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OPTIMAL CHEMOTHERAPY REGIMENS: INFLUENCE OF TUMORS ON NORMAL CELLS AND SEVERAL TOXICITY CONSTRAINTS

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Abstract. Cancer chemotherapy with application of one drug is studied. The negative and inhibiting effect of the tumor on normal cells is taken into account. Under certain hypotheses, we determine the optimal regimen that minimizes the tumor burden at the end of a fixed period of therapy while maintaining certain normal cell populations above prescribed levels. More precisely, it is demonstrated that the optimal strategy corresponds to injection of the drug at the maximal rate.

Keywords. Optimal chemotherapy regimen, influence of tumors on normal cells

1. INTRODUCTION

The last decade has witnessed valuable efforts in analysis of cancer chemotherapy via employing deterministic mathematical models. One of the main objectives was to verify the optimality of existing methods for chemotherapy administration and, in the cases where the answer is in the negative, to propose alternative regimens. Those models usually include one or more differential equations describing tumor growth. Furthermore, they often involve a model for toxic side-effects of the anti-cancer drug, which in many cases can be severe and so are required to be managed. Related to it is the aim to compromise between the destruction of the cancer and the containment of normal-cell toxicity. Within the above framework, a large diversity of settings was explored. For example, equations of various types (Gompertz, logistic, exponential, etc.) were employed to describe tumor growth. Various terms were used to express the influence of the anti-cancer drug on the tumor cells. In some cases, the tumor was assumed to be homogeneous, whereas in other ones, it was considered to consist of several fractions (e.g., the drug-resistant and drug-sensitive ones [6], or fractions, each encompassing all the tumor cells in a definite phase of the cell cycle). Analyzed were the effects on the optimal drug scheduling that result from taking into account a number of special phenomena. Among them, there are developing resistance of the malignant cells to the anti-cancer drug [6], blocking effect [9] (which means that the drug not only kills tumor cells but also blocks their progression through the cell cycle), etc. As a quantifier of toxicity, the total amount of the drug infused during the treatment can be used. Another approach is to constrain the toxicity by maintaining a certain normal cell population above a given level There is a similar diversity of objectives. In some cases, the goal was to minimize the total amount of drug infused under the constraint that the tumor size at the end of the treatment must not exceed a prescribed level. In other cases, the problem was to minimize the tumor burden after a fixed period of therapy, while constraining the drug toxicity. For further details and an excellent survey of the area, we refer the reader to [7,11].

However it seems that up to now the inter-influence of malignant and normal cells was not taken into account in analysis of optimal chemotherapy regimens. In most of the models employed, the tumor growth was represented as a factor neutral to the health of the patient, and the requirement to reduce the tumor burden was adopted as purely exogenous. At the same time, the malignant tumor is able to affect normal cells in many ways. Moreover, the pathophysiology of certain kinds of cancer, such as the human acute leukemia, was understood and modelled directly as an inter-play between the malignant clone of cells and the normal neutrophil cell population in

a number of researches [1–4,10]. As was remarked in [4], leukemic cells can impede the growth of normal hemopoietic tissue via the competition for essential nutrients, which might result in exclusion and extinction of normal cells, as well as contact inhibition and production of growth inhibitors. On the other hand, there is an a'priori likelihood that taking into account the negative effect of the tumor on the patient's body may alter the solutions of some optimization problems related to cancer chemotherapy. For instance, a number of such solutions prescribe to delay the treatment considerably and start it only near the end of the therapy period by applying the anti-cancer drug at the maximum rate in order to minimize the tumor size at the end of this period. This solution holds for both short and long periods. But in fact, in the absence of treatment for a considerable time, the cancer disorder may be fatal. So taking into account negative effects of the tumor on normal cells is, for example, likely to result in correcting the above solution via shortening or even discarding the delay period.

The objective of this paper is to contribute to qualitative understanding of effects on the optimal chemotherapy scheduling that are due to the negative influence of the malignant tumor on the patient. The sizes of certain normal cell populations are taken as measures of toxicity. This approach was adopted in numerous papers in the area. However up to now only one population was taken into account. At the same time, both cytotoxic drugs and tumors usually affect a series of normal tissues, which cannot be often viewed as a unique homogeneous cell population. In view of this, we consider several normal cell populations and impose size constraints on each of them.

In our analysis, we adopt the model from [1, 2]. Though this model was invented to describe the human acute leukemia, the assumptions underlying it are so general that it can be employed in analysis of a wider variety of cancers. The model to be considered consists of several Gompertz differential equations describing the dynamics of both the tumor and certain normal cell populations. Special terms account for the negative and inhibiting effect of the tumor on normal cells. Perturbation summands in the equations represent the effect of the anti-cancer drug on the tumor and normal tissues. The amalgamated negative effect on the patient that is due to both the tumor and the drug-originated toxicity is limited by the requirement to maintain the normal cell populations above given levels. The objective is to minimize the tumor burden at the end of a fixed period of therapy.

Following the lines of most of the preceding papers, we consider the case where only one drug is applied. In fact, this is rare in clinical practice, where a combination of drugs is usually employed. Nevertheless, the effect of such a combination can be sometimes amalgamated to lead to a model with only one idealized drug. Anyhow, the assumption of one drug is widely adopted in the literature since it simplifies the matters and is accompanied with a hope that the results obtained can be useful to comprehend certain qualitative features of optimal regimens in the case of several drugs. As in [5] etc., the control variable is the concentration of the anti-cancer drug at the tumor site. This means that the drug spreads within the body instantaneously so that the drug infusion rate is approximately proportional to the drug concentration. A more realistic case where a proper pharmacokinetic equation is used to express the relationship between the infusion rate and the concentration is left as a topic of further research.

By employing the optimal control theory, we show that the optimal drug administration conforms to the strategy of agressive chemotherapy. This means that the drug must be constantly applied at the maximum rate. During some periods of therapy, this rate may be determined by the toxicity constraints. Namely, if some normal cell population reaches its lowest admissible level, the drug infusion rate may be limited by the requirement to maintain the population at or above this level. Unlike the case where the influence of tumor on the patient is neglected, such periods may be followed by ones where all the normal cell populations are strictly above those levels and so the drug is delivered at the "absolutely" maximal rate. This takes place if, due to reducing the tumor during the treatment, its negative influence on the normal tissues reduces so that the complementary drug toxicity does not violate the prescribed toxicity constraint even if the drug is applied at the maximum rate. The periods of treatment of the first and second types can alternate several times. The number of the periods of the first type (where the rate of the drug delivery is determined by the toxicity constraints) does not exceed the number of the normal cell populations taken into account.

The proofs of the results presented below are available upon request and will be published in [8].

2. THE PROBLEM STATEMENT AND RESULTS

The model to be employed consists of several differential equations. One of them describes the dynamics of the tumor, whereas the others charac-

terize the dynamics of certain normal cell populations. The influence of the tumor on the normal cells is taken into account. The normal cell populations are not permitted to fall below given levels. The objective is to minimize the tumor at the end of the treatment. More specifically, the following assumptions are adopted.

1. Both tumor and any of the normal cell populations are homogeneous, i.e., their growth dynamics are the same for all parts of the population.
2. Both tumor and normal cell populations obey Gompertzian dynamics.
3. Tumor cells exhibit a negative and inhibiting effect on the normal ones.
4. The cytotoxic drug kills both tumor and normal cells.

Along the lines of [1,2], this leads to the following mathematical problem:

minimize $L(T)$ subject to the constraints

$$\left.\begin{array}{l} \dot{L} = \alpha L \ln \frac{\theta_L}{L} - \mathfrak{L}_0(c)L, \\ \dot{N}_i = \beta_i N_i \ln \frac{\theta_i}{N_i} - \mathfrak{L}_i(c)N_i - \Xi_i(L)N_i, \\ c = c(t) \in [0, c_{\max}], N_i = N_i(t) \geq N_i^-, \end{array}\right| \; t \in [0,T]$$

$$L(0) = L_0, \quad N_i(0) = N_i^0, \quad i = 1, \ldots, r.$$

Here $L = L(t)$ is the total number of tumor cells at time t; the symbol $N_i = N_i(t)$ denotes the size of the ith normal cell population; the control variable $c = c(t)$ stands for the concentration of the cytotoxic drug at the tumor site. The constant $\theta_L > 0$ represents the greatest size of the tumor; $\theta_i > 0$ is the normal size of the ith normal cell population. We assume that

$$0 < L_0 < \theta_L, 0 < N_i^- < N_i^0 \leq \theta_i, \quad i = 1, \ldots, r.$$

The constants $\alpha > 0, \beta_i > 0, c_{\max} > 0$ are given, so is the duration of treatment $T > 0$. The summand $-\Xi_i(L)N_i$ accounts for the negative effect of the tumor on the ith normal cell population.

(I) For any $i = 1, \ldots, r$, the function $\Xi_i(\cdot)$ is defined and continuously differentiable on $[0, +\infty)$; it strictly increases $\Xi_i'(L) > 0$ $\forall L \geq 0$ and $\Xi_i(0) = 0$.

(The function $\Xi_i(\cdot)$ was taken to be linear in [1,2].)

We consider general loss functions $\mathfrak{L}_i(\cdot)$ $(i = 0, \ldots, r)$. In particular, our assumptions take into account saturation phenomena, as well as that small drug concentrations may cause a void effect. More precisely, we suppose that

(II) For $i = 0, \ldots, r$, the function $\mathfrak{L}_i(\cdot)$ is defined and continuous on $[0, c_{\max}]$. Furthermore, there exists a threshold $c_i^{th} \in [0, c_{\max})$ such that $\mathfrak{L}_i(c) = 0$ for $c \in [0, c_i^{th}]$ and the function $\mathfrak{L}_i(\cdot)$ strictly increases on $[c_i^{th}, c_{\max}]$.

To simplify the formulations, we also assume that $\mathfrak{L}_i(\cdot) = l_i \mathfrak{L}_0(\cdot)$ for $i = 1, \ldots, r$, where $l_1, \ldots, l_r > 0$ are given constants.

In many cases, the normal cells have a higher rate of growth than the tumor ones (see e.g. the data in [1, 3, 4]). In view of this, we assume that

(III) The growth rate of any of the normal cell populations under consideration exceeds that of the tumor, i.e., $\beta_i > \alpha$ $\forall i = 1, \ldots, r$.

It is natural to demand that the constraint $N_i(t) \geq N_i^-$ must hold at least for a certain time after the treatment is completed, i.e., $N_i(t) \geq N_i^- \forall t > T, t \approx T$, provided $c := 0$ for $t > T$. However, the process is considered only till the time instant T. In view of this, we relax the above constraint via employing the first approximation of $N_i(t)$ in a vicinity of T and express this constraint in the form $N_i(t) \approx N_i(T) + (t - T)N_i'(T + 0) \geq N_i^-$ $\forall t \approx T, t > T$ or, in brief,

$$N_i'(T + 0) \geq 0 \quad \text{whenever} \quad N_i(T) = N_i^-. \quad (1)$$

Here $N_i'(T + 0) = \beta_i N_i^- \ln \frac{\theta_i}{N_i^-} - \Xi_i[L(T)]N_i^-$. So the above inequality shapes into

$$N_i^{st}[L(T)] := \theta_i e^{-\frac{\Xi_i[L(T)]}{\beta_i}} \geq N_i^-. \quad (2)$$

Here $N_i^{st}[L]$ is obviously the steady size of the ith normal cell population, provided the tumor keeps the size L (and $c := 0$ for $t > T$). So the condition (2) means that the size of that population will not fall below the admitted level N_i^- after the treatment, provided the tumor does not grow. In the case where the normal cell populations grow faster than the tumor, this condition can be viewed as a rough criterion for acceptability of the treatment result, irrespective of whether the relation $N_i(T) = N_i^-$ holds or not. In view of this, we add (2) to the problem constraints.

In some cases, no treatment of a fixed duration T can reduce the tumor to the "undangerous" size in the sense that (2) holds for $i = 1, \ldots, r$. A criterion for the goal (2) to be attainable will be offered by Lemma 4.

The last assumption to follow is not of principle. It excludes cases that are "almost never" encountered and is adopted to simplify the proofs.

(IV) For any $i, j = 1, \ldots, r, i \neq j$, no root L of the equation

$$\frac{1}{l_i}\left[\beta_i \ln \frac{\theta_i}{N_i^-} - \Xi_i(L)\right] = \frac{1}{l_j}\left[\beta_j \ln \frac{\theta_j}{N_j^-} - \Xi_j(L)\right]$$

satisfies some of the equations

$$\mu_i(L) \stackrel{\text{def}}{=\!=} \frac{1}{l_i}\left[\beta_i \ln \frac{\theta_i}{N_i^-} - \Xi_i(L)\right] = \alpha \ln \frac{\theta_L}{L},$$

$$\mu_i(L) = u_{\max}, \quad l_i^{-1}\Xi_i'(L) = l_j^{-1}\Xi_j'(L).$$

Whenever this property is violated, it can be evidently ensured by a small perturbation of the parameters (including the functions $\Xi_k(\cdot)$).

The change of the variables $x := \ln\frac{\theta_L}{L}, y_i := \ln\frac{\theta_i}{N_i}, u := \mathfrak{L}_0(c)$ shapes the problem into

$$\text{maximize} \quad x(T) \tag{3}$$

subject to the constraints

$$\left.\begin{array}{l} \dot{x} = -\alpha x + u \\ \dot{y}_i = -\beta_i y_i + l_i u + \xi_i(x) \end{array}\right| \quad \forall t \in [0,T], \tag{4}$$

$$0 \le u = u(t) \le u_{\max}, y_i = y_i(t) \le g_i \ \forall t, \tag{5}$$

$$x(0) = x_0, \quad y_i(0) = y_i^0, \quad \xi_i[x(T)] \le \beta_i g_i. \tag{6}$$

Here $i = 1,\dots,r$ and due to the above assumptions, $\xi_i(x) := \Xi_i(\theta_L e^{-x}) > 0, u_{\max} := \mathfrak{L}_0(c_{\max}) > 0, g_i := \ln\frac{\theta_i}{N_i} > 0, x_0 := \ln\frac{\theta_L}{L_0} > 0, 0 \le y_i^0 := \ln\frac{\theta_i}{N_i^0} < g_i$, $\xi_i'(x) < 0 \ \forall x, i = 1,\dots,r$. To make the statement of the problem more precise, we define a *process* to be a tuple

$$[x(\cdot), y_1(\cdot), \dots, y_r(\cdot), u(\cdot)] \tag{7}$$

of the functions $x(\cdot), y_1(\cdot), \dots, y_r(\cdot), u(\cdot) : [0,T] \to \mathbf{R}$ with $x(\cdot), y_1(\cdot), \dots, y_r(\cdot)$ absolutely continuous and $u(\cdot) \in \mathbb{L}_\infty[0,T]$ such that (4)—(6) hold. *The problem is to maximize $x(T)$ over all the processes.* For consistency, the variable u will be called the *drug concentration.*

Definition 1 A process (7) is said to *conform to the strategy of intensive chemotherapy* if the cytotoxic drug is constantly delivered at the rate that is maximal under the constraints (5), i.e., either $u(t) = u_{\max}$ or $y_i(t) = g_i$ with some $i = 1,\dots,r$ for almost all t.

Now we are in a position to present the main results of the paper.

Theorem 1 One and only one of the following two statements holds:

(i) The optimal process exists, is unique, and conforms to the strategy of intensive chemotherapy.

(ii) Either the normal cell populations under consideration cannot be kept above the prescribed levels on the entire time interval $[0,T]$, no matter what drug administration be applied, or no chemotherapy regimen can reduce the tumor to the "undangerous" size in the sense that (2) holds for $i = 1,\dots,r$.

By Theorem 1, the optimal chemotherapy regimen is to deliver the drug at the rate that is maximal under the constraints (5). The following Lemma 1 will show that this directive predetermines the drug administration and the process uniquely. Note also that in the case (ii), there evidently is no process. Thus the strategy of intensive chemotherapy either gives rise to an optimal process or fails to implement a process at all with the second event occurring if and only if the goals of the treatment are not attainable (in the sense that (ii) holds).

Lemma 1 There exists no more than one process that conforms to the strategy of intensive chemotherapy.

Moreover, this process (which equals the optimal one) can be implemented by a feedback

$$u(t) = U[x(t), y_1(t), \dots, y_r(t)]. \tag{8}$$

To specify $U(\cdot)$, we put for $\omega = (x, y_1, \dots, y_r) \in \mathbf{R}^{r+1}$ and $j = 1,\dots,r$,

$$\begin{array}{l} \widehat{v}_j(\omega) := l_j^{-1}[\beta_j y_j - \xi_j(x)], \\ v_j(x) := l_j^{-1}[\beta_j g_j - \xi_j(x)], \end{array} \tag{9}$$

$$\begin{array}{l} I^+(\omega) := \{i = 1,\dots,r : y_i > g_i\}, \\ I(\omega) := \{i = 1,\dots,r : y_i = g_i\}, \end{array} \tag{10}$$

$$\begin{array}{l} I'(\omega) := \Big\{ i \in I(\omega) : v_i(x) = v(\omega) \\ := \min_{k \in I(\omega)} v_k(x) \Big\} \quad \text{if} \quad I(\omega) \ne \emptyset \\ \text{and} \qquad I'(\omega) := \emptyset \qquad \text{otherwise.} \end{array} \tag{11}$$

Lemma 2 Suppose that $I^+(\omega) = \emptyset$ and $I(\omega) \ne \emptyset$. Then $I'(\omega) \ne \emptyset$ and

$$\max_{i \in I'(\omega)} l_i^{-1}[-\alpha x + v(\omega)]\,\xi_i'(x) \tag{12}$$

is attained at a single index $i = i(\omega)$.

The function $U(\cdot)$ in (8) is given by

$$U(\omega) := \begin{cases} \min\limits_{i \in I^+(\omega)} \widehat{v}_i(\omega) & \text{if} \quad I^+(\omega) \ne \emptyset, \\ u_{\max} & \text{if} \begin{cases} I^+(\omega) = \emptyset \text{ and either} \\ I(\omega) = \emptyset \text{ or } I(\omega) \ne \emptyset \\ \text{and } v_{i(\omega)}(x) \ge u_{\max}, \end{cases} \\ v_{i(\omega)}(x) & \text{if} \begin{cases} I^+(\omega) = \emptyset, I(\omega) \ne \emptyset, \\ \text{and } v_{i(\omega)}(x) < u_{\max}. \end{cases} \end{cases}$$

Definition 2 A tuple of functions (7) defined on an interval $[0,\tau]$ is called an *outcome of the feedback* (8) if it satisfies (4), (8) (for almost all $t \in [0,\tau]$),

and (6) except for the last relation.

Though the constraints from (5) are not required to hold, some of them are necessarily satisfied.

Lemma 3 For any outcome of the feedback (8), $u(t) \le u_{\max}$ for almost all t and $y_i(t) \le g_i$ for all t and $i = 1, \dots, r$.

At the same time, the drug concentration u may formally take meaningless negative values in general. From a nonformal point of view, this means that the feedback rule (8) fails to implement a process (on the time interval $[0, T]$). As the next lemma will show, the event in question signals that the statement **(ii)** from Theorem 1 holds. Moreover, it suffices to subject the outcome of the feedback (8) to a simple analysis to recognize which of the cases **(i)** and **(ii)** from Theorem 1 takes place.

Lemma 4 The initial data $x(0) = x_0, y_i(0) = y_i^0$ gives rise to only one outcome of the feedback (8). If this feedback rule forces the drug concentration u to take negative values at a time $\tau < T$ for that outcome, the statement **(ii)** from Theorem 1 is true. Otherwise, the outcome in question can be defined on the entire time interval $[0, T]$. Whenever it satisfies (6), the statement **(i)** from Theorem 1 holds and the outcome of the feedback (8) equals the optimal process. Otherwise, the statement **(ii)** from Theorem 1 is true.

To complete the mathematical analysis, we consider in more details the structure of an outcome of the feedback (8).

Lemma 5 Consider an outcome of the feedback (8). The time interval $[0, \tau]$ can be partitioned into a finite number of subintervals $0 = \tau_0 < \tau_1 < \dots < \tau_p = \tau$ such that for any of them $[\tau_k, \tau_{k+1}]$ $(k = 0, \dots, p-1)$ one and only one of the following two statements holds:

- **(i)** The drug is delivered at the "absolutely" maximal rate on this subinterval: $u(t) = u_{\max}$ for almost all $t \in [\tau_k, \tau_{k+1}]$;
- **(ii)** Some and only one of the normal cell populations stays at its lowest admitted level on this subinterval: $y_i(t) = g_i$ for all $t \in [\tau_k, \tau_{k+1}]$ and some $i = i_k$. All the other such populations are kept strictly above these levels within this subinterval except for, maybe, its endpoints $y_j(t) < g_j$ for $t \in (\tau_k, \tau_{k+1}), j \ne i_k$.

The case **(i)** occurs for $k = 0$. In the case **(ii)**,

$$u(t) = v_{i_k}[x(t)] \quad \text{for} \quad t \in [\tau_k, \tau_{k+1}], \qquad (13)$$

where $v_i(x)$ is defined in (9).

Further, we consider a partition from Lemma 5 with p minimal. The possible ways of alternation of the subintervals $[\tau_k, \tau_{k+1}]$ are shown in Fig. 1.

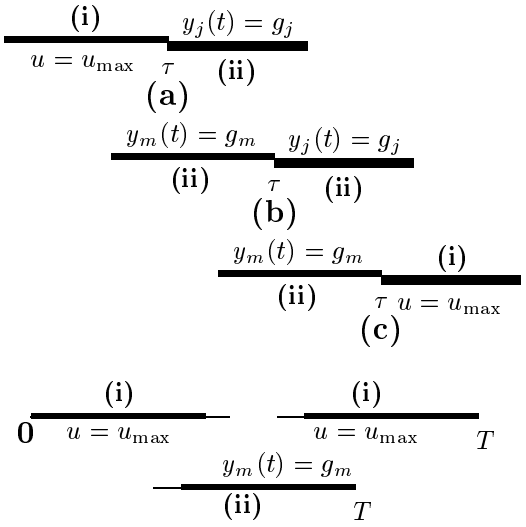

Fig. 1.

Lemma 6 The subintervals alternate in the ways (a) or (b) from Fig. 1 when the size of one of the normal cell populations y_j attains its lowest admissible level and applying the drug at the maximal rate $u_{\max}$ for $t > \tau, t \approx \tau$ violates the toxicity constraints $y_\nu(t) \le g_\nu \ \forall \nu$. [1] Here the index j is given by $j = i(\omega)$, where $\omega := [x(\tau), y_1(\tau), \dots, y_r(\tau)]$ and $i(\omega)$ is defined in Lemma 2. The subintervals alternate in the way (c) from Fig. 1 when the drug concentration u reaches its upper bound $u_{\max}$ and applying the drug at the maximal rate $u_{\max}$ for $t > \tau, t \approx \tau$ does not violate the constraints $y_\nu \le g_\nu \ \forall \nu$.

In connection with the last requirement, note that the constraint $y_m(t) \le g_m$ is not violated. The union of the maximal number of successively gearing (with endpoints) subintervals $[\tau_k, \tau_{k+1}]$ on which (ii) of Lemma 5 holds is called a *singular zone*. The optimal process may contain several such zones separated by subintervals where (i) of Lemma 5 is true. The number of such zones does not exceed the number of the normal cell populations under consideration, as easily follows from the concluding lemma.

Lemma 7 Along the optimal process, the tumor either evolves monotonically or first (strictly) decreases and then (nonstrictly) increases. Reversing the direction may take place only at a moment τ when the events described in (a) or (b) from Fig. 1 occur, with the entire interval $[\tau, T]$ lying in a singular zone. If the tumor increases

[1] The last requirement is true whenever $u_{\max} > v_\nu[x(\tau)]$ for an index ν such that $y_\nu(\tau) = g_\nu$. (Note that for any such index, $0 \le \dot{y}_\nu(\tau - 0) = -\beta_\nu g_\nu + l_\nu u(\tau - 0) + \xi_\nu[x(\tau)]$ and so $v_\nu[x(\tau)] \le u(\tau - 0) \le u_{\max}$.)

during the therapy, there exists no more than one singular zone. This zone spreads till the end of the treatment T. If a switch of regimens depicted in (c) from Fig. 1 takes place at a moment τ, this moment belongs to the time interval where the tumor decreases and the mth normal cell population will subsequently never reach its lowest admissible level within this interval.

3. DISCUSSION

The most of our simplifying assumptions are ordinary and can be found in many papers. Among these assumptions, there is that only one drug is employed. We also supposed that the drug spreads within the body instantaneously with no decay and so its concentration at the tumor site is proportional to the infusion rate. Furthermore, we assumed that the growth rates of the normal cells exceed that of the tumor. To our mind, more complex models (which, for example, contain pharmacokinetic equations giving a more precise relationship between the drug concentration and the infusion rate, or does not stipulate any relationship between the growth rates of the normal and tumor cells, respectively) should be certainly investigated. We consider this as a topic of further research. Another such a topic concerns application of the general theory developed in [12] to similar models with uncertainties.

Insertion of the constraint (2) into the problem statement is in fact related to our analysis of alternative settings. If this constraint is dropped, it can be shown that the optimal process either coincides with that from Theorem 1 or ends in a position where the toxicity constraints are never satisfied after the treatment, i.e., for $t > T$ (provided $c := 0$ for $t > T$). (In the second case, the drug is not applied during a certain concluding phase of the therapy, i.e., for $T - \Delta t \leq t \leq T$.) The second solution seems to be scarcely acceptable. The matters do not change in the essence if the toxicity that occurs just after the treatment is constrained explicitly by imposing the requirement (1). The point is that the above unacceptable solution can (at least, in many cases) be approximated by processes for which the constraint (1) is inactive since $N_i(T) \neq N_i^-$ $\forall i$ for them. As a result, this solution remains optimal, maybe, not exactly but at least asymptotically. This effect can be discarded by replacing (1) with a more rough constraint, e.g., $N_i'(T+0) + \mu_i \left[N_i(T) - N_i^-\right]^2 \geq 0$, where $\mu_i > 0$ are penalty coefficients. Another way is to require that the toxicity constraints be satisfied for a given time τ after the treatment is completed. All these issues await further research. However, we conjecture that the corresponding solutions may have the disadvantage of depending (at least, in some cases) explicitly on the parameters μ_i or τ.

4. ACKNOWLEDGEMENTS

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