorter, and then there appears a singular regime with $u \in (0, M)$, as depicted in Fig. 8.

The treatment strategy in Fig. 5 is more complicated. It includes two regimes with $u = M$, two singular regimes with $u \in (0, M)$, and one regime with $u = 0$. If Q is decreased and the constraint (4) becomes active, the control strategy takes a simpler form, as shown in Fig. 6. In particular, the starting regime with $u = M$ is shortened, the other regime with $u = M$ disappears, and the central role is now played by one of the singular regimes. In both Fig. 5,6, the final singular regimes (with small but nonzero intensities) make the state trajectories enter the corner (24) tangentially to the boundary $n = \bar{n}$.

The maximum viability time increases for a higher therapy coefficient. For instance, if we consider Case 3 with $k_1 = 7$ instead of $k_1 = 6.5$, then a greater viability time takes place: $\tilde{T}_3 \approx 2.385 > 2.219 \approx T_3$. The related optimal process is not illustrated, since it is qualitatively similar to the one in Fig. 5.

6. Conclusion

In this paper, we considered a nonlinear dynamic model for therapy of a lethal form of cancer and studied the related problem of maximizing the viability time. Under some simplification, a general optimality principle was obtained. It reflected the crucial role of the right lower corner of the safety region as the target that should be eventually approached by the optimal state trajectories in case of sufficient drug amounts. The results of numerical optimization were in good agreement with the optimality principle. Typical optimal treatment strategies were also indicated. By varying the competition coefficient β and the upper bound Q in the drug integral constraint, it was possible to observe different qualitative portraits, while preserving the property of the optimality principle.

Another significant characteristic of the model is the ratio k_1/k_2 between the therapy and damage coefficients. The greater this ratio, the more successful the treatment process can be, which is an additional theoretical justification for developing targeted medicines with lower toxicity effects on normal and immunocompetent cells.

Note that, when formulating the optimality principle, the finiteness of the viability time T was assumed. Deriving a sufficient condition for this and a uniform estimate for T remains an open theoretical problem and a possible subject for future research. Our numerical simulation results showed finite viability times. The best preliminary hint we had was the fulfillment of the condition

that, for any constant control, the corresponding asymptotically stable steady state was located outside the safety region. Another challenging problem is analytical characterization of extremal characteristic fields by using a state-constrained version of Pontryagin's principle. There are a number of essential difficulties, such as high dimensionality and nonlinearity of the dynamic system, mutual influence between the state variables and two second-order state constraints.

In biomedical practice, the therapy and damage functions (depending on the drug concentration) are not precisely known and can be affected by individual characteristics of patients, cancer sub-types, therapeutic agents, etc. Therefore, it is reasonable to take stochastic uncertainties into account there. The work [51] proposed an approach to develop stochastic extensions to deterministic models of cancer therapy. In perspective, it is worth investigating to consider the related stochastic problem of maximizing the mean viability time.

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