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Positive dynamic systems resulting from modeling cancer chemotherapy

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Abstract— We consider a specific class of mathematical bilinear models based on cell-cycle kinetics which are used to describe and improve treatment protocols in phase-specific cancer chemotherapy. This class of models contains a two compartmental model of single drug chemotherapy, three compartmental models of multidrug therapy combining blocking and killing actions, and recruitment from quiescence together with killing action, as well as more general multicompartmental model with many drugs. We demonstrate that these models are positive dynamic systems and it is very important from biological point of view. Moreover this property is crucial for elimination of singular controls from candidates for optimality.

I. Introduction

Mathematical modeling of cancer chemotherapy has had more than four decades of history. It has contributed to the development of ideas of chemotherapy scheduling, multidrug protocols, and recruitment. It has also helped in the refinement of mathematical tools of control theory applied to the dynamics of cell populations [10]. We consider a specific class of mathematical models based on cell-cycle kinetics which was introduced by Kimmel and Swierniak [18], [27] and has been analyzed in numerous papers since, both from numerical as well as theoretical perspectives.

In this paper, we would like to demonstrate that the models used by us in phase-dependent cancer chemotherapy optimization are always positive that is very important from biological point of view. On the other hand this property is crucial for some mathematical results derived in our previous works.

Cell-cycle-phase specificity of some cytotoxic drugs is important since it makes sense to apply anticancer drugs when cells gather in the sensitive phases of the cell cycle. It can be approached by considering dissection of the cell cycle into an increasing number of disjoint compartments, with drug action limited to only some of them. We provide a classification of several simplest models of this kind.

II. Modeling the Cell Cycle

The cell cycle is composed of a sequence of phases traversed by each cell from its birth to division. These phases are: G_1, or the growth phase; S, or the DNA synthesis phase; G_2, or the preparation for division phase; and M, or the division phase. After division, the two daughter cells usually re-enter G_1. It may however happen that one or both daughters deviate from this path and become dormant or resting, or in other words, they enter the quiescent G_0 phase. From there after a variable and usually rather long time cells may reenter the cell cycle in G_1 [2].

This idealized scheme is confounded in solid tumors by the existence of a geometric gradient of availability of oxygen and nutrients. This causes a stratification in viability of cells: usually, cycling cells are located near the surface or near blood vessels, further layers are occupied by dormant cells, while the deepest regions form a necrotic core. This may lead to self-limiting growth phenomena, which may be described by biologically based nonlinear models. We do not consider this structure in our models. Instead we build a set of models of cell cycle kinetics composed of compartments (see e.g. [15]) each of them containing a phase or a cluster of phases.

The transit times through all the phases of the cell cycle are variable, particularly in malignant cells. Usually it is assumed that most of this variability is concentrated in the G_1 phase (and in G_0 whenever it exists). The simplest models arise if the transit times through each compartment are assumed exponentially distributed.

Denote by $N_i(t)$ the average number of cells in the i-th compartment at time t, and by $x_i^+(t)$ and $x_i^-(t)$, the average flow rates of cells into and out of this compartment, respectively. Then,

$$\dot{N}_i(t) = x_i^+(t) - x_i^-(t), \tag{1}$$

and

$$x_i^-(t) = a_i N_i(t), \tag{2}$$

where a_i is the parameter of the exponential distribution, equal to the inverse of the average transit time. If the preceding compartment is numbered $i-1$, then

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

for $i = 2, 3, ..., n$ where n is a number of compartments. The boundary condition for the obtained set of equations is given by:

$$\dot{N}_1(t) = -a_1 N_1(t) + 2a_n N_n(t). \tag{4}$$

Therefore, under the exponentiality assumption, the unperturbed dynamics of cell cycle, i.e. the number of cells in various cell cycle compartments versus time, in the absence of external stimuli, is expressed by a system of ordinary linear differential equations. We consider three types of perturbations of the cell cycle [30]:

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Cell Killing. At time t, only a fraction $u(t)$ of the outflux from compartment i contains viable cells ($0 \leq u(t) \leq 1$). The remaining cells are dead and no longer considered part of the system.

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

$$\dot{N}_{i+1}(t) = -a_{i+1} N_{i+1}(t) + u(t) a_i N_i(t), \tag{6}$$

The reproductively dead cells may however continue to progress through the cycle for some time, thus confounding estimates of cell proliferation.

Cell Arrest. At time t, the outflux from compartment i is reduced to a fraction $v(t)$ of the normal value ($0 < v_m \leq v(t) \leq 1$) . The remaining cells are arrested in compartment i.

$$\dot{N}_i(t) = -v(t) a_i N_i(t) + a_{i-1} N_{i-1}(t), \tag{7}$$

$$\dot{N}_{i+1}(t) = -a_{i+1} N_{i+1}(t) + v(t) a_i N_i(t). \tag{8}$$

The complete arrest is not possible, and it is why v_m is always strickly positive.

Alteration of the Transit Time. The parameter of the exponential distribution of the transit time through compartment i is changed by factor $y(t) > 0$. Depending on whether $y(t)$ is less or greater than 1, this is equivalent to respectively extending or reducing the mean transit time. In the latter case it is used in the so called recruitment of dormant cells to the proliferation cycle. The mathematical description has the form:

$$\dot{N}_i(t) = -y(t) a_i N_i(t) + a_{i-1} N_{i-1}(t), \tag{9}$$

$$\dot{N}_{i+1}(t) = -a_{i+1} N_{i+1}(t) + y(t) a_i N_i(t), \tag{10}$$

Formally, these equations are identical as those describing cell arrest. This effect is caused by the exponentiality assumption.

Since our models describe an average behaviour of considered subpopulations the compartments which they represent are sometimes called "probabilistic" or "statistical" ones. "Deterministic" description of the continuously dividing population should be described by partial differential equations , integro-differential or integral equations. In this case the one independent variable represents the chronological time while the other age or size. In our models the age is simply discretized and the dynamics from one stage to the other is averaged.

The first class of drug actions is represented by G_2/M specific agents, which include the so-called spindle poisons like Vincristine, Vinblastine or Bleomycin which destroy a mitotic spindle [4] and Taxol [11] or 5-Fluorouracil affecting mainly cells during their division. Among the blocking drugs used to arrest the cells immediately before or during DNA synthesis we can mention antibiotics like Adriamycin, Daunomycin, Dexorubin, Idarudicin which cause the progression blockage on the border between the phases G_1 and S by interfering with the formator of the polymerase complex or by hindering the separation of the two polynucleotide strands in the double helix. Another blocking agent is Hydroxyurea - HU [8] which is found to synchronize cells by causing brief and invisible inhibition of DNA synthesis in the phase S and holding cells in G_1. The recruitment action was demonstrated [31] for Granulocyte Colony Stimulating Factors - G-CSF, Granulocyte Macrophage Colony Stimulating Factors - GM-CSF, Interleukin-3 - Il-3, specially when combined with Human Cloned Stem Cell Factor - SCF.

While the killing agent is the only control considered in the two-compartment model below, in the three-compartment model in addition a blocking agent is considered which slows down the development of cells in the synthesis phase S and then releases them at the moment when another G_2/M specific anticancer drug has maximum killing potential (so-called synchronization [3]). This strategy may have the additional advantage of protecting the normal cells which would be less exposed to the second agent (e.g. due to less dispersion and faster transit through G_2/M) [7], [1]. This cell cycle model includes separate compartments for the G_0/G_1, S and G_2/M phases.

One of the major problems in chemotherapy of some leukemias is constituted by the large residuum of dormant G_0 cells which are not sensitive to most cytotoxic agents. Similar findings for breast and overian cancers were reported, e.g. in [11], [5]. As indicated by these authors the insensitivity of dormant cells to the majority of anticancer drugs and percentage of tumor mass resting is a fact which, if ignored, leads not only to clinical problems but also to some erronomous theoretical considerations. The other three compartment model below uses separate compartments for the G_0, G_1 and $S + G_2/M$ phases and includes such a recruiting agent. Moreover, it enables also analysis of the alteration of the transit time through G_0 phase due to the feedback mechanism that recruits the cells into the cycle when chemotherapy is applied.

III. Optimal Control Problems and Positivity of the Models

We formulate a general n-compartment model for cancer chemotherapy as an optimal control problem over a fixed therapy interval with dynamics described by a bilinear system [28]. Let $N = (N_1, \ldots, N_n)^T$ denote the state-vector with N_i denoting the number of cancer cells in the i-th compartment, $i = 1, \ldots, n$. The control is a vector $u = (u_1, \ldots, u_m)^T$ with u_i denoting the drug dosage administered. The control set U is a compact m-dimensional cube of the form $[\alpha_1, \beta_1] \times \cdots \times [\alpha_m, \beta_m]$ with each interval $[\alpha_i, \beta_i] \subset [0, \infty)$. Let A and B_i, $i = 1, \ldots, m$, be constant $n \times n$ matrices, let $r = (r_1, \ldots, r_n)$ be a row-vector of positive numbers and let $s = (s_1, \ldots, s_m)$ be a row-vector of non-negative numbers. The vectors r and s represent subjective

weights in the objective. We then consider the following optimal control problem:

(P) minimize the objective

$$J = rN(T) + \int_0^T su(t)dt \to \min \tag{11}$$

over all Lebesgue-measurable functions $u : [0,T] \to U$ subject to the dynamics

$$\dot{N}(t) = (A + \sum_{i=1}^{m} u_i B_i)N(t), \quad N(0) = N_0. \tag{12}$$

We briefly recall three two- and three-compartment models which fit into this general class. For a more detailed description of the models we refer the reader to [30].

Model (A): In a 2-compartment model the phases G_0, G_1 and S are clustered into the first compartment, G_2 and M are combined into the second compartment, and only a killing agent u_1 is considered. Thus $n = 2$, $m = 1$, and the matrices A and $B = B_1$ are given by

$$A = \begin{pmatrix} -a_1 & 2a_2 \\ a_1 & -a_2 \end{pmatrix}, \quad B = \begin{pmatrix} 0 & -2a_2 \\ 0 & 0 \end{pmatrix}. \tag{13}$$

The a_i are positive coefficients related to the mean transit times of cells through the i-th compartment.

Model (B): In this three-compartment model in addition a blocking agent u_2 is considered which is active in the synthesis phase S and thus S is modelled as a separate compartment. Now $n = 3$, $m = 2$, and the matrices are given by

$$A = \begin{pmatrix} -a_1 & 0 & 2a_3 \\ a_1 & -a_2 & 0 \\ 0 & a_2 & -a_3 \end{pmatrix}, \tag{14}$$

and

$$B_1 = \begin{pmatrix} 0 & 0 & -2a_3 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \quad B_2 = \begin{pmatrix} 0 & 0 & 0 \\ 0 & a_2 & 0 \\ 0 & -a_2 & 0 \end{pmatrix}. \tag{15}$$

In both models the control u_1 represents the dose of the killing agent administered with the value $u_1 = 0$ corresponding to no treatment and $u_1 = 1$ corresponding to a maximum dose. It is assumed that the dose stands in direct relation to the fraction of cells which are being killed in the G_2/M phase. Therefore only the fraction $1 - u_1$ of the outflow of cells from the last compartment undergoes cell division and reenters the first compartment. However, all cells leave compartment G_2/M. In model (B) in addition the blocking agent u_2 is applied to slow the transit times of cancer cells during the synthesis phase S. As a result the flow of cancer cells from the second into the third compartment is reduced by a factor $1-u_2$ of its original flow to $(1-u_2(t))a_2N_2(t)$, $0 \le u_2(t) \le v_{\max} < 1$. Here the control $u_2(t) = 0$ corresponds to no drug being applied while a maximal reduction occurs with a full dose $v_{\max}$.

Model (C): A second 3-compartment model can be derived from model (A) if the dormant phase G_0 is considered separately. In this case the newly born cells either enter G_1 and immediately start the cell division process or they may enter the dormant stage G_0. Let b_0 and b_1, $b_0+b_1 = 1$, be the corresponding probabilities. In addition in this model we also consider a recruiting agent $w = u_3$ which is applied to reduce the average sejour time in the quiescent phase. As a result the average transit time through the compartment G_0 is reduced resulting in the outflow being increased by a factor $1+w$, $0 \le w \le w_{\max}$. Here again the control $w = 0$ corresponds to no drug being applied while $w = w_{\max}$ occurs with a full dose. For this model it is more natural to label the compartments $i = 0, 1, 2$ and the matrices for this 3-compartment model are given by

$$A = \begin{pmatrix} -a_0 & 0 & 2b_0a_2 \\ a_0 & -a_1 & 2b_1a_2 \\ 0 & a_1 & -a_2 \end{pmatrix}, \tag{16}$$

and

$$B_1 = \begin{pmatrix} 0 & 0 & -2b_0a_2 \\ 0 & 0 & -2b_1a_2 \\ 0 & 0 & 0 \end{pmatrix}, \quad B_3 = \begin{pmatrix} -a_0 & 0 & 0 \\ a_0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}. \tag{17}$$

For all three models we take as objective

$$J = rN(T) + \int_0^T u_1(t)dt, \tag{18}$$

(i.e. $s_1 = 1$ and $s_2 = s_3 = 0$ in the general formulation (1)). The penalty term $rN(T)$ in the objective represents a weighted average of the total number of cancer cells at the end of an assumed fixed therapy interval $[0,T]$. The number of cancer cells which do not undergo cell division at time t and are killed are given by the portion $u_1(t)$ of the outflow of the last compartment, i.e. $u_1(t)$ is proportional to the fraction of ineffective cell divisions. Since the drug kills healthy cells at a proportional rate, the control $u_1(t)$ is also used to model the negative effect of the drug on the normal tissue or its toxicity. Thus the integral in the objective models the cumulative negative effects of the treatment. In the 3-compartment model (B) it is assumed that the negative influence of the blocking agent u_2 which does not kill cells is negligible and it is therefore not included in the objective. However, since as mentioned above some blocking agents exhibit also killing effects it may be reasonable to include their cytotoxicity on normal tissues. It could easily be incorporated with a small weight s_2 without changing the structure of the results. For the 3-compartment model (C) the only reasonable choice for the recruitment agent is weight $s_3 = 0$.

The important assumption which is satisfied in all our models is that the control systems which they represent are internally positive [16] i.e.:

(+) The first orthant of the control system is positively invariant, that is for any admissible

control and for positive initial states, the state remains positive for all times $t > 0$.

Thus the obvious modelling state-space constraints that the state is positive, need not be included in our model explicitly and the analysis simplifies. A simple sufficient condition for (+) to hold (for example, see [16]) is that:

(M) all the system matrices for all admissible controls are so-called M-matrices, i.e. have negative diagonal entries, but non-negative off-diagonal entries.

This condition is natural and will be satisfied for any compartmental model whose dynamics is given by balance equations where the diagonal entries correspond to the outflows from the i-th compartments and the off-diagonal entries represent the inflows from the i-th into the j-th compartment, $i \neq j$. It is satisfied for each of the models described here. More generally, if condition (+) were violated, this is a strong indication that the modelling is inconsistent.

Now we present the more detailed analysis of the models A-C emphasizing the role of the (+) condition in the prove of important properties of the optimal solutions of the compartmental models of the chemotherapy.

A. Two Compartments, Single G_2M - Specific Killing Agent

This is probably the simplest situation in which it is possible to contemplate the effects of phase specificity [26], [27]. Compartment 1 consists of the G_1 and S phases and compartment 2 of the G_2 and M phases. The corresponding system of two differential equations has the form ($u = 1 - u_1$):

$$\begin{aligned} \dot{N}_1(t) &= -a_1 N_1(t) + 2u a_2 N_2(t), \quad & N_1(0) = N_{10} > 0, \\ \dot{N}_2(t) &= -a_2 N_2(t) + a_1 N_1(t), & N_2(0) = N_{20} > 0. \end{aligned} \tag{19}$$

The performance index has the form:

$$J = \sum_{i=1}^{2} r_i N_i(T) \; + \; \int_0^T [1 - u(t)]\, dt. \tag{20}$$

If the optimal control is of the bang-bang type, it can be found from the maximum principle [24] by minimizing the so called hamiltonian function:

$$H = p_1(-a_1 N_1 + 2u a_2 N_2) + + p_2(-a_2 N_2 + a_1 N_1) + 1 - u, \tag{21}$$

that results in:

$$u(t) = \begin{cases} 0; & 2a_2 N_2(t) p_1(t) > 1, \\ 1; & 2a_2 N_2(t) p_1(t) < 1, \end{cases} \tag{22}$$

where $p = (p_1, p_2)^T$ is the costate vector defined by the conjugate equations,

$$\begin{aligned} \dot{p}_1(t) &= a_1(p_1(t) - p_2(t)), & p_1(T) = r_1, \\ \dot{p}_2(t) &= a_2(p_2(t) - 2p_1(t)u(t)), & p_2(T) = r_2, \end{aligned} \tag{23}$$

Since the control system satisfies condition (M), then it follows from the adjoint equation that for any admissible control the first orthant in costate-space is negatively invariant under the flow of the adjoint system, i.e. if $p_i(T) > 0$ for all $i = 1, 2$, then $p_i(t) > 0$ for all times $t \leq T$. In this case, since $N(0)$ and $p(T)$ have positive components, it follows that all states N_i and costates p_i are positive over $[0, T]$.

The case $2a_1 N_2 p_2 = 1$ leads to the singular control problems which cannot be excluded using only the first order necessary conditions .

Recently singularity of optimal arcs was excluded with the use of high-order necessary conditions for optimality and sufficient conditions for optimal bang-bang strategies were found which enable to determine whether controls found by the use of Pontryagin maximum principle are at least locally optimal [20]. More precisely singular controls are calculated by differentiating the switching function in time until the control variable explicitly appears in the derivative, then finding the control which makes it equal to 0. For a single-input system which is linear in the control it is known [19] that the order of this derivative must be even, say $2k$, and k is called the order of the singular arc on the interval I. It is a necessary condition for optimality of a singular arc of order k, the so-called generalized Legendre-Clebsch condition [19], that

$$(-1)^k \frac{\partial}{\partial u} \frac{d^{2k}}{dt^{2k}} \frac{\partial H}{\partial u} \geq 0. \tag{24}$$

Note that the term $\frac{\partial H}{\partial u}$ in (24) represents the switching function for the problem. This framework directly applies to the 2-compartment model which has a scalar control. Elementary and direct calculations show that in this case singular arcs are of order 1 and that

$$\frac{\partial}{\partial u} \frac{d^2}{dt^2} \frac{\partial H}{\partial u} = 4a_1 a_2 > 0 \tag{25}$$

violating the Legendre-Clebsch condition.

B. Three Compartments, Cell Arrest in S and Killing in G_2M

One of the conceivable strategies of protocol optimization, exploiting drug specificity, is to arrest cancer cells in the S phase [3], [13], and then release them at the moment when another G_2M specific anticancer drug has the maximum killing potential.

The control problem is to find $u(t) \in [0, 1]$ and $v(t) \in [v_m, 1]$ such that ($u = 1 - u_1$, $v = 1 - u_2$):

$$\begin{aligned} \dot{N}_1(t) &= -a_1 N_1(t) + 2u(t) a_3 N_3(t), & N_1(0) = N_{10} > 0, \\ \dot{N}_2(t) &= -v(t) a_2 N_2(t) + a_1 N_1(t), & N_2(0) = N_{20} > 0, \\ \dot{N}_3(t) &= -a_3 N_3(t) + v(t) a_2 N_2(t), & N_3(0) = N_{30} > 0. \end{aligned} \tag{26}$$

and the index

$$J = \sum_{i=1}^{3} r_i N_i(T) \; + \; \int_0^T [1 - u(t)]\, dt, \tag{27}$$

is minimized.

The bang-bang solution found from the maximum principle has the following form:

$$u(t) = \begin{cases} 0; & 2a_3N_3(t)p_1(t) > 1 \\ 1; & 2a_3N_3(t)p_1(t) < 1 \end{cases} \tag{28}$$

$$v(t) = \begin{cases} v_m; & p_2(t) < p_3(t) \\ 1; & p_2(t) > p_3(t) \end{cases} \tag{29}$$

where the costate vector satisfies the following set of equations:

$$\begin{array}{ll} \dot{p}_1(t) = a_1(p_1(t) - p_2(t)), & p_1(T) = r_1, \\ \dot{p}_2(t) = a_2(p_2(t) - p_3(t))v(t), & p_2(T) = r_2, \\ \dot{p}_3(t) = a_3(p_3(t) - 2p_1(t))u(t), & p_3(T) = r_3, \end{array} \tag{30}$$

The arising TPBVP may be once more treated numerically [9] by the gradient method in the way similar as for two-compartmental models. Analytical treatment becomes much more complicated since the problem could not be projected into the plane. But also in this case it is possible to eliminate singular controls as not optimal and formulate sufficient conditions for local optimality of bang-bang strategies [21]. In this case the generalized Legendre-Clebsch condition (24) still applies to the first control u if we freeze the second control v. Assuming v is constant, it can be shown that a singular control u must be of order 2, but again (24) is violated. Direct, but longer calculations verify that

$$\frac{\partial}{\partial u}\frac{d^4}{dt^4}\frac{\partial H}{\partial u} = -12a_1a_2a_3^2v(a_1 + a_2v)p_1(t)N_2(t) < 0. \tag{31}$$

Note that these results strongly depend on the fact that states and also multipliers are positive.

Furthermore, if the control v is singular on an interval I, then it can easily be seen that u also must be singular on I. In this case it is a necessary condition for optimality, the so-called Goh condition [19], that on I we have

$$\frac{\partial}{\partial v}\frac{d}{dt}\frac{\partial H}{\partial u} \equiv 0. \tag{32}$$

However, a direct calculation gives

$$\frac{\partial}{\partial v}\frac{d}{dt}\frac{\partial H}{\partial u} = 2a_2a_3p_1(t)N_2(t) > 0 \tag{33}$$

violating the Goh-condition . Once more these results strongly depend on the fact that states and also multipliers are positive.

C. Three Compartments, Cell Recruitment from G_0 and Killing in G_2M

One of the major problems in chemotherapy of some leukemias is constituted by the large residuum of dormant G_0 cells which are not sensitive to most cytotoxic agents. It became recently possible to efficiently recruit these cells into the cycle using cytokines [31], substances playing a role in the regulation of normal hemopoiesis. Then, a cytotoxic agent may be used. To model such a system , we use separate compartments for the G_0, G_1 and S + G_2M phases, numbered 0, 1 and 2 [30].

The control problem is to find $u(t) \in [0,1]$ and $y(t) \in [1, y_m]$ such that $(y = 1 + w)$:

$$\begin{array}{l} \dot{N}_0(t) = -ya_0N_0(t) + 2b_0u(t)a_2N_2(t), \\ \dot{N}_1(t) = -a_1N_1(t) + ya_0N_0(t) + 2b_1u(t)a_2N_2(t), \\ \dot{N}_2(t) = -a_2N_2(t) + a_1N_1(t), \\ N_0(0) = N_{00} > 0, N_1(0) = N_{10} > 0, N_2(0) = N_{20} > 0. \end{array} \tag{34}$$

where b_0 and b_1 are the probabilities of the daughter cell entering after division G_0 and G_1, respectively. The index to be minimized is

$$J = \sum_{i=0}^{2} r_iN_i(T) \; + \; \int_0^T [1 - u(t)]\, dt. \tag{35}$$

The bang-bang solution found using the maximum principle has the following form

$$u(t) = \begin{cases} 0; & 2a_2N_2(t)(b_0p_0(t) - b_1p_1(t)) > 1 \\ 1; & 2a_2N_2(t)(b_0p_0(t) - b_1p_1(t)) < 1 \end{cases} \tag{36}$$

$$y(t) = \begin{cases} 1; & p_1(t) > p_0(t) \\ y_m; & p_1(t) < p_0(t) \end{cases} \tag{37}$$

where the costate vector satisfies the following set of equations,

$$\begin{array}{l} \dot{p}_0(t) = y(t)a_0(p_0(t) - p_1(t)), \\ \dot{p}_1(t) = a_1(p_1(t) - p_2(t)), \\ \dot{p}_2(t) = a_2\left[p_2(t) - 2u(t)(b_0p_0(t) + b_1p_1(t))\right], \\ p_0(T) = r_0, p_1(T) = r_1, p_2(T) = r_2, \end{array} \tag{38}$$

The arising two-point boundary value problem (TPBVP) expressed by equations (34) and (36)-(38) is formally similar to the TPBVP expressed by equations (26) and (28)-(30) and leads to the same mathematical problems. In this case the analysis of singular arcs is slightly more cumbersome [28]. For constant y we have:

$$\frac{\partial}{\partial u}\frac{d^2}{dt^2}\frac{\partial H}{\partial u} = 4a_1a_2b_1 > 0 \tag{39}$$

violating the Legendre-Clebsch condition. These calculations therefore exclude the optimality of singular controls u when y is constant. It might still be possible, however, that y is singular and not constant over any subinterval $J \subset I$. In this case u also must be singular on I. For this example the Goh condition is actually satisfied but after some simple but lenghty calculations we have found that it is possible only for $u = 0.5$ and leads to constant N_is and p_is and in consequence to constant y but it, in turn, implies violation of the Legendre-Clebsch condition.

Generaly we have obtained the following theorem:

Theorem 1: Due to positivity of the models (A)-(C) optimal controls are not singular on any subinterval $I \subset [0, T]$.

IV. Discussion

In this paper we discuss the cell-cycle-phase dependence of cytotoxic drug action and drug resistance in the context of optimization of cancer chemotherapy.

Attempts at optimization of cancer chemotherapy using optimal control theory have a long history ([25]

is a review by Swan). The idea has been criticized many times (see e.g. [32], [33]). Only simplest concepts have won attention in the medical world. These include the clonal resistance model [12] and the kinetic resistance theory by Norton and Simon [23].

The simplest cell-cycle-phase dependent models of chemotherapy can be classified based on the number of compartments and types of drug action modeled. In all these models the attempts at finding optimal controls are confounded by the presence of singular and periodic trajectories, and multiple solutions but recently singular trajectories are excluded and sufficient conditions for strong local optimality are found for a class of bang-bang strategies [28].

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