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IRREGULARITY IN SCHEDULING OF CANCER CHEMOTHERAPY

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The paper presents a problem of optimal control of a bilinear system in the plane which has irregular properties although the optimization problem is similar to those ones which admit the "regular synthesis" (Sussman, 1987c). The number of switchings derived from the maximum principle can be arbitrarily large in any time interval and multiple solutions to the two-point boundary-value problem are possible. An example from modelling cancer chemotherapy was derived to demonstrate irregularities.

1. Introduction

It is well known that the maximum principle (Pontryagin *et al.*, 1962), although being one of the most powerful tools for solving optimal control problems, gives only the necessary optimality conditions. Therefore, a considerable effort has been made to identify problems in which the maximum principle states both the necessary and sufficient conditions of their optimality. An important class of such problems is time-optimal control of non-linear systems in the plane. The optimal control is of bang-bang type and it was proven in (Sussman, 1982; 1987a; 1987b; 1987c), provided that some additional conditions are satisfied, that the optimal control admits the "regular synthesis", i.e. the number of switchings is (locally) limited and the maximum principle gives a unique optimal solution.

In this paper we present a problem of optimal control of a bilinear system in the plane which although looks similar to those discussed in (Sussman, 1982; 1987a; 1987b; 1987c), has irregular properties. The number of switchings of trajectories derived from the maximum principle can be arbitrarily large and multiple solutions are possible.

Our example was derived in order to demonstrate irregularities and it comes from modelling cancer chemotherapy (Swan, 1990; Świerniak, 1989). Moreover, the multiple solutions given by the maximum principle seem to have some practical importance. Although in the family of solutions usually only one is optimal, the other solutions are very close to the optimal one in the sense of the value of performance index. Then, they form a family of suboptimal solutions, so it is be reasonable to apply one of them if additional factors, such as drug dynamics are taken into account.

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2. Cancer Chemotherapy Model

We consider the second order, bilinear model of cancer chemotherapy derived in (Świerniak, 1989). The model consists of two compartments composed of the phases of cancer cell proliferation cycle, namely $G_1 + S$ and G_2M. Its block diagram is presented in Fig. 1.

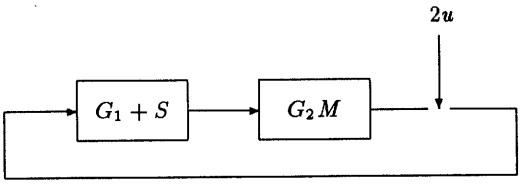

Fig. 1. Block diagram of the cancer cell proliferation cycle with two bilinear compartments.

The citotoxic agent is assumed to be phase specific, it affects only the cells leaving G_2M.

The equations of the model are bilinear:

$$\begin{aligned} \dot{N}_1(t) &= -a_1 N_1(t) + 2u(t)a_2 N_2(t), \qquad N_1(0) = N_{10} \\ \dot{N}_2(t) &= a_1 N_1(t) - a_2 N_2(t), \qquad N_2(0) = N_{20} \end{aligned} \tag{1}$$

with $N_1(t)$ and $N_2(t)$ representing average numbers of cancer cells in $G_1 + S$ and G_2M at time instant t, the control $u(t)$ is the killing effect of a citotoxic drug (i.e. the fraction of cells able to survive after the drug was used) $0 \leq u(t) \leq 1$, where $u(t) = 0$ means that all cells leaving G_2M are killed, while $u(t) = 1$ that no drug was used.

Equation (1) can be expressed as one state equation

$$\dot{N}(t) = [A + Bu(t)]N(t), \qquad N(0) = N_0 \tag{2}$$

where

$$N(t) = \begin{bmatrix} N_1(t) \\ N_2(t) \end{bmatrix}, \qquad N_0 = \begin{bmatrix} N_{10} \\ N_{20} \end{bmatrix} \tag{3}$$

and the matrices A and B are composed of the model parameters:

$$A = \begin{bmatrix} -a_1 & 0 \\ a_1 & -a_2 \end{bmatrix}, \qquad B = \begin{bmatrix} 0 & 2a_2 \\ 0 & 0 \end{bmatrix} \tag{4}$$

For model (2) the problem of reaching the desired terminal state $N(T_H) = N_1$ from a given initial state $N(0) = N_0$ belongs to the class described in (Sussan, 1982; 1987a; 1987b; 1987c) and admits a regular synthesis. Of course, the requirement $N(T_H) = N_1$ means that terminal average numbers of cancer cells should be made sufficiently small. However, in cancer chemotherapy there is another factor which

must be taken into account, namely the negative cumulated effect of citotoxic drugs to normal tissues. Then, it is reasonable to minimize the following performance index:

$$J = r_H^T N(T_H) + \int_0^{T_H} (1-u)\,\mathrm{d}t \tag{5}$$

which reflects the compromise between two effects. Its first term is a penalty for the terminal numbers of cancer cells, while the other represents the cumulated negative effect of the citotoxic drug. In formula (5) $N(T_H)$ is a final state vector representing average numbers of cells in the proliferation cycle, r_H^T – a weighting vector, T_H – a given control horizon (the superscript T denotes transposition).

The necessary conditions of the optimality for the control of (2) with the performance index (5) given by the Pontryagin maximum principle (Pontryagin *et al.*, 1962) lead to the two-point boundary-value problem (TPBVP) of the following form:

i) conjugate equations:

$$\dot{N}(t) = [A + Bu(t)]N(t) \tag{6}$$

$$\dot{p}(t) = -[A + Bu(t)]^T p(t) \tag{7}$$

ii) switching rule:

$$u(t) = \begin{cases} 0 & \text{if} \quad p^T(t)BN(t) > 1 \\ 1 & \text{if} \quad p^T(t)BN(t) < 1 \end{cases} \tag{8}$$

iii) boundary conditions:

$$N(0) = N_0, \qquad p(T_H) = r_H \tag{9}$$

In equation (7) $p(t)$ is a two-dimensional costate vector, the switching rule (4) follows from the form of the performance index (5). In our further considerations we do not assume that matrices A and B are of special form (4). However we make another, quite restrictive, assumption that both matrices A and $A+B$ have real, distinct eigenvalues and that the commutator matrix $BA - AB$ is non-singular. Note that this condition is satisfied when matrices A and B are given by (4) (with $a_1 \neq a_2$).

When solving the TPBVP (6)–(9) with the use of numerical algorithms (Mohler, 1973), for system (2) with coefficients coming from some biomedical experiments, a solution with exactly one switching is always obtained. It is either the optimal solution or the local minimum, depending on the initial conditions of the algorithm.

In what follows we present an analytical approach to the TPBVP (6)–(9) which exploits some symmetry relations between the trajectories of the Hamiltonian system (6)–(8). Using the symmetries of the TPBVP we derive an algorithm which enables us to find *all* the solutions.

3. Symmetries in the TPBVP. Periodic Solutions

We call the dynamical system given by equations (6)–(8) the *Hamiltonian system*. The trajectories of (6)–(8) with $u(t) = 0$ are called *killing trajectories*, and those with $u(t) = 1$ — *rest trajectories*. At first consider the simplified situation when killing and rest trajectories are analyzed separately. One can observe that if we do not take switchings into account, i.e. we consider only conjugate equations (6)–(7) with constant $u(t)$ equal to 0 or 1, then this system is invariant under the two parametric group of scaling transformations; if $N(t)$, $p(t)$ is the solution, then the same is true for $\alpha N(t)$, $\beta p(t)$, α, $\beta \geq 0$. The invariance enables us to reduce the dimension of the system, which is 4, by 2. The standard method is to use polar coordinates ϕ_N, ϕ_p, R_N, R_p, where ϕ_N, ϕ_p are polar angles and R_N, R_p – polar radii of the vectors $N(t), p(t)$, and to represent solutions of (6)–(7) on the (two-dimensional) torus $\phi_N - \phi_p$. The situation is very simple. It is possible to plot "portraits" of the trajectories (killing and rest) on the torus $\phi_N - \phi_p$. The information about the radii can be obtained by integration along these trajectories.

In contrast to the simplified situation described above, in the "real" problem, killing and rest trajectories cannot be considered separately. There are switchings between killing and rest which depend, as it follows from (8), on the value of the switching function $f_s(N,p)$:

$$f_s(N,p) = p^T(t)BN(t) \tag{10}$$

The value of the switching function (10) is *not* invariant under the two parametric group of scaling transformations. Therefore, the torus $\phi_N - \phi_p$ is "too poor" to represent the trajectories of the Hamiltonian system (6)–(8). However, it is possible to define some characteristic points and regions on the torus $\phi_N - \phi_p$ which on one hand, are related to the properties of trajectories of (6)–(8) and on the other, are *invariant* under the two parametric group of scaling transformations. Their detailed description is given in (Świerniak and Polański, 1994). Here we recall only those which are important for the subsequent discussion.

Calculating the derivative of f_s along trajectories of (6)–(8) we obtain

$$\frac{\mathrm{d}}{\mathrm{d}t} f_s = p^T(t)(BA - AB)N(t) \tag{11}$$

It is then easily seen that the sets

$$Df_0 = \left\{\phi_N, \phi_p : \frac{\mathrm{d}}{\mathrm{d}t} f_s = 0\right\} \tag{12}$$

$$\mathcal{K} = \left\{\phi_N, \phi_p : \frac{\mathrm{d}}{\mathrm{d}t} f_s > 0\right\} \tag{13}$$

$$\mathcal{R} = \left\{\phi_N, \phi_p : \frac{\mathrm{d}}{\mathrm{d}t} f_s < 0\right\} \tag{14}$$

of constant, increasing, decreasing f_s, respectively, are invariant under scaling transformations. The set Df_0 consists of two curves Df_0^1 and Df_0^2, which divide the torus $\phi_N - \phi_p$ into two regions $\mathcal{K}$ and $\mathcal{R}$.

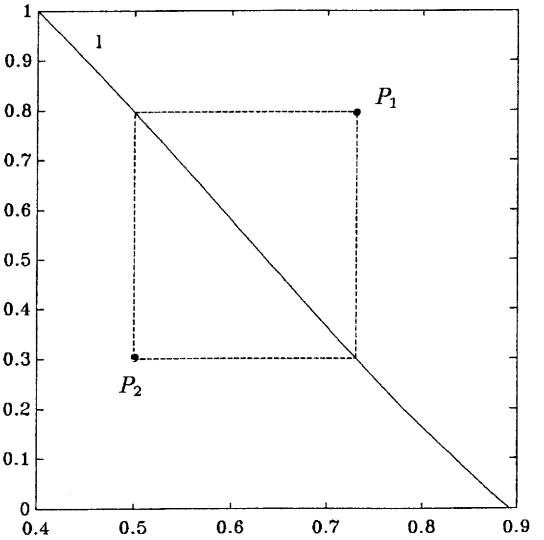

Fig. 2. The points P_1 and P_2 are symmetric with respect to the regular curve l.

The curves Df_0^1 and Df_0^2 have the *regularity property* (a curve on the torus $\phi_N - \phi_p$ is called *regular* iff it is closed and it has exactly one common point with each line of the form $\{\phi_N = \text{const}\}$, $\{\phi_p = \text{const}\}$).

The regularity of the curves Df_0^1 and Df_0^2 follows from the non-singularity of the matrix $BA - AB$. The important observation is that the characteristic regions as well as the points on the torus where switchings take place, are all symmetric with respect to the regular curves Df_0^1 and Df_0^2. The symmetry with respect to a regular curve is defined as follows. Two torus points $P_1 : \phi_{N1}, \phi_{p1}$, $P_2 : \phi_{N2}, \phi_{p2}$ are called *symmetric with respect to a regular curve* l or l–symmetric iff $\phi_{N1}, \phi_{p2} \in l$ and $\phi_{N2}, \phi_{p1} \in l$. We denote the l–symmetry relation by

$$P_1 \underset{l}{\sim} P_2 \tag{15}$$

By a straightforward extension the l-symmetry relation can be defined for sets of points. The above definition is illustrated in Fig. 2.

The analysis of all characteristic sets allows classification of all trajectories for the Hamiltonian system (6)–(8) (Świerniak and Polański, 1994). One of the conclusions was the existence of periodic solutions to (6)–(8) with multiple switchings. It can be proven that the periodic solutions occur in the rectangular subset of the torus $\phi_N - \phi_p$, with the bounds depending on coefficients of matrices A and B. The rectangle of periodic solutions is divided into two parts by a segment of the Df_0 line. This segment contains singular solutions of (6)–(8).

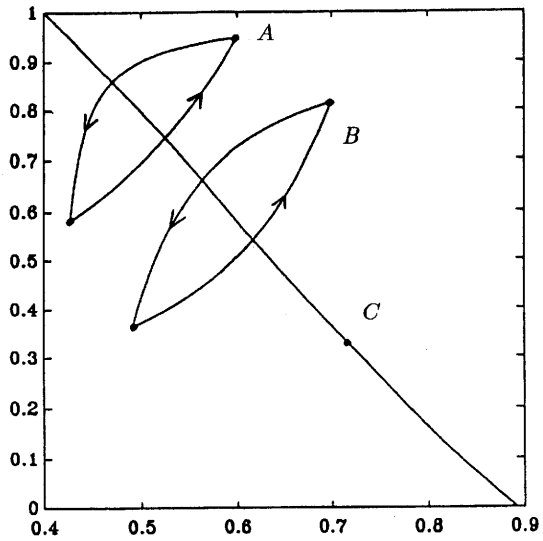

Fig. 3. The rectangle of periodic solutions.

The properties mentioned above are illustrated in Fig. 3. The arrowed arcs are segments of killing and rest trajectories, while the bold dots represent switchings. A and B are two different periodic solutions to (6)–(8), while C is a singular solution.

Since the points where switchings take place are symmetric with respect to Df_0 curve, it is clear that it is possible to find the solution to (6)–(8) an with arbitrary large number of switchings in an arbitrary short time interval. The situation in Fig. 3 is similar to the "antiturnpike" case described (and excluded) in (Sussman, 1982; 1987a).

4. The Algorithm for Solving the TPBVP

The idea of the algorithm consists in embedding the "original" TPBVP (6)–(9) in the family of problems with variable radii of boundary vectors N_0, p_H. The construction of the algorithm depends on the position of the cross-point of the lines

$$\phi_N^* = \phi(N_0), \qquad \phi_p^* = \phi(p_H) \tag{16}$$

where $\phi(\cdot)$ denotes the function which assigns its respective polar angle to each of the two-dimensional vectors. It can be proven that the position of the cross-point determines the number of possible switchings. The most interesting situation arises when the cross-point lies inside the rectangle of periodic solutions and belongs to the line Df_0. In such a case a singular solution is possible. The existence of a singular solution to the TPBVP implies an infinite number of solutions to the TPBVP.

We illustrate the algorithm using the data which have some biomedical interpretation. They come from "in vitro" experiments with leukemia cells (Kimmel and

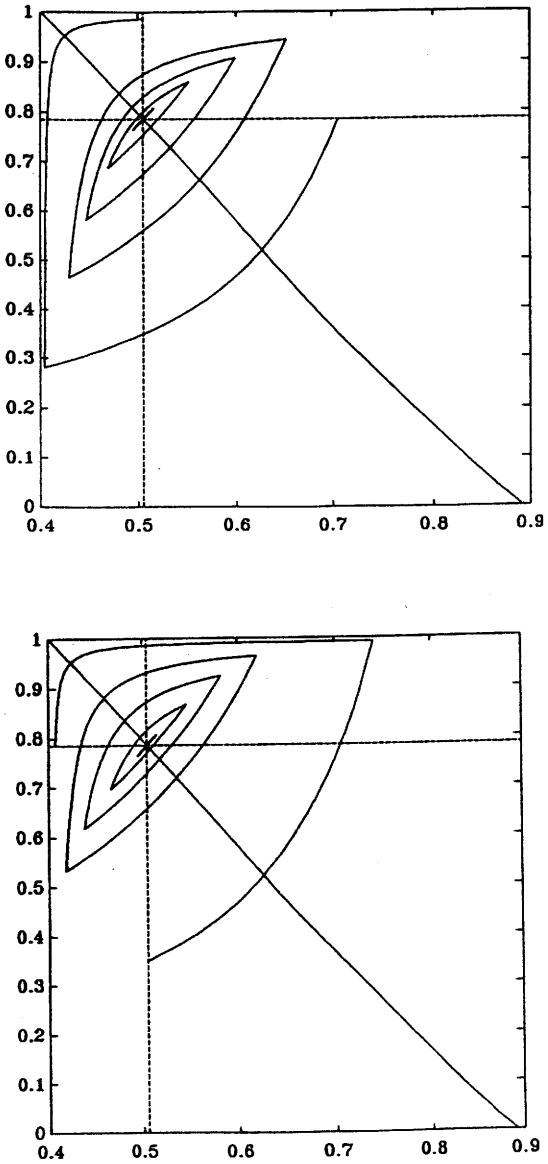

Fig. 4. The family of solutions to the TPBVP.

Traganos, 1986). The matrices A and B are given by

$$A = \begin{bmatrix} -0.197 & 0 \\ 0.197 & -0.356 \end{bmatrix}, \qquad B = \begin{bmatrix} 0 & 0.712 \\ 0 & 0 \end{bmatrix} \tag{17}$$

We assume that the boundary vectors are

$$N(0) = \begin{bmatrix} 0.875 \\ 0.4842 \end{bmatrix}, \qquad p(T_H) = 4.1023 \begin{bmatrix} 0.7071 \\ 0.7071 \end{bmatrix} \tag{18}$$

and $T_H = 10$. From (16) we have

$$\phi_N^* = \phi(N_0), \qquad \phi_p^* = \phi(p_H) \tag{19}$$

The pair ϕ_N^*, ϕ_p^* belongs to the Df_0 line and lies inside the rectangle of periodic solutions. Moreover, it is easy to check that with the data (17), (18) the TPBVP (6)–(9) has the singular solution

$$N(t) = N(0), \qquad p(t) = p(T_H), \qquad u(t) = 0.5 \tag{20}$$

with constant values of all signals. The performance index for the singular solution is $J_s = 8.943$.

Using our algorithm we are able to calculate the whole family of other solutions to the TPBVP, which consist of infinite number of elements. It appears that the optimization problem has two distinct solutions, both of them have exactly one switch, (one starts with killing, then switchings to rest, whereas the other one starts with rest and then switches to killing). The optimal value of the performance index is $J_0 = 8.359$. The remaining solutions are multiple-switchings. The values of their performance indices belong to the interval $< J_0, J_s >$.

The diagrams of some members of the family of solutions are presented in Fig. 4. The solutions are plotted on the torus $\phi_N - \phi_p$. The singular solution is the cross-point of the dashed lines. The diagram on the right presents solutions which start with killing, while the one on the left those starting with rest. The numbers of switchings for both plots are: 1, 3, 5, 10, 40. The solutions with multiple switchings make many "encirclements" around the cross-point.

The difference between the minimum and maximum values of the performance index is less than 7% which enables us to treat the solutions with many switchings as suboptimal ones.

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