On a Synthesis of Controls for a Mathematical Model of Cancer Chemotherapy

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Abstract

A simple mathematical model for cancer chemotherapy from the literature is given by an optimal control problem over a finite horizon with control constraint and dynamics given by a bilinear system. We describe some aspects of its synthesis of optimal controls for the cases of an L_1- respectively L_2-objective in the control. In the first case optimal controls are bang-bang while a saturated smooth control is optimal for the quadratic objective.

1 Introduction.

Optimal control methods have been widely used in models from mathematical biology [3] and there always has been a consistent interest in mathematical models for chemotherapy (e.g., [5, 7, 9, 10]). A recent paper analyzes optimal control of chemotherapy for HIV [6]. Many of these models are based on the cell-cycle dynamics [14]. A recent paper by Fister and Panetta [4] proposes and analyzes a mathematical model in which both the grug dose and bone marrow are maximized over the therapy interval. Here we discuss a mathematical model based on papers by Kimmel and Swierniak [11, 12, 14]. We briefly describe the model and some of the biology behind it. In the model the *state* variable is given by the *number of cancer cells* and the *control* is the *drug dosage*. The active ingredient in the drug is a cytostatic agent which kills cancer cells and healthy cells alike. The goal is to maximize the number of cancer cells which the agent kills while keeping the toxicity to the normal tissues acceptable. The dynamics of the cell cycle indeed allows for such a feature by having the agents be active at different stages. The cell cycle is modeled in the form of *compartments* which describe the different cell phases or, in simplified models, combine cell cycles into clusters of phases. By modeling the state equation after cell cycle kinetics, this cell cycle becomes the object of control [12, 14]. Each cell passes through a sequence of phases from cell birth to cell division. Starting point is a growth phase G_1, after which the cell enters a phase S where DNA synthesis occurs. Then a phase G_2 takes place in which the cell prepares for mitosis or phase M. Here cell division occurs. Each of the two daughter cells can either reenter phase G_1 or for some time may simply lie dormant in a separate phase G_0 until reentering G_1, thus starting the entire process all over again.

The simplest mathematical models which describe optimal control of cancer chemotherapy treat the entire cell cycle as one compartment. Many of these single compartment models like for instance the classical "Gompertzian" model have been analysed using the Maximum Principle [11, 14], but the solutions are not very informative due to an over-simplified model. Both the mathematical biology and medical community realised that more precise models, i.e., multi-compartmental models, need to be considered. Of these still the simplest and at the same time most natural are two- and three-compartment models, i.e., models which divide the cell cycle into two and three compartments, respectively. In various papers [13, 14] these models have been analysed with the Maximum Principle for the case of an L_1-objective and large quantitative studies of the dynamics of these systems have been done [2]. However, typically only extremals which satisfy the conditions of the Maximum Principle are computed numerically. No analytic solutions or results about the qualitative structure of optimal controls are obtained. Using an L_1-objective which is linear in the control generates bang-bang and singular controls as extremals, but in the literature the question about optimality of the singular arcs is left unanswered. We will show below that singular extremals violate the Legendre-Clebsch condition and thus are not optimal. Optimal controls are bang-bang, but we need to defer to a later publication for a more precise analysis of the switchings. In this paper we also briefly introduce a second objective which is quadratic in the control, i.e. an L_2-type criterion. A model of this kind has not been considered in the literature on cancer chemotherapy,

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but it has mathematical advantages without violating the underlying modelling aspects. In this case the optimal controls are given by a saturated smooth function.

2 The compartment model

(This review is based on [14].) In these models the number of cancer cells in the i-th compartment at time t is denoted by $N_i(t)$, the average flow rates of cells entering the compartment is denoted by $x_i^+(t)$ and those exiting by $x_i^-(t)$. The change in the number of cells in compartment i is therefore given by $\dot{N}_i(t) = x_i^+(t) - x_i^-(t)$. The transit times of cells through phases of the cell cycle vary, particularly in malignant cells. The simplest models use an exponential distribution to model the transit times. For this model the expected number of cells exiting from compartment i is given by $x_i^-(t) = a_i N_i(t)$, where a_i is the parameter of the exponential distribution related to the inverse of the transit time. Thus with $x_i^+(t) = x_{i-1}^-(t)$ denoting the cells flowing in from the $(i-1)$-th compartment we obtain

$$\dot{N}_i(t) = -a_i N_i(t) + a_{i-1} N_{i-1}(t). \tag{1}$$

Cell division is represented by a factor 2 in the equation which links the first with the last compartment:

$$\dot{N}_1(t) = -a_1 N_1(t) + 2a_n N_n(t). \tag{2}$$

Hence, the unperturbed dynamics of the cell cycle, or the number of cells in a particular compartment, can be represented by a system of ordinary differential equations if there are no external stimuli present. A drug treatment influences the cell cycle in many possible ways. Here we only consider two simple and basic features and their models:

1. Cell Arrest: The outflux of cells from compartment i at time t is reduced by a factor of $v(t)$, $0 < v_{\min} < v(t) \leq 1$. The cells that remain in compartment i are considered to be under cell arrest:

$$\dot{N}_i(t) = -v(t) a_i N_i(t) + a_{i-1} N_{i-1}(t) \tag{3}$$

and

$$\dot{N}_{i+1}(t) = -a_{i+1} N_{i+1}(t) + v(t) a_i N_i(t). \tag{4}$$

2. Cell Killing: Only a fraction $1-u(t)$ of the cells exiting compartment i at time t are viable, $0 \leq u(t) \leq 1$. We assume the rest of the cells are no longer alive or in the system, so $\dot{N}_i(t)$ is given by equation (1) and

$$\dot{N}_{i+1}(t) = -a_{i+1} N_{i+1}(t) + (1 - u(t)) a_i N_i(t). \tag{5}$$

The implications of cell-killing are obvious; cell arrest tries to slow down the growth of malignant cells by preventing cells from reaching the phase where cell division occurs.

2.1 A two compartment model with a single G_2/M specific killing agent

Taking into account only the phase sensitivity of the drug as discussed in [14], the cell cycle is broken into two compartments of which the first compartment combines the G_1 and S phases while the second contains the G_2 and M phases. It is assumed that the cytotoxic agent is specific to the G_2/M phases. This makes sense from a biological standpoint for a couple reasons. First, in mitosis M the cell becomes very thin and porous; hence, the cell is more vulnerable to an attack while there will be a minimal effect on the normal cells. Second, chemotherapy during mitosis will prevent the creation of daughter cells. The control u represents the dose of the drug administered with the value $u = 0$ corresponding to no treatment and $u = 1$ corresponding to a maximum dose. It is assumed that the dose stands in a direct relation to the fraction of cells which are being killed in the G_2/M phase. Therefore only the fraction $(1-u)a_2N_2$ of cells reenters phase G_1/S and undergoes cell division. All cells a_2N_2 leave compartment G_2/M. Thus the mathematical model becomes

$$\dot{N}_1 = -a_1 N_1 + 2(1-u) a_2 N_2, \qquad N_1(0) = N_{10} > 0, \tag{6}$$

$$\dot{N}_2 = a_1 N_1 - a_2 N_2, \qquad N_2(0) = N_{20} > 0. \tag{7}$$

In the literature [11, 14] the following performance index is used:

$$J = r_1 N_1(T) + r_2 N_2(T) + \int_0^T u(t)\,dt \to \min. \tag{8}$$

In the objective the coefficients r_i are weighing factors and the penalty term $r_1N_1(T) + r_2N_2(T)$ represents an average of the total number of cancer cells at the end of an assumed fixed therapy interval $[0, T]$. The Lagrangian models the cumulative negative effects of the treatment, i.e. the control u, the drug administered, is also used to model the negative effect of the drug on the normal tissues or its toxicity. Although u can be connected with the fraction of ineffective cell-divisions, there seems to be no compelling biological justification why an L_1-norm on the control should be used to model the negative drug effects. From a mathematical point of view it seems more reasonable to use an L_2-objective which will generate a strictly convex Hamiltonian. We will consider both problems and compare optimal solutions. Thus we use as performance indices

$$J_k = r_1 N_1(T) + r_2 N_2(T) + \frac{1}{k} \int_0^T u^k(t)\,dt \to \min \tag{9}$$

with $k = 1$ and $k = 2$.

2.2 A three compartment model with cell arrest in S and a single G_2/M specific killing agent

In this model cell arrest in phase S is considered and cells are released when a second G_2/M-specific cytotoxic agent is at a maximum destroying potential.

This will allow better protection for the normal cells since they will be less dispersed, thus travelling faster through the G_2/M phases. As in the two compartment model cell division in the G_2/M phases is affected by a cytostatic agent u (with $u = 0$ corresponding to no dose being administered) and the fraction of ineffective cell divisions is u. Another cytostatic agent v changes the transit times through phase S. Thus the control problem becomes to find u and v, $0 \leq u \leq 1$, and $0 < v_{\min} \leq v \leq 1$, to minimize the objectives $(k = 1, 2)$

$$J_k = r_1 N_1(T) + r_2 N_2(T) + r_3 N_3(T) + \int_0^T \frac{1}{k} u^k(t) dt \tag{10}$$

subject to

$$\dot{N}_1 = -a_1 N_1 + 2(1-u) a_3 N_3, \qquad N_1(0) = N_{10} > 0, \tag{11}$$

$$\dot{N}_2 = -v a_2 N_2 + a_1 N_1, \qquad N_2(0) = N_{20} > 0, \tag{12}$$

$$\dot{N}_3 = -a_3 N_3 + v a_2 N_2, \qquad N_3(0) = N_{30} > 0. \tag{13}$$

3 The structure of the mathematical model

The dynamics of both the two- and three-compartment model is described by a *bilinear system*. If we set $N = (N_1, \ldots, N_n)$ and consider a multi-dimensional control variable $u = (u_1, \ldots, u_m)$, then the general form of the dynamics is given by

$$\dot{N}(t) = (A + \sum_{i=1}^{m} u_i B_i) N(t), \tag{14}$$

where A and the B_i, $i = 1, \ldots, m$, are fixed $(n \times n)$-matrices. For instance, for the two compartment model we have $m = 1$ and the matrices A and B are given by

$$A = \begin{pmatrix} -a_1 & 2a_2 \\ a_1 & -a_2 \end{pmatrix} \quad \text{and} \quad B = \begin{pmatrix} 0 & -2a_2 \\ 0 & 0 \end{pmatrix}.$$

For any admissible control $u(\cdot)$ defined over the interval $[0, T]$ the right-hand side of the differential equation (14) is linearly bounded and it follows from well-known results about ordinary differential equations that the corresponding trajectory (i.e. solution to the dynamics) exists on all of $[0, T]$. In general, if we set $r = (r_1, \ldots, r_n)$, then the optimal control problem Σ is to minimize

$$J_k(u) = rN(T) + \int_0^T \frac{1}{k} (u_1)^k (t) dt \tag{15}$$

over all Lebesgue measurable functions $u = (u_1, \ldots, u_m)$ for which each component takes values in a specified compact interval $[\alpha_i, \beta_i] \subset [0, \infty)$, $i = 1, \ldots, m$, subject to the dynamics (14) and given initial condition $N(0) = (N_{10}, \ldots, N_{n0})$.

Only states $N(t)$ for which each coordinate is positive are meaningful. It follows from the general form of the compartment model, and is easily verified directly for the two- and three-compartment models given above, that $\dot{N}_i(t)$ qualitatively has the structure

$$\dot{N}_i(t) = -\beta_{ii}(t) N_i(t) + \sum_{i \neq j} \beta_{ij}(t) N_j(t) \tag{16}$$

where, regardless of the admissible control used, all the functions β_{ij}, $i, j = 1, \ldots, n$, are non-negative while the diagonals $\beta_{ii}(t)$, $i = 1, \ldots, n$, are positive. It can easily be seen from these conditions that, if each coordinate of $N(t_0)$ is positive, then all coordinates of $N(t)$ remain positive for all times $t \geq t_0$. Hence *the physically meaningful part of the state space*,

$$\mathbb{P} = \{N \in \mathbb{R}^n : N_i > 0 \text{ for } i = 1, \ldots, n\},$$

is positively invariant for the control system Σ. It is therefore not necessary to add this condition as a state-space constraint.

If u_* is an optimal control defined over the interval $[0, T]$, then it follows from the Pontryagin Maximum Principle that there exist a constant $\lambda_0 \geq 0$ and an absolutely continuous function λ, which we write as row-vector, $\lambda : [0, T] \to (\mathbb{R}^n)^*$, such that $(\lambda_0, \lambda(t)) \neq (0, 0)$ for all $t \in [0, T]$, which satisfy the following conditions:
(a) adjoint equation and transversality condition:

$$\dot{\lambda} = -\lambda (A + \sum_{i=1}^{m} u_i B_i), \qquad \lambda(T) = \lambda_0 r, \tag{17}$$

(b) minimum condition: the optimal controls minimize the Hamiltonian H over the control set,

$$H = \frac{\lambda_0}{k} (u_1)^k + \lambda (A + \sum_{i=1}^{m} u_i B_i) N. \tag{18}$$

It follows that λ_0 cannot vanish for this model (otherwise also $\lambda(T) = 0$ and thus $\lambda(t) \equiv 0$ contradicting the nontriviality of the multipliers) and therefore without loss of generality we can normalize $\lambda_0 = 1$. Thus the problem is normal. Furthermore, the first octant in the dual space,

$$\mathbb{P}^* = \{\lambda \in (\mathbb{R}^n)^* : \lambda_i > 0 \text{ for } i = 1, \ldots, n\},$$

is negatively invariant under the flow of the adjoint equation (17). This again follows from the structure of the matrix which was already exploited to get the positve invariance of $\mathbb{P}$ under the dynamics. Thus, since $N_0 \in \mathbb{P}$ and $r \in \mathbb{P}^*$, we have

Theorem 3.1 *All the states x_i and costates λ_i will be positive over $[0, T]$.*

Even for low-dimensional systems the structure of optimal controls can be quite complicated. In the literature on the two- and three-compartment models so far only a preliminary analysis of optimal trajectories has been undertaken. In [2] extremals for specific parameter values are calculated, but no attempt is made to construct the optimal field as it would be done in a regular synthesis. Furthermore, these numerical results are almost exclusively focussed on the analysis of bang-bang trajectories. The existence of singular arcs is only observed without analysis of their optimality. We will provide such an analysis below excluding them from optimality.

We aim at a qualitative understanding of the solution to the models for cancer chemotherapy in terms of Lie-bracket relationships depending on the relevant parameters a_i of the model. We achieve this by constructing a parametrized family of (normal) extremals in the sense defined in [8] by integrating the dynamics and the adjoint equation backward from the terminal time T with the terminal condition $x(T) = p \in \mathbb{P}$ being a free parameter. (Once this is done, however, the positivity of the trajectories needs to be enforced. Trajectories which have negative coordinates started at inadmissible terminal states.) For the moment, denoting the corresponding minimizing control by $u_* = u(t,p)$, $0 \le t \le T$, then the dynamics for the system and adjoint equation are determined as the solution to the terminal value problem

$$\dot{x}(t,p) = (A + \sum_{i=1}^{m} u_i(t,p)B_i)x(t,p), \qquad x(T,p) = p, \tag{19}$$

$$\dot{\lambda}(t,p) = -\lambda(t,p)(A + \sum_{i=1}^{m} u_i(t,p)B_i), \qquad \lambda(T,p) = r. \tag{20}$$

The crucial step is to determine the control $u(t,p)$ depending on the terminal value of the trajectory. Here it matters whether $k = 1$ or $k = 2$ and we consider these cases separetely, but only for the two-compartment model. Essentially, if the flow map σ defined by

$$\begin{aligned} \sigma : [0,T] \times \mathbb{P} &\to [0,T] \times \mathbb{P}, \\ (t,p) &\mapsto \sigma(t,p) = (t, x(t,p)) \end{aligned} \tag{21}$$

is a diffeomorphism away from switching surfaces and if mild additional transversality conditions are satisfied at the switching surfaces [8], a regular synthesis in the sense of Boltyansky [1] can be constructed and these controls are optimal. Below we will briefly outline some aspects of such a construction.

4 The case of an L_1-objective

For the two-compartment model the Hamiltonian is given by

$$H = u + \lambda(A + uB)N$$

and (18) determines the optimal control as

$$u^*(t,p) = \begin{cases} 0 & \text{if } \Phi(t,p) > 0 \\ 1 & \text{if } \Phi(t,p) < 0 \end{cases} \tag{22}$$

where Φ denotes the so-called *switching function* given by

$$\Phi(t,p) = 1 + \lambda(t,p)BN(t,p). \tag{23}$$

A priori the control is not determined by the minimum condition at times where $\Phi(t,p) = 0$. However, if $\Phi(t,p)$ vanishes on an open interval, also all its derivatives 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.

For this model a singular arc exists which is of order 1, but violates the Legendre-Clebsch condition and therefore is not optimal. Nevertheless, the existence of this arc is crucial for the synthesis, and, in fact, its non-optimality complicates matters. Typically a synthesis around an optimal singular arc is quite simple consisting of short concatenations with bang trajectories leading to and from the singular arc using it like a fast turnpike. Intuitively one can think of the singular arc in this case as the limit of trajectories with an increasing number of switchings when these switches improve the objective. If the singular arc is not optimal, then heuristically the opposite happens, more switchings slow the system down. But it is not clear apriori how many switchings will be necessary for particular data and the number of switchings can be high in certain regions of the state-space.

To analyze the structure of the optimal controls we need to consider the switching functions and its derivatives. In general, if M is a matrix and

$$\Psi(t) = \lambda(t,p)Mx(t,p), \tag{24}$$

then a direct calculation verifies that

$$\dot{\Psi}(t) = \lambda(t,p)[A + uB, M](t,p) \tag{25}$$

where $[A + uB, M]$ denotes the commutator of the matrices defined here as

$$[A + uB, M] = M(A + uB) - (A + uB)M. \tag{26}$$

This definition is consistent with a definition of the Lie-bracket of vector fields f and g as

$$[f,g](x) = Dg(x)f(x) - Df(x)g(x). \tag{27}$$

Equation (25) allows to calculate higher order derivatives of the switching function simply by calculating commutators of matrices (i.e. Lie derivatives of linear vector fields). In particular,

$$\dot{\Phi}(t,p) = \lambda(t,p)[A,B]x(t,p), \tag{28}$$

$$\ddot{\Phi}(t,p) = \lambda(t,p)[A+u(t,p)B,[A,B]]x(t,p). \tag{29}$$

Direct calculations verify the following relations for the two-compartment model:

$$[A,B] = 2a_1a_2\begin{pmatrix} -1 & 0 \\ 0 & 1 \end{pmatrix} + (a_1-a_2)B, \tag{30}$$

$$[A,[A,B]] = (a_1-a_2)[A,B] + 4a_1a_2B + 4a_1^2a_2\begin{pmatrix} 0 & 0 \\ 1 & 0 \end{pmatrix}, \tag{31}$$

$$[B,[A,B]] = -4a_1a_2B. \tag{32}$$

Along a singular arc we have

$$0 \equiv \Phi(t,p) = \dot{\Phi}(t,p) = \ddot{\Phi}(t,p) \tag{33}$$

and thus

$$u_{\sin}(t,p) = -\frac{\lambda(t,p)[A,[A,B]]x(t,p)}{\lambda(t,p)[B,[A,B]]x(t,p)} \tag{34}$$

provided $\lambda(t,p)[B,[A,B]]x(t,p)$ does not vanish. Since $\Phi(t,p) = 1+\lambda(t,p)Bx(t,p) \equiv 0$, we have

$$\lambda(t,p)[B,[A,B]]x(t,p) = -4a_1a_2\lambda(t,p)Bx(t,p) = 4a_1a_2 > 0. \tag{35}$$

However, it is a necessary condition for optimality of a singular arc, the so-called Legendre-Clebsch condition, that $\lambda(t,p)[B,[A,B]]x(t,p)$ must be non-positive along an optimal singular arc. Thus

Corollary 4.1 *Singular controls are not optimal.*

Consequently bang-bang trajectories become the prime candidates for optimality. But it is not possible to restrict the number of switchings apriori. In fact, the Lie-bracket relations in conjunction with the positivity of state and adjoint variables indicate trajectories with many switchings.

The question about the number of switchings can easily be settled for a particular value p by integrating backward from the terminal time T. It follows from the transversality condition that

$$\Phi(T,p) = 1 + rBp = 1 - 2a_2r_1p_2. \tag{36}$$

Hence for time T the optimal control is given by

$$u(T,p) = \begin{cases} 1 & \text{if } 2a_2r_1p_2 > 1 \\ 0 & \text{if } 2a_2r_1p_2 < 1 \end{cases} \tag{37}$$

while it still needs to be determined on the set where $\Phi(T,p) = 0$, i.e. when $p_2 = p_2^* = \frac{1}{2a_2r_1}$. For this it suffices to consider the derivative of the switching function,

$$\begin{aligned}\dot{\Phi}(T,p) &= r[A,B]p \\ &= 2a_2\left(-a_1r_1p_1 + [a_1(r_2-r_1)+a_2r_1]\,p_2\right)\end{aligned} \tag{38}$$

If $\dot{\Phi}(T,p) < 0$, then $u(T,p) = 0$ while $u(T,p) = 1$ if $\dot{\Phi}(T,p) > 0$. If $a_1(r_2-r_1)+a_2r_1 \le 0$, then we have $\dot{\Phi}(T,p_1,p_2^*) < 0$ for all $p_1 > 0$ and thus $u(T,p_1,p_2^*) = 0$ for all admissible p_1. If $a_1(r_2-r_1)+a_2r_1 > 0$, then there exists a unique point

$$p_1 = p_1^* = \frac{a_1(r_2-r_1)+a_2r_1}{2a_1a_2r_1^2} > 0 \tag{39}$$

where also $\dot{\Phi}(T,p^*) = 0$. In this case

$$u(T,p) = \begin{cases} 1 & \text{if } p_1 < p_1^* \\ 0 & \text{if } p_1 > p_1^* \end{cases}. \tag{40}$$

The parameter value $p = p^*$ corresponds to the unique point in the terminal manifold where a singular arc can end. Although this arc is not optimal, it still determines the structure of the synthesis around (T,p^*). Figures 1-3 show how the number of switchings increases while the amplitude of the switching function diminshes (it is of the order 10^{-5} in Fig. 3) as the parameter p approaches p^*. The numerical values used in the simulations were $a_1 = .197$, $a_2 = .356$, $r_1 = 6.94$ and $r_2 = 3.94$. The values for the terminal point p are given in Table 1. The terminal value chosen in Fig. 3 agrees with p_* in its first four digits.

	p_1	p_2
Fig. 1	.2785	.2000
Fig. 2	.2782	.2034
Fig. 3	.2782	.2024

Table 1: Terminal Points

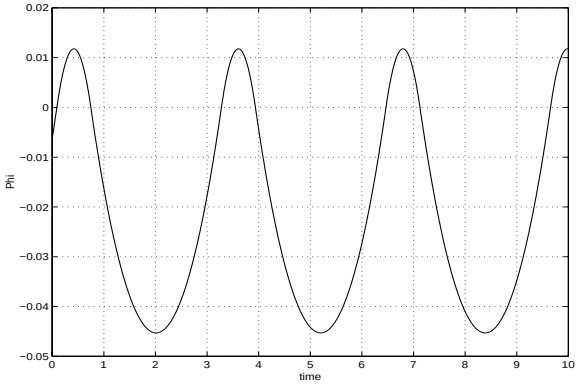

Figure 1: p closer to p^*

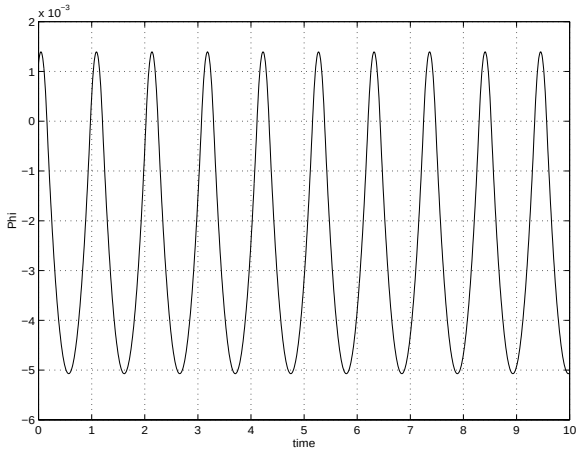

Figure 2: p really close to p^*

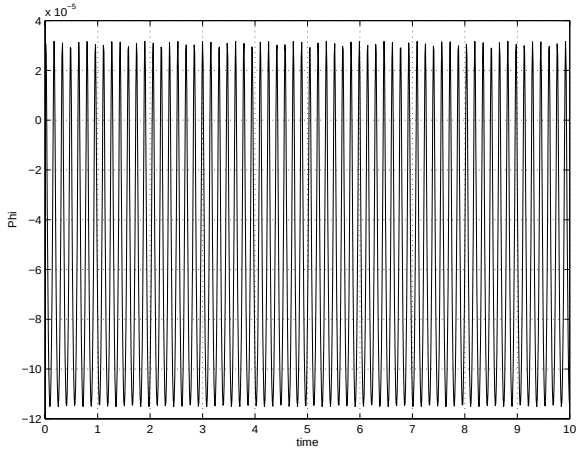

Figure 3: p almost equal p^*

5 The case of an L_2-objective

In this case the Hamiltonian is given by

$$\begin{aligned} H &= \frac{1}{2}u^2 + \lambda(A + uB)N \\ &= \frac{1}{2}u^2 - 2a_2\lambda_1(t,p)N_2(t,p)u(t,p) \end{aligned} \tag{41}$$

and thus the optimal control is determined as

$$u^*(t,p) = sat\left[2a_2\lambda_1(t,p)N_2(t,p)\right] \tag{42}$$

where

$$sat\left[x\right] = \begin{cases} -1 & \text{if } x < -1 \\ x & \text{if } |x| < 1 \\ 1 & \text{if } x > 1 \end{cases} \tag{43}$$

denotes the standard saturation-function. Since we always have $\lambda_1(t,p)N_2(t,p) > 0$ only the upper saturation becomes effective. However, in this problem with control constraint saturation will occur and, similarly as in the case of an L_1-criterion, now the control switches between its smooth unsaturated value and $u \equiv 1$.

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