Optimal Control Applied to Drug Administration in Cancer Chemotherapy: the Case of Several Toxicity Constraints*

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Abstract

Cancer chemotherapy for the case of one drug is studied. The negative and inhibiting effect of the tumor on normal cells is taken into account. Under certain assumptions, 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.

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 drugs 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 [5,7], or fractions, each encompassing all the tumor cells in a definite phase of the cell cycle [9]). 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 [5, 7], blocking effect [15] (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 [10, 23, 24]. Another approach is to constrain the toxicity by maintaining a certain normal cell population above a given level [6, 13–15]. There is a similar diversity of objectives. In some cases, the goal was to minimize the total amount of the 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. There are known attempts to minimize the toxicity and the tumor burden simultaneously [25]. For further details and an excellent survey of the area, we refer the reader to [10, 24].

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, 18]. 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 affect 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

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this period. (In fact, this pattern of treatment is very rare in clinical practice though it may be beneficial in maintenance therapy [11].) 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 [21, 22]. So taking into account negative effects of tumor on normal cells is, for example, likely to result in correction the above solution via shortening or even discarding the delay period.

In this paper, we analyze effects on the optimal chemotherapy scheduling that are due to the negative influence of the malignant tumor on the patient. The size of a normal cell population is taken as a measure 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 the cytotoxic drugs and the 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 independent 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 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, 6] 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 concentration is approximately proportional to the drug infusion rate. 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 ([12, 16] etc.), 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. Note that during some periods of therapy, this rate may be determined by the toxicity constraints. Namely, if some normal cell population arrives at its lowest admissible level, the drug infusion rate may be limited by the requirement to maintain the population at or above this level.

The proofs of the results formulated in this paper are available upon request.

2 The problem statement

The model to be employed consists of several differential equations. One of them describes the dynamics of the tumor, whereas the others characterize 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 diminish below given levels. The objective is to minimize the tumor at the end of the treatment. The control variable is the concentration of the anti-cancer drug at the tumor site. More specifically, we adopt the following assumptions:

1. Both the 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:

$$\text{minimize } L(T) \text{ subject to the constraints}$$

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

$$L(0) = L_0, \quad , N_i(0) = N_i^0,$$

where $i = 1, \ldots, r$. 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 the initial data L_0, N_i^0 and the minimal allowed size of the ith normal cell population N_i^- meet the following natural requirements:

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

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. We assume that

(I) For any $i = 1,\dots,r$, 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 $\Xi_i(0) = 0$.

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

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

(II) For $i = 0,\dots,r$, 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 $i = 1,\dots,r$, where $l_1,\dots,l_r > 0$ 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 [1,3,4,8,13,17,19]). 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.,

$$\beta_i > \alpha \qquad \forall i = 1,\dots,r.$$

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 ($c := 0$ 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,

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

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

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

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 constraint 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 $i = 1,\dots,r$. A criterion for the goal (2) to be attainable will be offered by Lemma 3.4.

The last assumption to follow is not of principle. It excludes cases that are rarely encountered but, being taken into account, result in considerable complication of formulations.

(IV) For any $i,j = 1,\dots,r, i \neq j$, no root $L \in [0,\theta_L]$ 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

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

$$\frac{1}{l_i}\left[\beta_i \ln\frac{\theta_i}{N_i^-} - \Xi_i(L)\right] = u_{\max},$$

$$l_i^{-1}\Xi_i'(L) = l_j^{-1}\Xi_j'(L).$$

(If $L = 0$, then $\ln\frac{\theta_L}{L} := \infty$.) Whenever this property is violated, it can be ensured by a small perturbation of the parameters (including the functions $\Xi_k(\cdot)$). At the same time, if this property takes place, no such a perturbation violates it. This implies that assumption **(IV)** holds "almost always".

The change of the variables

$$x := \ln\frac{\theta_L}{L}, \quad y_i := \ln\frac{\theta_i}{N_i}, \quad u := \mathfrak{L}_0(c)$$

shapes the problem into

$$\text{maximize} \quad x(T) \quad \text{subject to the constraints}$$

$$\dot{x} = -\alpha x + u \qquad \forall t \in [0,T], \tag{3}$$

$$\dot{y}_i = -\beta_i y_i + l_i u + \xi_i(x) \qquad \forall t \in [0,T], i = 1,\dots,r, \tag{4}$$

$$0 \leq u \leq u_{\max},\ y_i = y_i(t) \leq g_i\ \forall t \in [0,T], i = 1,\dots,r \tag{5}$$

$$x(0) = x_0, \qquad y_i(0) = y_i^0, \quad i = 1,\dots,r \tag{6}$$

$$\xi_i[x(T)] \leq \beta_i g_i, \quad i = 1,\dots,r. \tag{7}$$

Here $\xi_i(x) := \Xi_i(\theta_L e^{-x})$, $u_{\max} := \mathfrak{L}_0(c_{\max}) > 0$, $g_i := \ln\frac{\theta_i}{N_i^-} > 0, x_0 := \ln\frac{\theta_L}{L_0} > 0$, $0 \leq y_i^0 := \ln\frac{\theta_i}{N_i^0} < g_i$. To

[†]Indeed, under the above idealized circumstances where $L(t) = L = \text{const}\ \forall t \geq T$, the necessity of (2) is evident since $\lim_{t\to\infty} N_i(t) = N_i^{st}(L)$. Conversely, let (2) hold. For $t \geq T$, the growth of the ith normal cell population is described by an autonomous ordinary differential equation and so the function $N_i(t)$ is monotone. Hence the inequalities $N_i(T) \geq N_i^-$ and $\lim_{t\to\infty} N_i(t) \geq N_i^-$ ensure that $N_i(t) \geq N_i^-$ for $t \geq T$.

make the statement of the problem more precise, we define a *process* to be a tuple $[x(\cdot),y_1(\cdot),\dots,y_r(\cdot),u(\cdot)]$ of the function $x(\cdot),y_1(\cdot),\dots,y_r(\cdot),u(\cdot):[0,T]\to\mathbf{R}$ with $x(\cdot),y_1(\cdot),\dots,y_r(\cdot)$ absolutely continuous and $u(\cdot)$ measurable and bounded such that (3)—(7) hold. *The problem is to maximize $x(T)$ over all processes*.

3 The main results

Definition 3.1 *A process $[x(\cdot),y_1(\cdot),\dots,y_r(\cdot),u(\cdot)]$ 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 results of the paper.

Theorem 3.1 *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 3.1, the optimal chemotherapy regimen is to deliver the drug at the rate that is maximal under the constraints (5). The following Lemma 3.1 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 3.1 *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

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

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

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

$$I^+(\omega):=\{i:y_i>g_i\},\quad I(\omega):=\{i:y_i=g_i\},$$
$$I'(\omega):=\left\{i\in I(\omega):v_i(x)=v(\omega):=\min_{k\in I(\omega)}v_k(x)\right\}.$$

(If $I(\omega)=\emptyset$, then $I'(\omega)=\emptyset$.) To introduce the function $U(\cdot)$, we need the following fact.

Lemma 3.2 *Suppose that $I^+(\omega)=\emptyset$ and $I(\omega)\neq\emptyset$. Then $I'(\omega)\neq\emptyset$ and*

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

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

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

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

The process generated by the feedback (8) is determined by the dynamics equations (3) and (4), along with the initial conditions (6). The following definition introduces a name for this process and specifies related details.

Definition 3.2 *A tuple of the functions $[x(\cdot),y_1(\cdot),\dots,y_r(\cdot),u(\cdot)]$ defined on an interval $[0,\tau]$ is called an* outcome of the feedback (8) *if it satisfies* (3), (4), (8) *(for almost all $t\in[0,\tau]$), and* (6)*.*

In order that the feedback rule (8) can be actually implemented, the drug concentration value $u(t)$ given by (8) must always lie within the bounds $0\leq u(t)\leq u_{\max}$ from (5). The following lemma shows that the rule (8) partly meets this requirement. Moreover, this rule "automatically" prevents the toxicity constraints $y_i\leq g_i$ from violation.

Lemma 3.3 *For any outcome of the feedback* (8)*, $u(t)\leq u_{\max}$ for almost all t and $y_i(t)\leq g_i$ for all t and $i=1,\dots,r$.*

As for the other part $u\geq 0$ of the implementability requirement $0\leq u\leq u_{\max}$, there is no guarantee that it will necessarily be met. In general, the situation cannot be excluded where the drug concentration value given by (8) reduces to zero $u(\tau)=0$ in course of time and an attempt to follow the rule at hand for $t>\tau, t\approx\tau$ results in getting meaningless negative values of u. Then the above feedback cannot be employed any longer and the outcome of the feedback cannot be continued on $t>\tau$. The next lemma demonstrates that this event signals that the goals of the treatment are not attainable (in the sense that (ii) of Theorem 3.1 holds). Moreover, related to the feedback rule (8) is not only sufficient,

but also necessary and sufficient criterion for (ii) of Theorem 3.1 to occur.

Lemma 3.4 *The initial data* (6) *gives rise to only one outcome of the feedback* (8)*. If the drug concentration value u generated by* (8) *arrives at zero* $u(\tau) = 0$ *in course of time and the feedback* (8) *cannot be implemented for* $t > \tau$ *(an attempt to follow this rule for* $t > \tau, t \approx \tau$ *results in getting negative values of u), the statement* **(ii)** *from Theorem* 3.1 *is true. Otherwise, the outcome in question can be defined on the entire time interval* $[0,T]$*. Whenever it satisfies* (7)*, the statement* **(i)** *from Theorem* 3.1 *holds and the outcome of the feedback* (8) *equals the optimal process. Otherwise, the statement* **(ii)** *from Theorem* 3.1 *is valid.*

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

Lemma 3.5 *Suppose that* $[x(t), y_1(t), \ldots, y_r(t), u(t)]$ $(0 \le t \le \tau)$ *is an outcome of the feedback* (8)*. The time interval* $[0,\tau]$ *can be partitioned into a finite number of subintervals* $0 = \tau_0 < \tau_1 < \cdots < \tau_p = \tau$ *such that for any of them* $[\tau_k, \tau_{k+1}]$ $(k = 0, \ldots, p-1)$*, one and only one of the following two statements holds:*

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

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

$$u(t) = v_{i_k}[x(t)] \quad \textit{for almost all} \quad t \in [\tau_k, \tau_{k+1}],$$

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

Consider such a partition with p minimal. The possible ways of alternation of the subintervals $[\tau_k, \tau_{k+1}]$ where **(i)** and, respectively, **(ii)** of Lemma 3.5 hold are shown in Fig. 1.

Lemma 3.6 *The subintervals alternate in the ways* (a) *and* (b) *from Fig.* 1 *when one of the normal cell populations* y_j *(where* $j \ne m$ *in the case* (b)*) arrives at its lowest admissible level. If several such populations do so simultaneously, then* $j = i(\omega)$ *in Fig.* 1(a,b)*. Here* $\omega := [x(\tau), y_1(\tau), \ldots, y_r(\tau)]$ *and the index* $i(\omega)$ *is defined in Lemma* 3.2*. The subintervals alternate in the way* (c) *from Fig.* 1 *when the drug concentration u reaches its upper level* $u_{\max}$*.*

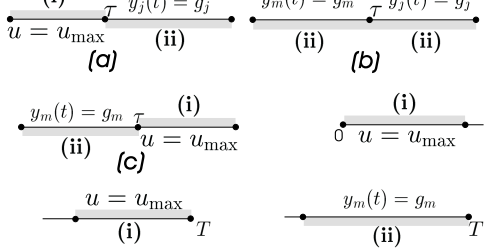

Figure 1:

The union of the maximal number of successively gearing (with endpoints) subintervals on which (ii) of Lemma 3.5 holds is called a *singular zone*. The optimal process may contain several such zones separated by subintervals where (i) of Lemma 3.5 is true. The number of such zones does not exceed the number of the normal cell populations under consideration, as easily follows from our concluding lemma.

Lemma 3.7 *Along the optimal process, the tumor either evolves monotonically or first decreases and then increases. Reversing the direction may take place only at a moment* τ *when the events depicted in* (a) *or* (b) *from Fig.* 1 *occur, with the entire interval* $[\tau, T]$ *lying in a singular zone. If the tumor increases during the therapy, no more than one singular zone exists. This zone spreads till the end of the treatment* T*. If a switch of regimens depicted in* (c) *from Fig.* 1 *occurs at a moment* τ *from the time interval where the tumor decreases, the mth normal cell population will subsequently never arrive at its lowest admissible level within this time interval.*

4 Discussion

The paper analyzes how taking into account the negative influence of the tumor on normal cells affects the optimal drug administration in cancer chemotherapy. The levels of certain normal cell populations were taken as measures of toxicity. It was demonstrated that the optimal regimen of treatment conforms to the strategy of aggressive chemotherapy. In other words, the drug must be constantly applied at the rate that is maximal under the constraints on both the drug concentration and the sizes of the normal cell populations. In particular, there may be periods of therapy where the rate of drug delivery is determined by the requirement to maintain the normal cell populations at or above given levels. Unlike the case where the influence of tumors on the patient is neglected, these periods may be followed by ones where the drug infusion rate is determined only by the constraint on the drug concentration. The periods of treatment where the rate of drug delivery is determined by the toxicity constraints and by the constraint on the drug concentration, respectively, can alternate several times. The number of the periods first mentioned does not exceed the number of the normal cell populations taken into account.

Most of our simplifying assumptions are quite ordinary for the literature in the area. Among these assumptions, there is that only one drug is employed. We also supposed that the drug spreads within the body instantaneously 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, respectively, tumor cells) should be investigated. We consider this as a topic of further research. Another interesting direction of research is application of the general theory developed in [16, 20] to similar models with uncertainties.

Insertion of the constraint (2) into the problem statement is 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 3.1 or ends in a position where the toxicity constraints are never satisfied after the treatment (and the drug is not applied during a certain concluding phase of the therapy). The solution of the second kind seems to be scarcely acceptable, which reveals that the problem setting does need constraints on the toxicity after the treatment. There is a variety of more or less natural ways to impose such constraints; one of them was examined in this paper.

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