Controlling the Bone Marrow Dynamics in Cancer Chemotherapy*

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Abstract

In the paper a mathematical model for the growth of the bone marrow under cell-cycle specific cancer chemotherapy is analyzed. The model is formulated as an optimal control problem with control representing the drug dosage and objective of Bolza type linearly depending on the control, a so-called L^1-objective. We apply the Maximum Principle followed by high-order necessary conditions for optimality of singular arcs and sufficient conditions for optimality of bang-bang controls based on the method of characteristics. Singular controls are eliminated as candidates for optimality and easily verifiable conditions for strong local optimality of bang-bang controls are formulated in the form of transversality conditions at the switching surfaces. Numerical simulations are given.

1 Introduction

In the last two decades there has been growing interest in developing and analyzing models for cancer chemotherapy (for instance, [4, 12, 17, 18]). While biomedical research concentrates on new drugs and treatments, mathematicians analyze the models for the purpose of testing various treatment strategies and searching for the optimal ones. After early, simple structures were considered [4], classes of models which are *cell-cycle-specific* were developed. These so-called *compartmental models*, introduced in the nineties [12, 20] and analyzed further recently [8, 9, 19], divide the cell-cycle into clusters, called compartments, which allow to model drug applications at the stages where they are the most effective. For example, the drug Cyclophosphamide acts upon cells in the DNA replication phase of the cycle while other drugs such as Taxol more effectively influence cells in the division phase. Due to this specification the compartmental models have been well received by practitioners and the results of working on them were of interest to the medical community. But clearly several aspects of these models still are questionable and an important one is monitoring the influence of the chemotherapy on healthy cells. In these models the state variable represents only the cancer cells at various stages of the cell cycle and the model focuses on minimizing them. Hence the negative effects on the healthy cells are represented only indirectly through the drug dosage in the objective. However, the toxicity to the bone marrow is one of the main limiting factors in cell-cycle-specific chemotherapy and should be taken into account.

In this paper we analyze a different model for cancer chemotherapy which precisely compensates for this deficiency. This bone marrow model introduced in the late nineties by Panetta [15] and analyzed by Fister and Panetta in [5]. It focuses on modelling a class of healthy cells the most effected by chemotherapy, namely, bone marrow cells. Since the bone marrow produces the blood cells, clinicians typically will take a *blood cell count* from a patient prior to giving further doses of chemotherapy to see if the blood cell count is above some minimum level. If it is too low, clinicians will either delay the treatment or give a reduced dose. Thus the blood count becomes a deciding factor in designing the treatment. The purpose of the model presented here and its analysis is to

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find optimal strategies for chemotherapy treatments of the cancer, where the blood cell count and then indirectly the bone marrow are kept above a minimum level. The bone marrow model which is under investigation fills the gap in this aspect by directly modelling bone marrow cells and taking advantage of the white cells count which is routinely performed in medical practice.

A first analysis of this model as an optimal control problem was given in [5] with an objective of Lagrange type (no terminal payoff), which was quadratic in the control, a so-called L^2-objective. The analysis led to protocols which starting from no dose were gradually increasing achieving a full dose at the terminal time of the therapy. On the other hand, both experimental and clinical trials [11, 6] as well as preliminary analysis of the model both from a probabilistic or deterministic point of view [22] led to the general conclusion that *"short drug pulses at appropriate intervals are less toxic to the bone marrow compared to the arbitrary treatment intervals or slowly infused continuous treatments"* [5]. Researchers suggested the use of *"on-off" type drug functions* (the drug is either active or not active) to describe the effect of the cell-cycle-specific drugs on the bone marrow. In this paper, by using our previous experience with cancer chemotherapy models [8, 9, 19], we propose and analyze the bone marrow dynamics with an objective which is linear in control, a so-called L^1-objective, and contains a terminal payoff term representing the total count of the bone marrow cells at the end of the therapy.

The application of the Maximum Principle to the problem done in section 2 leads to two types of controls: singular controls (with values in the interior of the control set corresponding to partial drug dosages) and bang-bang controls (which take values in the boundary of the control set corresponding to alternating full dose and no-dose periods). In Section 3 further analysis of both classes is performed. A high-order condition for optimality, the Legendre-Clebsch condition, is used to eliminate singular controls in section 3.1 and further analysis of bang-bang controls with the use of the method of charcteristics is outlined in section 3.2. The results are supported by some numerical simulations which are presented in Section 4. Comparisons of the results obtained with an L^2 -objective case as well as remarks on future directions of research conclude the paper.

2 Mathematical Model

2.1 Dynamics

This model has originally been discussed in [15] and then was analyzed as an optimal control problem with an objective which is quadratic in the control in [5]: In the model in the bone marrow proliferating cells P and quiescent cells Q are distinguished. The growth rate of the proliferating cells is denoted by γ and the transition rates from proliferating to quiescent cells and vice versa are denoted by α and β respectively. The rate at which bone marrow enters the blood stream is denoted by ρ and the natural death rate of the proliferating cells is called δ. It is assumed that all these parameters governing the cell cycle are constant over the time horizon considered. Thus the overall dynamics of the uncontrolled system is described by

$$\dot{P} = (\gamma - \delta - \alpha)P + \beta Q, \qquad P(0) = P_0, \tag{1}$$

$$\dot{Q} = \alpha P - (\rho + \beta)Q, \qquad Q(0) = Q_0, \tag{2}$$

with all initial conditions positive.

Drug treatment is modelled by a bounded measurable function u which takes values in the compact interval $[0, 1]$ and represents the drug dosage with $u = 1$ corresponding to a full dose and $u = 0$ stands for no control being applied. While the drugs are given to kill cancer cells, they also kill normal tissue which is considered as bone marrow in this model. If a parameter $s > 0$ is added to model the effectiveness of the drug as in [5], then the overall dynamics can be described as

$$\dot{P} = (\gamma - \delta - \alpha - su(t))P + \beta Q, \qquad P(0) = P_0, \tag{3}$$

$$\dot{Q} = \alpha P - (\rho + \beta)Q, \qquad Q(0) = Q_0. \tag{4}$$

If we set $N = (P, Q)$, then the general form of the dynamics is given by the bilinear system

$$\dot{N}(t) = (A + uB)N(t), \quad N(0) = N_0, \tag{5}$$

where A and B are fixed (2×2)-matrices given by

$$A = \begin{pmatrix} \gamma - \delta - \alpha & \beta \\ \alpha & -(\rho + \beta) \end{pmatrix}, \; B = \begin{pmatrix} -s & 0 \\ 0 & 0 \end{pmatrix} \tag{6}$$

It follows from well-known results about ordinary differential equations that for any admissible control u the corresponding trajectory exists on all of $[0, T]$. Furthermore, the fact that the off-diagonal terms in the matrix $A + uB$ are positive implies that the first quadrant in the state-space is positively invariant, i.e. if each coordinate of $N(t_0)$ is positive, then all coordinates of $N(t)$ remain positive for all times $t \geq t_0$.

2.2 Objective

The objective of any treatment is to kill the cancer, but to keep the toxicity to the normal tissue acceptable. Since bone marrow produces blood cells, clinically this is realized by taking a blood cell count of the patient before a treatment session and a full treatment is only administered if the blood cell count is above a certain minimum and usually fixed level. The objective therefore becomes to give as much of the drug as possible since this will kill the cancer cells, but at the same time keep the bone marrow high. In [5] Fister and Panetta therefore maximize the objective

$$J = \int_0^T a(P(t) + Q(t)) - \frac{b}{2}(1 - u(t))^2 dt \to \max \tag{7}$$

over the class $\mathcal{U}$ of all Lebesgue measurable functions which take values in the control set $U = [0, 1]$ a.e; a and b are positive constants. The use of an objective which is quadratic in the control makes the problem easier mathematically since the Hamiltonian will be strictly convex in the control with a unique minimum over $[0, 1]$ and it is shown in [5] that for T sufficiently small a unique optimal control exists which is continuous on $[0, T]$. However, only at the terminal time T does the optimal control take the maximum value $u = 1$ and otherwise it is strictly smaller than one, $u(t) < 1$ for $t < T$. In all the simulations in [5] the optimal controls are first given by $u = 0$ and from a certain time the drug dosages strictly increase to reach level 1 at the terminal time. This of course leads to a depletion of bone marrow towards the end which is natural since the later values have a much smaller influence in the objective.

From a modelling perspective a quadratic control term in the objective somewhat undermines the negative effects of the drug since for example half a dose is only measured as a quarter. Thus naturally optimal solutions will have the tendency to give partial doses of the drug, if at all. An objective which is linear in the control does not provide such an incentive to give partial doses. In this paper we therefore chose the performance index in the form to maximize

$$J = r_1 P(T) + r_2 Q(T) + \int_0^T a(P(t) + Q(t)) + bu(t) dt \to \max \tag{8}$$

In the objective, as in [5] we have incorporated a term $a(P+Q)$ in the Lagrangian in an effort to keep the number of bone-marrow cells high. Rather than requiring an absolute lower bound, this so-called "soft" constraint implicitly maximizes the bone marrow. In addition we have added a terminal term which prevents that the bone marrow would be depleted towards the end of the therapy interval. The coefficients r_1 and r_2 are non-negative weights and the penalty term $r_1 P(T) + r_2 Q(T)$ represents a weighted average of the total bone marrow at the end of an assumed fixed therapy interval $[0, T]$. It is assumed implicitely in this model that the drug dosage $u(t)$ is proportional to the number of cancer cells killed. Since the drug kills healthy tissue at a proportional rate, the control $u(t)$ is also used to model the negative effect of the drug on the normal tissue or its toxicity. Using an L_1-objective rather than an L_2-objective on the control avoids distortions due to the square which would put a smaller penalty on lower doses. Thus the integral in the objective models the cumulative negative effects of the treatment.

Writing $r = (r_1, r_2)$ and using $e = (1, 1)$, the mathematical objective therefore can be formulated as to maximize

$$J(u) = rN(T) + \int_0^T aeN(t) + bu(t) dt \tag{9}$$

over all Lebesgue measurable functions u which take values in $[0,1]$, subject to the dynamics (5) and given initial condition $N(0)$. Without loss of generality one of the parameters may be normalized and we thus set $b = 1$.

2.3 Necessary Conditions for Optimality

First-order necessary conditions for optimality are given by the Pontryagin Maximum Principle [16] which for this model can be stated as follows: If u_* is an optimal control with corresponding trajectory N_*, then there exists an absolutely continuous function λ, which we write as row-vector, $\lambda : [0,T] \to (\mathbb{R}^2)^*$, satisfying the adjoint equation with transversality condition,

$$\dot{\lambda} = -\lambda(A + uB) - ae, \qquad \lambda(T) = r, \tag{10}$$

with the property that an optimal control maximizes the Hamiltonian

$$H = aeN + u + \lambda(A + uB)N \tag{11}$$

over the control set $[0,1]$ along $(\lambda(t), N_*(t))$. We call a pair (x,u) consisting of an admissible control u and corresponding trajectory for which there exists a multiplier λ such that the conditions of the Maximum Principle are satisfied an *extremal* (pair) and the triple (x,u,λ) is an extremal lift (to the cotangent bundle).

While the first quadrant in the state-space is positively invariant, the first quadrant in the dual space becomes negatively invariant under the adjoint flow (10). Even a bit stronger, it holds that if $\lambda_i(T) \geq 0$ for $i = 1,2$, then $\lambda_i(t) > 0$ for all $t < T$. This result, which will be important in the further analysis of the problem, again easily follows from the fact that the off-diagonal elements in the matrix defining the dynamics, α and β, are positive. Summarizing, since the initial conditions N_0 and the coefficients r_i are non-negative, we therefore have that

Proposition 2.1 *All states N_i are positive over $[0,T]$ and the costates λ_i are positive over $[0,T)$ with the possible exception of the endpoints if $r_i = 0$.*

Optimal controls u_* maximize the Hamiltonian H, i.e.

$$(1 + \lambda(t)BN(t))u_*(t) = \max_{0 \leq u \leq 1} (1 + \lambda(t)BN(t))u. \tag{12}$$

Thus, if we define the so-called switching function Φ by $\Phi(t) = 1 + \lambda(t)BN(t)$, then the optimal controls are given as

$$u_*(t) = \begin{cases} 1 & \text{if } \Phi(t) > 0 \\ 0 & \text{if } \Phi(t) < 0 \end{cases}. \tag{13}$$

A priori the control is not determined by the maximum condition at times when $\Phi(t) = 0$. However, if $\Phi(t) \equiv 0$ on an open interval, then also all its derivatives, and thus all derivatives of $\Phi(t)$ must vanish and this may determine the control. Controls of this kind are called *singular* while we refer to the constant controls as *bang* controls. Optimal controls then need to be synthesized from these candidates.

3 Analysis of Extremals - High-Order Conditions

The structure of optimal controls is determined by the switching function and its derivatives. For instance, if $\Phi(t) = 0$, but $\dot{\Phi}(t) \neq 0$, then the control has a switch at time t. In order to analyze the structure of the optimal controls we therefore need to analyze the switching function and its derivatives. The following lemma, which is verified by a direct calculation, allows to calculate first and higher order derivatives of the switching function simply by calculating commutators of matrices.

Lemma 3.1 *Let M be a constant matrix and let $\Psi(t) = \lambda(t)MN(t)$, where N is a solution to the system equation (5) for control u and λ is a solution to the corresponding adjoint equation. Then*

$$\dot{\Psi}(t) = \lambda(t)[A + uB, M]N(t) - aeMN(t), \tag{14}$$

where $[A,M]$ denotes the commutator of the matrices A and M defined as $[A,M] = MA - AM$. $\square$

Note that we have chosen the order in the commutator so that it is consistent with the Lie derivative of the linear vector fields $f(N) = AN$ and $g(N) = MN$. For,

$$[f, g](N) = Dg(N)f(N) - Df(N)g(N) = MAN - AMN = [A, M]N. \tag{15}$$

3.1 Singular Controls

We will show that singular controls in fact are locally minimizing instead of maximizing, hence not optimal. Suppose a control u is singular on a non-empty open interval I. Thus the switching function is constant on I and we get that

$$\dot{\Phi}(t) = \lambda(t)[A, B]N(t) - aeBN(t) \equiv 0. \tag{16}$$

Differentiating once more yields

$$\ddot{\Phi}(t) = \lambda(t)[A + u(t)B, [A, B]]N(t) - ae\left([A, B] + B(A + uB)\right)N(t) \equiv 0. \tag{17}$$

Note that the coefficient multiplying the control u is given by the expression

$$\frac{\partial}{\partial u}\frac{d^2}{dt^2}\frac{\partial H}{\partial u} = \lambda[B, [A, B]]N - aeB^2N \tag{18}$$

evaluated along the extremal lift of the singular control. The singular control is of order 1 on the interval I if this quantity does not vanish on I. In this case the equation (17) can formally be solved for the control and if the corresponding control value is admissible, i.e. has a value between 0 and 1, this defines the singular control. Otherwise the singular arc is not admissible. It is a second-order necessary condition for optimality of a singular arc of order one, the so-called generalized Legendre-Clebsch condition [7], that

$$\frac{\partial}{\partial u}\frac{d^2}{dt^2}\frac{\partial H}{\partial u}(\lambda(t), x(t), u(t)) \geq 0. \tag{19}$$

Since $B^2 = -sB$ and $\dot{\Phi} \equiv 0$ along a singular arc, for this model we have that

$$aeB^2N = -saeBN = -s\lambda[A, B]N. \tag{20}$$

Thus (all quantities are evaluated along the singular lift)

$$\frac{\partial}{\partial u}\frac{d^2}{dt^2}\frac{\partial H}{\partial u} = \lambda\left([B, [A, B]] + s[A, B]\right)N. \tag{21}$$

Direct calculations show that

$$[A, B] = s\begin{pmatrix} 0 & -\beta \\ \alpha & 0 \end{pmatrix}, \qquad [B, [A, B]] = -s^2\begin{pmatrix} 0 & \beta \\ \alpha & 0 \end{pmatrix}. \tag{22}$$

and thus

$$\frac{\partial}{\partial u}\frac{d^2}{dt^2}\frac{\partial H}{\partial u} = s^2\lambda\begin{pmatrix} 0 & -2\beta \\ 0 & 0 \end{pmatrix}N = -2s^2\beta\lambda_1 Q < 0 \tag{23}$$

violating the Legendre-Clebsch condition. Thus all singular arcs locally minimize the objective. Hence we have:

Proposition 3.1 *Singular controls are not optimal.* □

3.2 Bang-bang Controls

Consequently, and although more complicated structures (like for example chattering arcs, which would have an infinite number of switchings,) cannot be excluded a priori, bang-bang controls with only a finite number of switchings become the prime candidates for optimality. However, due to the presence of non-optimal singular arcs, one expects that there exist bang-bang extremals with an arbitrary large number of switchings in a vicinity of this non-optimal singular arc and it therefore

becomes of importance to develop high-order conditions which allow to distinguish between locally optimal and locally non-optimal bang-bang controls. In this section we formulate an algorithm which allows to separate optimal from non-optimal bang-bang controls. This algorithm is based on an earlier construction by Noble and Schättler [14] specifically tailored to the type of problems under consideration. Recently there has been significant activity on the question of high-order necessary and sufficient conditions for optimality of bang-bang controls, specifically the papers by Agrachev, Stefani and Zezza [1] and by Maurer and Osmolovskii [13], and either of these constructions could equally well be employed in the further analysis, but we use the more geometric approach pursued in [14]. We have the following theorem about optimality of bang-bang controls:

Theorem 3.1 *Let u_* be a bang-bang control with switchings at times t_i, $i = 1, \dots, m$, $0 < t_m < \cdots < t_1 < t_0 = T$ and denote the values of the control on the interval (t_i, t_{i-1}) by u_i. Let N_* be the corresponding trajectory and suppose $\Gamma = (N_*, u_*)$ is an extremal pair (control and trajectory) with corresponding multiplier λ_*. Assume that the derivative $\dot{\Phi}_*(t_i)$ of the switching function $\Phi_*(t) = \lambda_*(t)BN_*(t)$ does not vanish at the switching times t_i, $i = 1, \dots, m$. Set $R_0^- = 0$ and for $i = 1, \dots, m$, inductively define*

$$R_i^+ = \exp\left((A + u_i B)^T (t_{i-1} - t_i)\right) R_{i-1}^- \exp\left((A + u_i B)(t_{i-1} - t_i)\right), \tag{24}$$

$$G_i = \frac{1}{\left|\dot{\Phi}_*(t_i)\right|} \left(\lambda_*(t_i)B + N_*^T(t_i)B^T R_i^+\right), \tag{25}$$

$$R_i^- = \left(B^T \lambda_*^T(t_i) G_i + R_i^+\right) \left(Id + \frac{BN_*(t_i)G_i}{1 - G_i BN_*(t_i)}\right). \tag{26}$$

Here we have $G_i BN_*(t_i) \neq 1$ if and only if $\left|\dot{\Phi}_*(t_i)\right| \neq s + N_*^T(t_i)B^T R_i^+ BN_*(t_i)$. If for $i = 1, \dots, m$, we have that

$$\left|\dot{\Phi}_*(t_i)\right| > s + N_*^T(t_i)B^T R_i^+ BN_*(t_i), \tag{27}$$

then u_* is a strong relative minimum for the 2-compartment model. If the transversality condition

$$\left|\dot{\Phi}_*(t_i)\right| > s + N_*^T(t_i)B^T R_i^+ BN_*(t_i), \tag{28}$$

is satisfied for $i = 1, \dots, \ell - 1$, but

$$\left|\dot{\Phi}_*(t_i)\right| < s + N_*^T(t_i)B^T R_i^+ BN_*(t_i), \tag{29}$$

then u_* is optimal for initial times $t > t_\ell$, but is no longer optimal for initial times $t \leq t_\ell$.

The proof of this theorem is rather lengthy. The calculations are based on the results in [14] for a general system and the arguments are similar to those of [8] for a model for cancer chemotherapy, but with several modifications due to the structure of the equations. A complete proof of this theorem can be found in [10]. Here instead we will give an application of the algorithm presented above to analyze the optimality of specific extremals in the simulations given below.

4 Simulations

By using our version of the gradient method for the calculation of extremal bang-bang controls developed earlier by Duda [3], we ran some simulations for the model presented here for a therapy interval of length $T = 2$ with the following parameter values taken from [5]: $\alpha = 5.643$, $\beta = 0.48$, $\gamma = 1.47$, $\delta = 0$, and $\rho = 0.164$. The initial conditions were also selected as $P_0 = Q_0 = 1$ and in the objective we took $r_1 = r_2 = 1$, but varied the coefficient a at the integral term of the states. We include two simulation results for $a = 2$ and $a = 1$.

The controls and corresponding trajectories are presented in the figures below. The dashed line in the graphs of the states gives the evolution of Q while the regular line gives the state P. In both cases the controls are bang-bang with one switching (from no dose to full dose.) At the corresponding switchings the transversality conditions (27) were satisfied (with values 1.0902 in case of $a = 2$ and 2.1769 in case of $a = 1$). However, in the case $a = 1$ the switching time is earlier, at $\tau = 0.33$, versus

$\tau = 0.63$ in the case of $a = 2$. This is consistent with the fact that more "weight" put on the bone marrow cells count delays the time at which the full dose can be applied.

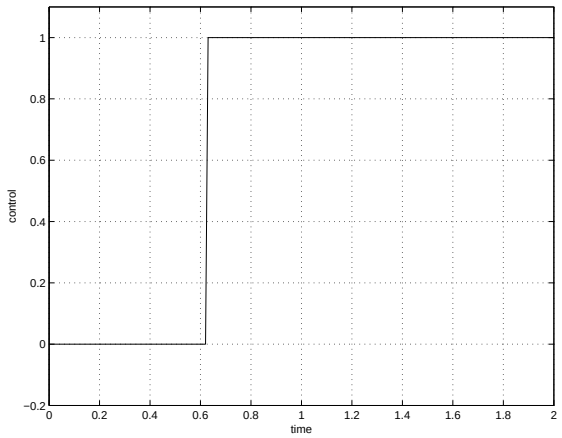

Fig. 1: Control for $a = 2$

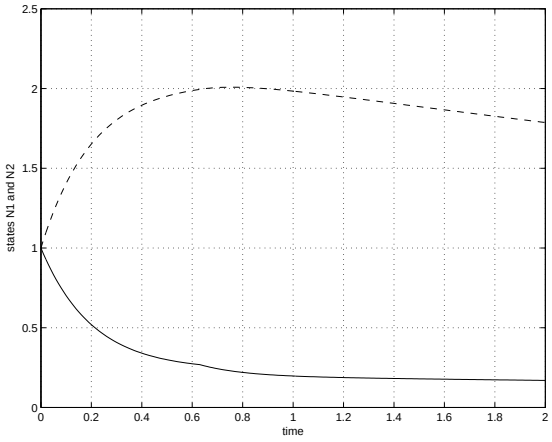

Fig. 2: States P and Q for $a = 2$

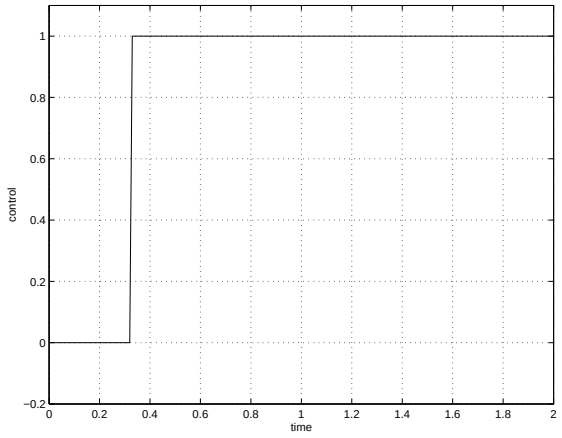

Fig. 3: Control for $a = 1$

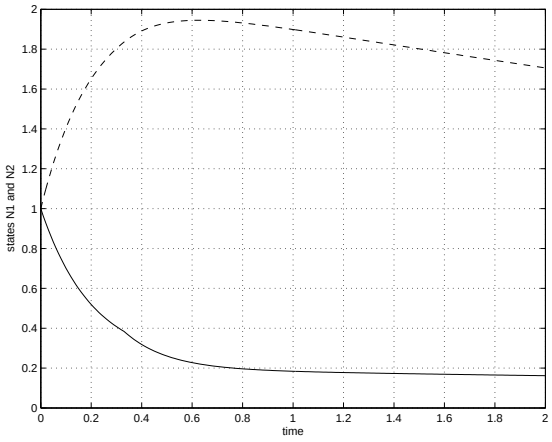

Fig. 4: States P and Q for $a = 1$

5 Comparisons and Conclusion

The simulations above exhibit some similarities to the ones obtained with the use of an L^2-objective. Also, in runs performed for the same time interval as in [5], ($T = 14$), the solutions in both cases start with a no dose period which in the case of an L^1 -objective lasts longer, but then the control switches to the full dose whereas in the L^2-objective case the control starts earlier increasing slowly reaching a full dose only at the terminal time. Thus in the case of an L^1-objective analyzed here, a full dose is applied more than just at the final time and partial doses are not optimal. This would agree with experimental and clinical data on the model, but only to some extent. All the controls we obtained in our simulations have only one switching which means that in one therapy interval there is only one "full-dose session" rather than *"short drug pulses at appropriate intervals"* as clinical data indicate. However, it is our belief that combining several short therapy intervals one should be able to achieve the desired effect. Another approach would be to maximize an objective which measures the bone marrow not just at the final time, but at some intermediate times as well. All of this will be pursued in future research on the topic.

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