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DRUG RESISTANCE IN CANCER CHEMOTHERAPY AS AN OPTIMAL CONTROL PROBLEM

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Abstract. We analyze non cell-cycle specific mathematical models for drug resistance in cancer chemotherapy. In each model developing drug resistance is inevitable and the issue is how to prolong its onset. Distinguishing between sensitive and resistant cells we consider a model which includes interactions of two killing agents which generate separate resistant populations. We formulate an associated optimal control problem for chemotherapy and analyze the qualitative structure of corresponding optimal controls.

1. **Introduction.** Mathematical modeling of cancer chemotherapy has more than four decades of history (e.g. [6], [25]). Its contributions mostly lie the development of qualitative ideas for chemotherapy scheduling, but practical quantitative applications are lacking. The reasons for this lie both in biomedicine and mathematics. On the biological side important cell processes still are not well understood and crucial parameters in the modelling are not known or simply vary too much from case to case so that data are not readily transferrable. On the mathematical side the only feasible approach to deal with realistic (and thus necessarily high-dimensional, complicated and intricate) models is through numerical simulation studies relying on computational power [23]. But if there is a high uncertainty or a great range for relevant parameter values from patient to patient, these simulation studies are inherently of limited quantitative practical value. "The best average treatment may be the poorest option for a particular patient" [9]. Theoretical analysis on the other hand is limited to small and hence overly simplified models whose results are thus not applicable quantitatively. Nevertheless their analysis can further our understanding of some simplified aspects of the overall system, a necessary step towards the goal of analyzing more medically relevant models. For example, these investigations can help in determining how sensitive some protocols are with respect to specific parameters and thus point to relevant, respectively, less relevant medical parameters in quantitative approaches.

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Of all the limiting factors in chemotherapy, and there exist many of them, "probably the most important - and certainly the most frustrating - is drug resistance" [11, pg. 335]. The entire process of the drugs' actions is "forbiddingly complex" [9] and given the complicated biochemical processes that are necessary for the cytotoxic agents to be effective, many defense mechanisms are open to the cell. For example, many cytotoxic agents are susceptible to ABC transport proteins which remove molecules out of the cell. Thus an over-expression (for example, by gene-amplification) in these molecules is an important mechanism for resistance to various drugs. Another one is that repair systems within the cells become activated which overcome the damage done by the drug. Malignant cancer cell populations are highly heterogeneous - the number of genetic errors present within one cancer cell lies in the thousands [16] - and fast duplications combined with genetic instabilities provide just one of several mechanisms which allow for quickly developing acquired resistance to anti-cancer drugs. In addition, so-called intrinsic resistance (i.e. the specific drug's activation mechanism simply doesn't work) makes some cancer cells not susceptible to many cytotoxic agents. " ... the truly surprising thing is that some malignancies can be cured even with current approaches." [9, pp. 65]. Several mechanisms to circumvent the problem of acquired drug resistance have been tried, but so far without success and currently no medical solution to the problem of drug resistance in chemotherapy exists. In fact, it is acquired or intrinsic drug resistance which eventually makes most chemotherapy fail and in view of the manifold ways in which the cell can react to an attack by cytostatic agents [9, 31] it appears unlikely that there ever will exist a drug whose effectiveness will not ultimately be limited in this way. While a "cure for cancer" thus may simply be the "holy grail" of medicine, a more realistic objective of treatment is to increase the life expectancy of the patient. For this combination therapies in which different types of drugs are administered still provide a valuable option. They are based on the idea that cells may become resistant to some particular agent, but then still can be treated through other cytotoxic agents which have an entirely different mode of action. Since cancer cells can in fact lose acquired drug resistance, (for example, by gene de-amplification), alternate treatments with different type of drugs therefore may prolong the onset of resistance. While this is true to some extent, in reality, unfortunately often multi-drug resistance and unacceptable levels of toxicity to the patient limit these approaches as well.

Several probabilistic models for developing drug resistance exist in the literature (e.g. [4, 8, 12, 33]). For example, in one of the early classical works by Coldman and Goldie the tumor size is analyzed as a stochastic process and the probability to have no resistant cells is maximized [4]. In this paper, as in numerous others like [5], simple non cell-cycle specific two-compartment models distinguishing only resistant and sensitive cells are considered. More recently, a probabilistic model for the evolution of the drug sensitive cancer subpopulation from a single mutational cell has been formulated and analyzed numerically by Westman et al. in [32, 33] in a cell-cycle specific context distinguishing between the clonogenic (or quiescent) and the growth (or proliferating) fraction. In these and earlier papers drug resistance is treated as a sudden event, only distinguishing resistant and sensitive cells. While drug resistance may be induced by a single mutational event (clinical resistance sometimes appears so rapidly in patients that this would be a plausible explanation,) the more common mechanism seem to be random mutations over time. "a partially resistant clone may ... undergo further mutations and become progressively more

resistant [9, pg. 64]." A broad class of models which describe drug resistance not as a single mutation event, but as a branching process, was developed by Harnevo and Agur [7, 8] and Kimmel and Axelrod [12, 13]. Corresponding infinite-dimensional deterministic models have been formulated and analyzed by Swierniak et al. [14, 28, 30]. However, due to high dimensionality these models often only allow a limited analysis.

All these models have in common that they analyze developing drug resistance with respect to a single cytotoxic agent or a group of drugs which can be lumped together in their effect. In this paper we consider a mathematical model for combination cancer chemotherapy under evolving drug resistance which considers *multiple killing agents*. The underlying model was formulated jointly with A. Swierniak in [21]. It is probabilistic, a branching random walk model with a finite number of states [12], but averaged over the populations in individual compartments. The model for acquired drug resistance is based on the mechanism of *gene amplification*, but the equations can easily be adjusted to fit other mechanisms. For simplicity and as starting point, the models considered in this paper are not yet cell-cycle specific and treat drug resistance as a "complete event" [33] only distinguish between resistant and sensitive compartments of cancer cells. Developing drug resistance is unavoidable and will eventually lead to a halt of treatment. The problem therefore is not to eliminate the cancer, but to prolong the patient's life expectancy.

There are many non-equivalent ways of trying to formulate such a problem mathematically. In this paper we consider an optimal control approach. In section 2 we briefly consider the simpler model with one killing agent which falls into a well researched class of bilinear optimal control problems mathematically (e.g. [17, 18, 20, 27]). This is no longer the case when combination drug treatments are considered. In this case considered in section 3 the minimization of an indefinite quadratic function on a compact set determines the controls also leading to interesting mathematical questions. We initiate the analysis of this model with tools of modern optimal control in order to gain some qualitative insights into the structure of optimal protocols. Section 4 gives some simulations of corresponding multi-drug protocols comparing them with reasonable ad-hoc strategies.

2. **Mathematical Models for Cancer Chemotherapy with a Single Killing Agent under Drug Resistance.** In this section, as a precursor to multi-drug models, we briefly consider a model with a single cytotoxic agent. We only use the simpler model to discuss the mechanism for drug resistance underlying this model and to introduce some of the mathematical tools of optimal control.

2.1. **Drug Resistance and Gene Amplification.** *Amplification* of a gene is an increase in the number of copies of that gene present in the cell after cell division, *deamplification* corresponds to a decrease in its number of copies. As mentioned before, cancer cells are genetically highly unstable and due to mutational events and gene amplification during cell division, cells can acquire additional copies of genes which as a result make the cells more resistant to certain drugs, for example by addition of genes which aid removal or metabolization of the drug. The more copies of such a gene will be present, the more resistant the cells become to even higher concentrations of the drug. Gene amplification is thus well-documented as one of the reasons for evolving drug resistance of cancer cells (see, for example, [1, 9, 24]). Mathematical models for drug resistance based on gene amplification have been proposed and analyzed probabilistically by Harnevo and Agur [7, 8] in connection

with a *one-copy forward gene amplification hypothesis* which states that in cell division at least one of the two daughter cells will be an exact copy of the mother cell while the second one with some positive probability undergoes gene amplifications. These concepts form the background for models developed by Swierniak, Smieja et al. [26, 29, 30] where various levels of drug resistance are considered. Taking into account an increasing degree of gene amplification leads to infinite-dimensional models [14] involving integro-differential equations which, however, are difficult to analyze. Thus, assuming some level of simplification and staying within a finite-dimensional structure enables a better analysis of these problems. In this paper we keep the number of levels of drug resistance minimal, i.e. we only distinguish sensitive and resistant compartments, but our aim is to analyze multi-drug treatments. As a precursor we first briefly discuss the 2-dimensional model corresponding to a one drug treatment.

2.2. **The basic 2-compartment model.** We only consider two compartments consisting of drug sensitive and resistant cells, and we denote the numbers of cells in the sensitive and resistant compartments by S and R, respectively. Within the one-copy forward gene amplification model, once a sensitive cell undergoes cell division, the mother cell dies and one of the daughters will remain sensitive. The other daughter, with probability q, $0 < q < 1$, changes into a resistant cell. Similarly, if a resistant cell undergoes cell division, then the mother cell dies, and one of the daughters remains resistant. However, for cancer cells (and different from viral infections like HIV) it is possible that a resistant cell may mutate back into a sensitive cell. This phenomenon is well-documented in the medical literature where experiments have shown that the resistant cell population decreases in a drug free medium [24]. We therefore include a probability $r \geq 0$ that one of the daughters of a resistant cell may become sensitive. Generally r will be small. The case $r = 0$ where this is excluded is called *stable gene amplification* while *unstable gene amplification* refers to the phenomenon $r > 0$. If we denote the inverses of the transit times of cells through the sensitive and resistant compartments by a and c, respectively, then the uncontrolled dynamics therefore takes the form

$$\dot{S} = -aS + (2-q)aS + rcR, \tag{1}$$

$$\dot{R} = -cR + (2-r)cR + qaS. \tag{2}$$

Here the first terms on the right hand sides account for the deaths of the mother cells, the second terms describe the return flows into the compartments, and the third terms give the cross-over flows. We now assume that a cytotoxic agent kills sensitive cells, but has no effect on the resistant population. Let u denote the drug dose, $0 \leq u \leq u_{\max} \leq 1$, with $u = 0$ corresponding to no drug being used and $u = u_{\max}$ corresponding to a full dose. For simplicity here it is assumed that the dosage, the concentration and the effect of the drug are equal, i.e. pharmacokinetics (PK) or pharmacodynamics (PD) are not modelled. It is assumed that the drug kills a fixed proportion u of the outflow of the sensitive cells at time t, $aS(t)$, and therefore only the remaining fraction $(1-u)aS(t)$ of cells undergoes cell division. Of these new cells then $(2-q)(1-u)aS(t)$ remain sensitive, while a fraction $q(1-u)aS(t)$ mutates to resistant cells. It is assumed that the drug has no effect on resistant

cells. Thus overall the controlled dynamics can be represented as

$$\dot{S} = -aS + (1-u)(2-q)aS + rcR, \tag{3}$$

$$\dot{R} = -cR + (2-r)cR + (1-u)qaS, \tag{4}$$

and the initial condition is given by positive numbers S_0 and R_0 at time $t = 0$. Setting $N = (S, R)^T$, the dynamics is described by a bilinear system

$$\dot{N} = (A + uB)N \tag{5}$$

where

$$A = \begin{pmatrix} (1-q)a & rc \\ qa & (1-r)c \end{pmatrix} \qquad \text{and} \qquad B = a \begin{pmatrix} q-2 & 0 \\ -q & 0 \end{pmatrix}. \tag{6}$$

We first show that the system has a well-defined response for any admissible control.

Proposition 1. *For any Lebesgue measurable control $u : [0, \infty) \to [0, u_{\max}]$ the solution $N(\cdot) = (S(\cdot), R(\cdot))^T$ exists on $[0, \infty)$ and all its components are positive.*

Proof. For any control u defined on $[0, \infty)$ this is a linear system with bounded coefficients and thus solutions exist over $[0, \infty)$. Define τ as the supremum over all times η such that both S and R are positive on $[0, \eta]$,

$$\tau = \sup\{\eta \geq 0 : S(t) > 0 \text{ and } R(t) > 0 \text{ for } 0 \leq t \leq \eta\}.$$

If τ were finite, one of S or R must vanish at τ while both are positive on $[0, \tau)$. The stated invariance property directly follows from the following well-known comparison lemma for 1-dimensional linear ODE's: Suppose α and β are bounded Lebesgue-measurable functions on $\mathbb{R}$ and consider the ODE $\dot{\mu} = \alpha\mu + \beta$. If $\mu(t_0) > 0$ and $\beta(t) \geq 0$ for $t \geq t_0$, then $\mu(t) > 0$ for all $t \geq t_0$. This is obvious from the representation

$$\mu(t) = \exp\left(\int_{t_0}^{t} \alpha(s)ds\right)\left[\mu(t_0) + \int_{t_0}^{t} \exp\left(\int_{s}^{t_0} \alpha(r)dr\right)\beta(s)ds\right].$$

Hence neither S nor R can vanish first. Contradiction. □

2.3. **Asymptotic Properties.** In no control is applied, i.e. for $u \equiv 0$, the dynamics is a simple model of exponential growth. Roughly, sensitive cells grow at the rate a and resistant cells grow at rate c, or, more precisely,

$$\dot{R} + \dot{S} = aS + cR. \tag{7}$$

The quotient $x = \frac{S}{R}$ satisfies a Riccati equation of the form

$$\dot{x} = rc + ((1-q)a - (1-r)c)\, x - qax^2 \tag{8}$$

with positive initial condition $x(0) > 0$. Clearly the interval $[0, \infty)$ is invariant for (8) and this equation has a unique stable equilibrium in this interval at

$$\bar{x} = \frac{(1-q)a - (1-r)c + \sqrt{((1-q)a - (1-r)c)^2 + 4rqac}}{2rc} > 0. \tag{9}$$

Thus, left alone, cancer cells grow exponentially reaching the relative proportions $S = \bar{x}R$.

If full control is applied throughout, i.e. $u \equiv 1$ on $[0, \infty)$, the sensitive cells can be reduced with rate a, while the resistant compartment still will grow with rate c. Again, more precisely now

$$\dot{R} + \dot{S} = -aS + cR. \tag{10}$$

Thus, in principle the cancer cells can be reduced through chemotherapy provided $aS > cR$, the typical situation initially. However, since applying drugs diminishes only the sensitive population the resistant population eventually takes over and the total number of cancer cells then will still grow exponentially. Now the quotient $x = \frac{S}{R}$ satisfies a linear ODE,

$$\dot{x} = rc + (a + (1-r)c)\, x,$$

with stable equilibrium at

$$\bar{x} = \frac{rc}{a + (1-r)c}. \tag{11}$$

This value is small (since r is), even 0 in case of no gene de-amplification ($r = 0$). Thus drug resistance takes over in the model, no matter what, and this is consistent with medical experience. Clearly, in a specific case the actual parameters may be favorable and it may take a very long time. These precisely are the situations when chemotherapy will be successful.

2.4. **The role of the objective in an optimal control formulation.** In general therefore the problem becomes to delay the onset of the time when drugs are no longer effective. We consider this problem now as an optimal control problem. Obviously there exist many, and non-equivalent, ways how to formulate this as a mathematical model. In an optimal control problem, the general structure has the form to minimize (or maximize) some objective given in the form

$$J = \int_0^T L(N,u)dt + \varphi(T, N(T)) \tag{12}$$

over all admissible controls $u : [0,T] \to [0, u_{\max}]$ subject to the dynamics (5) and additional constraints that may be imposed. For example, the objective might be chosen as to maximize the total time T while restricting the overall amount of drug given, $\int_0^T u(t)dt \leq A$, and requiring not to violate an upper bound on the number of cancer cells, $S(t) + R(t) \leq \bar{N}$. State space constraints, besides leading to a much more difficult problem mathematically, have the disadvantage that in principle they require to monitor the number of cancer cells constantly which is not feasible. It therefore is more practical, and easier to handle mathematically, to formulate the constraints on drugs and cancer cells implicitly by including these terms in the objective. Since chemotherapy is normally given over some specified time period, it also seems reasonable to minimize an objective of the type (12) over a fixed time interval $[0,T]$. The objective of treatment is to kill as many of the sensitive cancer cells possible while limiting both the size of the resistant subpopulation and the overall toxicity to the patient. Mathematically we therefore for a moment consider the general problem

(P): minimize $J = \int_0^T L(N,u)dt + \varphi(N(T))$ over all Lebesgue measurable controls $u : [0,T] \to [0, u_{\max}]$ subject to the dynamics $\dot{N} = (A + uB)N$ with $N(0) = N_0$ given and with positive components.

Necessary conditions for optimality of a control $u_* : [0,T] \to [0, u_{\max}]$ are given by the Pontryagin Maximum Principle [22]. It is easily seen that for our case the abnormal situation is not possible and hence these conditions can be stated as follows: if u_* is an optimal control with corresponding trajectory $N_* : [0,T] \to \mathbb{P} = \{(S,R) : S > 0, R > 0\}$, then it follows that there exists an absolutely continuous function λ,

which we write as row-vector, $\lambda = (\lambda_0, \lambda_1) : [0,T] \to (\mathbb{R}^2)^*$, satisfying the adjoint equation

$$\dot{\lambda} = -\lambda(A + u_* B) - \frac{\partial L}{\partial N}(N_*, u_*), \qquad \lambda(T) = \frac{\partial \varphi}{\partial N}(N_*(T)), \tag{13}$$

such that the optimal control u_* minimizes the Hamiltonian H,

$$H = L(N,u) + \lambda(A + uB)N, \tag{14}$$

over the control set $[0, u_{\max}]$ along $(\lambda(t), N_*(t))$.

If the partial derivatives of the Lagrangian L and penalty function φ along the optimal trajectory and control are non-negative, then analogously to the positive invariance of the states under the dynamics, it follows that the adjoint space $\mathbb{P}^* = \{(\lambda_0, \lambda_1) : \lambda_0 > 0,\ \lambda_1 > 0\}$ is negatively invariant under the adjoint flow.

Proposition 2. *For any Lebesgue measurable control $u : [0,T] \to [0, u_{\max}]$ the solution $\lambda(\cdot)$ to (18) exists on $[0,T]$. If all partial derivatives $\frac{\partial L}{\partial N_i}(N_*(t), u_*(t))$ are non-negative on $[0,T]$ and if the partial derivatives $\frac{\partial \varphi}{\partial N_i}(N_*(T))$ are positive, then λ_1 and λ_2 are both positive.*

Proof. As solution to a linear ODE the adjoint variable exists over the full interval. Let σ denote the infimum over all times η such that both λ_0 and λ_1 are positive on $[\eta, T]$,

$$\sigma = \inf\{\eta \le T : \lambda_0(t) > 0 \text{ and } \lambda_1(t) > 0 \text{ for } \eta \le t \le T\}.$$

The proof is exactly as for Proposition 1, but now using the reverse comparison: Suppose α and β are bounded Lebesgue-measurable functions on $\mathbb{R}$ and consider the ODE $\dot{\mu} = \alpha\mu + \beta$. If $\mu(t_1) > 0$ and $\beta(t) \le 0$ for $t \le t_1$, then $\mu(t) > 0$ for all $t \le t_1$. □

Corollary 1. *Under the assumptions of Proposition 2 both the states R and S and the costates λ_0 and λ_1 are positive over $[0,T]$.* □

The form of the Lagrangian L and the penalty function φ will largely determine the structure of optimal controls. There exists no clear biological indication for the choice of the mathematical objective and here some degree of freedom can be exercised with really no clear favorite. Many researchers elect to use objectives which are quadratic in the control, like, for example,

$$L(N,u) = N^T Q N + u^2 \quad \text{and} \quad \varphi(N) = N^T Q_T N, \tag{15}$$

with positive semi-definite matrices Q and Q_T. (If the entries of Q and Q_T are chosen non-negative, then the conditions in Proposition 2 are satisfied.) This choice has the advantage that it generates a strictly convex Hamiltonian function H which has a unique minimum. However, this minimum is given as a function of N and λ, $u = u(\lambda, N)$, i.e. is dependent on the multiplier. Thus a two-point boundary value problem given by the dynamics (5) and the adjoint equation (13) needs to be solved with $u = u(\lambda, N)$ given as the solution of the minimization problem (14). Essentially the problem then is one of numerical analysis. Because of the bilinear dynamics this leads to nonstandard nonlinear equations and questions related to the existence of multiple solutions to the two-point boundary value problem can complicate the structure of solutions. At least they raise the issue of optimality of any numerically found solution. In [19] we have considered a general class of problems which also matches these quadratic models and we have formulated sufficient conditions for optimality which allow to verify at least strong local minimality of such solutions.

From a practical point of view, choosing an objective that is quadratic in the control tends to undermine the side effects and it favors giving partial doses. Typically solutions will have segments when the control is given by the stationary point of the Hamiltonian (whenever this minimum lies in the interior of the control set) implying the use of time-varying partial doses dependent on the number of cancer cells at the moment. Controls of this type are not yet realistically medically.

An alternative way, and this is the one we pursue in this paper, is the use of a Lagrangian function L which is linear in the control u. There exists some biological justification for this if one equates the numbers of cells killed with the numbers of ineffective cell divisions (and, at least for some range, this number can reasonably be assumed to be proportional to the overall amount of drugs given). Mathematically, we thus consider the problem to minimize an objective of the form

$$J = kN(T) + \int_0^T (\ell N(t) + u(t))\, dt \to \min \tag{16}$$

where k and ℓ are row-vectors of weights with the components of k positive and those of ℓ non-negative. The penalty term $kN(T)$ represents a weighted average of the total number of cancer cells at the end of an assumed fixed therapy interval $[0, T]$ and the term $\ell N(t)$ models cumulative effects during the therapy. The control term $u(t)$ in the Lagrangian models the negative side effects of the drugs, measured in the L_1 norm. The parameters k and ℓ can also be used to put a stronger emphasis on the number of cancer cells since it can be argued that a duplication of the cancer or the drug dose is more hazardous than a duplication of the objective would represent. For the methods used below it is important that the Hamiltonian is linear in the control u, but its structure in N can be rather arbitrary, i.e. more generally we could consider

$$J = \varphi(N(T)) + \int_0^T (L(N(t)) + u(t))\, dt \to \min \tag{17}$$

with smooth penalty functions φ and Lagrangian L depending on the state N if such an effect is considered important. In this paper, however, we use linear functions. The mathematical problem therefore becomes to find a Lebesgue-measurable function $u : [0, T] \to [0, u_{\max}]$ which minimizes (16) subject to the dynamical equations (3) and (4).

2.5. **Analysis of optimal controls.** Necessary conditions for optimality of a control $u_* : [0, T] \to [0, u_{\max}]$ are given by the Pontryagin Maximum Principle [22]. As mentioned already, the abnormal situation is not possible and hence these conditions can be stated as follows: if u_* is an optimal control with corresponding trajectory $N_* : [0, T] \to \mathbb{P} = \{(S, R) : S > 0, R > 0\}$, then it follows that there exists an absolutely continuous function λ, which we write as row-vector, $\lambda = (\lambda_0, \lambda_1) : [0, T] \to (\mathbb{R}^2)^*$, satisfying the adjoint equation

$$\dot\lambda = -\lambda(A + u_* B) - \ell, \qquad \lambda(T) = k, \tag{18}$$

such that the optimal control u_* minimizes the Hamiltonian H,

$$H = \ell N + u + \lambda(A + u_* B)N, \tag{19}$$

over the control set $[0, u_{\max}]$ along $(\lambda(t), N_*(t))$. Since the Hamiltonian is linear in u and the control set is an interval, defining the switching function Φ by

$$\Phi(t) = \frac{\partial H}{\partial u} = 1 + \lambda(t) B N(t) \tag{20}$$

we therefore have that

$$u_*(t) = \begin{cases} 0 & \text{if } \Phi(t) > 0 \\ u_{\max} & \text{if } \Phi(t) < 0 \end{cases}. \tag{21}$$

A priori the control is not determined by the minimum condition at times where $\Phi(t) = 0$. However, if $\Phi(t)$ vanishes on an open interval, also all its derivatives must vanish and this for our problem will determine the control. Controls of this kind are called *singular* while we refer to piecewise constant controls as *bang-bang* controls. Optimal controls then need to be synthesized from these and other, possibly more complicated, candidates. For this purpose we need to compute the derivatives of the switching functions using the system and adjoint equations. A simple direct verification proves the following basic formula:

Lemma 1. *Suppose G is a constant matrix and let $\Psi(t) = \lambda(t)GN(t)$, where N is a solution to the system equation (5) corresponding to the control u and λ is a solution to the corresponding adjoint equation (45). Then*

$$\dot{\Psi}(t) = \lambda(t)[A + uB, G]N(t) - \ell GN(t), \tag{22}$$

where $[F, G]$ denotes the commutator of the matrices F and G defined as $[F, G] = GF - FG$.

Differentiating the switching function $\Phi(t) = 1 + \lambda(t)BN(t)$ twice gives

$$\dot{\Phi}(t) = \lambda(t)[A, B]N(t) - \ell BN(t), \tag{23}$$

$$\begin{aligned} \ddot{\Phi}(t) &= \lambda(t)[A + u(t)B, [A, B]]N(t) - \ell[A, B]N(t) - \ell B(A + uB)N(t) \\ &= \{\lambda(t)[A, [A, B]]N(t) - \ell[A, B]N(t) - \ell BAN\} \\ &\qquad + u\{\lambda(t)[B, [A, B]]N(t) - \ell B^2N(t)\}. \end{aligned} \tag{24}$$

If the control u is singular on an open interval I, then we have

$$0 \equiv \Phi(t) \equiv \dot{\Phi}(t) \equiv \ddot{\Phi}(t) \tag{25}$$

and formally the control can be computed as

$$u_{\sin}(t) = -\frac{\lambda(t)[A, [A, B]]N(t) - \ell[A, B]N(t) - \ell BAN(t)}{\lambda(t)[B, [A, B]]N(t) - \ell B^2N(t)} \tag{26}$$

provided the denominator doesn't vanish. Whether the singular control will be admissible, i.e. whether it will obey the control bounds $0 \le u \le u_{\max}$, will depend on the parameter values, but also on the region in the state space where the state $(S, R)^T$ lies and cannot be answered in general. In this case the singular control is called of order 1 and it is then a necessary condition for optimality of $u_{\sin}$, the so-called generalized Legendre-Clebsch condition [15], that this denominator actually is negative, i.e.

$$\frac{\partial}{\partial u}\frac{d^2}{dt^2}\frac{\partial H}{\partial u} < 0. \tag{27}$$

For this problem we have

$$B^2 = (q - 2)aB \tag{28}$$

and therefore it follows from $\dot{\Phi}(t) \equiv 0$ that

$$\ell B^2N(t) = (q - 2)a\ell BN(t) = (q - 2)a\lambda(t)[A, B]N(t). \tag{29}$$

Hence

$$\frac{\partial}{\partial u}\frac{d^2}{dt^2}\frac{\partial H}{\partial u} = \lambda\left([B, [A, B]] + a(2 - q)[A, B]\right)N. \tag{30}$$

A straightforward, but somewhat tedious computation shows that

$$[B,[A,B]] + a(2-q)[A,B] = 2a^2rc \begin{pmatrix} q(2-q) & -(2-q)^2 \\ q^2 & -q(2-q) \end{pmatrix} = 2a^2rcww^\perp \quad (31)$$

where

$$w = \begin{pmatrix} 2-q \\ q \end{pmatrix} \quad \text{and} \quad w^\perp = (q, q-2). \quad (32)$$

Thus we get

$$\begin{aligned} \frac{\partial}{\partial u}\frac{d^2}{dt^2}\frac{\partial H}{\partial u} &= 2a^2rc\lambda ww^\perp N \\ &= 2a^2rc\left\{(2-q)\lambda_0 + q\lambda_1\right\}(qS - (2-q)R)\,. \end{aligned} \quad (33)$$

Since $(2-q)\lambda_0 + q\lambda_1 > 0$ the generalized Legendre-Clebsch condition therefore implies:

Proposition 3. *Singular controls are not optimal in regions of the state space where* $qS > (2-q)R$.

This holds as long as the resistant population is very small and then optimal controls will be bang-bang, i.e. correspond to sessions of full dose chemotherapy with rest periods interlaced. However, as the portion of resistant cells R increases, the Legendre-Clebsch condition will be satisfied and if admissible, there are mathematical reasons to suspect that it indeed will be the optimal control in this case. It is also quite intuitive that a full dose may do more harm than good once resistance builds up and thus the optimal strategy may switch to give partial doses, i.e. use singular controls.

3. Mathematical Models for Cancer Chemotherapy with Multiple Killing Agents under Evolving Drug Resistance.

Medical experience shows that over time cancer cells will develop resistance to the killing drug until treatment no longer will be effective, in fact even detrimental. For the model above, even with constant maximum dose (which of course is unrealistic) the dynamics for the resistant group is growing exponentially, $\dot{R} \geq (1-r)cR$, and resistance will eventually take over. The best one can therefore hope for is to keep the resistant population small as long as feasible. It has been noted in clinical experiments that in the absence of the drug cancer cells can lose acquired drug resistance through *gene deamplification* [2, 10]. However, drug free sessions allow for unrestricted growth of the tumor and it is important to inhibit this process of "repopulation" [31]. Thus an important therapy strategy is to use *combinations of drugs* in order to delay developing acquired drug resistance. We are assuming that the drugs used are different in their operating mechanism, hence acquired drug resistance is due to different molecular mechanisms. Otherwise there is no need to distinguish between them and they can be grouped together. Mathematically this leads to a structurally quite different model which we here consider for the case of two killing agents. Due to the drugs' interactions the dynamics now will be quadratic in the controls, but with an indefinite structure, and the corresponding Hamiltonian needs to be minimized over a compact control set. These are non-standard, fully nonlinear problems which to the best of our knowledge have not been considered before in this form.

3.1. **Modeling Aspects.** We consider two cytostatic killing agents whose dosages are labelled u_1 and u_2, both with values in intervals $[0, u^i_{\max}]$, $i = 1, 2$. (As before, the value 0 represents "no dose" and the value $u^i_{\max}$ corresponds to a "maximum dose"). The state space now is comprised of four compartments, a compartment $\mathcal{S}$ of cells sensitive to both drugs, a compartment $\mathcal{L}_1$ of cells sensitive to drug u_1, but resistant to drug u_2, a compartment $\mathcal{L}_2$ of cells sensitive to drug u_2, but resistant to drug u_1, and a compartment $\mathcal{R}$ of cells resistant to both drugs. We denote the average numbers of cells in these compartments by the corresponding capital Roman letters.

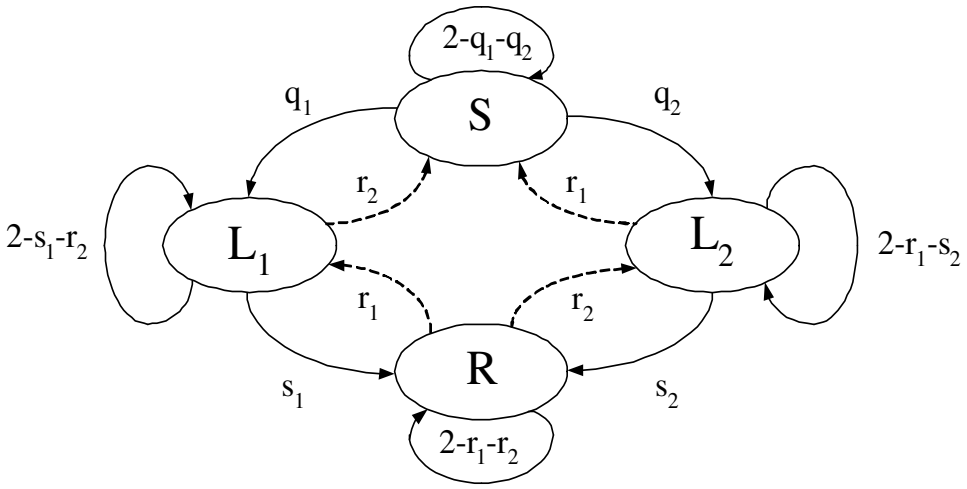

FIGURE 1. Drug resistance with two killing agents

As above, it is assumed that the drugs kill a fixed proportion u_1 respectively u_2 of the outflow of the sensitive cells at time t and therefore only the remaining fraction of cells undergoes cell division. If we denote the mean inverse transit times through the compartments by a, b_1, b_2 and c respectively, then, for example, and exactly as above, only a fraction

$$(1 - u_1)(2 - s_1 - r_2)b_1 L_1 \tag{34}$$

of cells from $\mathcal{L}_1$ reenters $\mathcal{L}_1$. Here s_1 is the probability that the second of the two daughter cells becomes resistant also to the second drug u_2, i.e. enters $\mathcal{R}$, and r_2 gives the probability of gene deamplification to go from $\mathcal{L}_1$ into $\mathcal{S}$, i.e. the drug resistance to the second drug u_2 is removed or lost. As above it is assumed that one of the two daughter cells will reenter $\mathcal{L}_1$ (see Fig. 1). However, the terms involving cross-over flows with the sensitive compartment change considerably simply since the two drugs cannot kill the same cell twice. Since the drugs interact with large numbers of cancer cells, it is reasonable to assume that the drugs act independently. Other dependency relations can be postulated, but this will change the return flows to the sensitive compartment. We limit ourselves to making this independence assumption. In this case the return flow is given by

$$(1 - u_1)(1 - u_2)(2 - q_1 - q_2)aS \tag{35}$$

and thus becomes quadratic in the controls. In many probabilistic models (e.g. [4]) in order to simplify the analysis similar quadratic terms are linearized with the reasoning that the probabilities involved are small. But for this model the validity of such an argument is questionable and is not needed. Overall the dynamics we consider is therefore given as follows:

$$\dot{S} = -aS + (1-u_1)(1-u_2)(2-q_1-q_2)aS + (1-u_1)r_2b_1L_1 + (1-u_2)r_1b_2L_2, \tag{36}$$

$$\dot{L}_1 = -b_1L_1 + (1-u_1)(2-s_1-r_2)b_1L_1 + (1-u_1)(1-u_2)q_1aS + r_1cR, \tag{37}$$

$$\dot{L}_2 = -b_2L_2 + (1-u_2)(2-s_2-r_1)b_2L_2 + (1-u_1)(1-u_2)q_2aS + r_2cR, \tag{38}$$

$$\dot{R} = -cR + (2-r_1-r_2)cR + (1-u_1)s_1b_1L_1 + (1-u_2)s_2b_2L_2. \tag{39}$$

Proposition 4. *For all Lebesgue measurable controls $u = (u_1, u_2) : [0,\infty) \to [0, u_{\max}^1] \times [0, u_{\max}^2]$ the solution $N(\cdot) = (S(\cdot), L_1(\cdot), L_2(\cdot), R(\cdot))^T$ exists on $[0,\infty)$ and its components are positive.*

Proof. As in Proposition 1 a contradiction arises if we assume there is a finite first time any of the components would vanish. □

The dynamical equations become more transparent if we change the control variables to $v_i = 1 - u_i$. Then the dynamical equations can be written in the form

$$\dot{N} = (A + v_1B_1 + v_2B_2 + v_1v_2C)N \tag{40}$$

where

$$A = \begin{pmatrix} -a & 0 & 0 & 0 \\ 0 & -b_1 & 0 & r_1c \\ 0 & 0 & -b_2 & r_2c \\ 0 & 0 & 0 & (1-r_1-r_2)c \end{pmatrix},\ C = a\begin{pmatrix} 2-q_1-q_2 & 0 & 0 & 0 \\ q_1 & 0 & 0 & 0 \\ q_2 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, \tag{41}$$

$$B_1 = b_1\begin{pmatrix} 0 & r_2 & 0 & 0 \\ 0 & 2-s_1-r_2 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & s_1 & 0 & 0 \end{pmatrix},\ B_2 = b_2\begin{pmatrix} 0 & 0 & r_1 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 2-s_2-r_1 & 0 \\ 0 & 0 & s_2 & 0 \end{pmatrix}. \tag{42}$$

As above, the optimal control problem becomes to choose Lebesgue measurable functions $v_i : [0,T] \to [v_{\min}^i, 1]$, $v_{\min}^i = 1 - u_{\max}^i$, $i = 1, 2$, to minimize an objective of the form

$$J = kN(T) + \int_0^T \ell N(t) - mv(t)dt \to \min \tag{43}$$

subject to the dynamics (40). Here $m = (m_1, m_2)$ also is a row-vector of positive weights.

3.2. **Analysis of optimal controls.** It is again easily seen that optimal controls are normal. Thus, if $v = (v_1^*, v_2^*)$ is an optimal control with corresponding trajectory

$$N_* = (S_*, L_1^*, L_2^*, R_*) : [0,T] \to \mathbb{P} = \{(S, L_1, L_2, R) : S > 0, L_1 > 0, L_2 > 0, R > 0\}, \tag{44}$$

then it follows that there exists an absolutely continuous function λ, which we write as row-vector, $\lambda = (\lambda_0, \lambda_1, \lambda_2, \lambda_3) : [0,T] \to (\mathbb{R}^4)^*$, satisfying the adjoint equation

$$\dot{\lambda} = -\lambda(A + v_1^*B_1 + v_2^*B_2 + v_1^*v_2^*C) - \ell, \qquad \lambda(T) = k, \tag{45}$$

such that the optimal control v_* minimizes the Hamiltonian H,

$$H = \ell N - mv_1^* - mv_2^* + \lambda(A + v_1^* B_1 + v_2^* B_2 + v_1^* v_2^* C)N, \tag{46}$$

over the control set $V = [v_{\min}^1, 1] \times [v_{\min}^2, 1]$ along $(\lambda(t), N_*(t))$. For sake of a simpler notation we henceforth take $v_{\min}^1 = v_{\min}^2 = 0$. The qualitative results do not change.

Analogously to the positive invariance of $\mathbb{P}$ under the dynamics, it follows that the adjoint space $\mathbb{P}^* = \{(\lambda_0, \lambda_1, \lambda_2, \lambda_3) : \lambda_i > 0 \text{ for } i = 0, 1, 2, 3\}$ is negatively invariant under the adjoint flow.

Proposition 5. *For any Lebesgue measurable control $v : (-\infty, T] \to V$ the solution $\lambda(\cdot)$ to (45) exists on $(-\infty, T]$ and all its components are positive.*

Proof. The adjoint equation is of the form $\dot{\lambda} = -\ell - \lambda M$ with M is matrix with only non-negative entries and $\lambda(T) = k$ has positive entries. Again let σ denote the infimum over all times η such that all components of λ are positive on $[\eta, T]$,

$$\sigma = \inf\{\eta \leq T : \lambda_i(t) > 0 \text{ for } i = 0, \ldots, 4, \text{ and } \eta \leq t \leq T\}.$$

But if ι denotes an index where $\lambda_\iota(\tau) = 0$, then we have $\dot{\lambda}_\iota(\tau) < 0$. Contradiction. □

Corollary 2. *All states R, L_1, L_2 and S and all costates λ_i, $i = 0, 1, 2, 3$ are positive over $[0, T]$.* □

We now analyze properties of optimal controls. Define functions

$$\Theta(t) = \lambda(t)CN(t), \qquad \Xi(t) = \ell N(t) + \lambda(t)AN(t), \tag{47}$$

$$\Psi_1(t) = -m_1 + \lambda(t)B_1 N(t), \qquad \Psi_2(t) = -m_2 + \lambda(t)B_2 N(t), \tag{48}$$

so that the Hamiltonian takes the form

$$H = \Theta(t)v_1 v_2 + \Psi_1(t)v_1 + \Psi_2(t)v_2 + \Xi(t). \tag{49}$$

By Corollary 2 we have that

$$\Theta(t) = \{(2 - q_1 - q_2)\lambda_0(t) + q_1\lambda_1(t) + q_2\lambda_2(t)\}\, aS(t) > 0 \tag{50}$$

and thus the minimization of the Hamiltonian is equivalent to minimize

$$\hat{H} = v_1 v_2 + \hat{\Psi}_1(t)v_1 + \hat{\Psi}_2(t)v_2 \tag{51}$$

over $V = [0, 1] \times [0, 1]$ where

$$\hat{\Psi}_i(t) = \frac{\Psi_i(t)}{\Theta(t)}, \qquad i = 1, 2. \tag{52}$$

Define switching curves $\mathcal{C}_1$ and $\mathcal{C}_2$ in $(\hat{\Psi}_1, \hat{\Psi}_2)$-space as the graphs of functions $\mathcal{C}_1 : \hat{\Psi}_1 = \Gamma(\hat{\Psi}_2)$ and $\mathcal{C}_2 : \hat{\Psi}_2 = \Gamma(\hat{\Psi}_1)$ where

$$\Gamma(x) = \begin{cases} -1 & \text{if } x \leq -1 \\ x & \text{if } -1 \leq x \leq 0 \\ 0 & \text{if } x \geq 0 \end{cases}. \tag{53}$$

These two curves divide the $(\hat{\Psi}_1, \hat{\Psi}_2)$-space into four sectors as shown in Fig. 2 and the optimal control is given by one of the vertices of V as the vector $(\hat{\Psi}_1(t), \hat{\Psi}_2(t))$ lies in one of these regions. More precisely, we have:

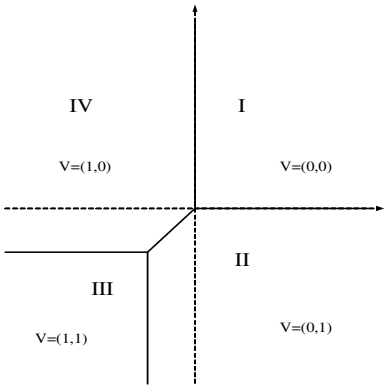

FIGURE 2. Switching curves for optimal controls

Proposition 6. *If $v_* = (v_1^*, v_2^*) : [0,T] \to [0,1] \times [0,1]$ is an optimal control, then*

$$v_*(t) = \begin{cases} (0,0) & \text{if } \hat\Psi_1(t) > 0 \text{ and } \hat\Psi_2(t) > 0; \\ (1,0) & \text{if } \hat\Psi_1(t) < 0,\ \hat\Psi_1(t) < \hat\Psi_2(t), \text{ and } \hat\Psi_2(t) > -1; \\ (0,1) & \text{if } \hat\Psi_2(t) < 0,\ \hat\Psi_1(t) > \hat\Psi_2(t), \text{ and } \hat\Psi_1(t) > -1; \\ (1,1) & \text{if } \hat\Psi_1(t) < -1 \text{ and } \hat\Psi_2(t) < -1. \end{cases} . \tag{54}$$

On the boundary segments between these regions we have that

$$v_1^*(t) = \begin{cases} 0 & \text{if } \hat\Psi_1(t) < \Gamma(\hat\Psi_2(t)) \\ 1 & \text{if } \hat\Psi_1(t) > \Gamma(\hat\Psi_2(t)) \end{cases} \quad \text{and} \quad v_2^*(t) = \begin{cases} 0 & \text{if } \hat\Psi_2(t) > \Gamma(\hat\Psi_1(t)) \\ 1 & \text{if } \hat\Psi_2(t) < \Gamma(\hat\Psi_2(t)) \end{cases} . \tag{55}$$

If $\hat\Psi_1(t) = \hat\Psi_2(t) \in (-1,0)$, then the control is either $v_*(t) = (1,0)$ or $v_*(t) = (0,1)$.

Proof. The minimization problem is equivalent to minimizing the indefinite quadratic form

$$(v_1 + \hat\Psi_2(t))(v_2 + \hat\Psi_1(t)) \tag{56}$$

over $[0,1] \times [0,1]$ and the minimum is always attained at one of the vertices. The values of $\hat H$ at the vertices are 0 at $(0,0)$, $\hat\Psi_1(t)$ at $(1,0)$, $\hat\Psi_2(t)$ at $(0,1)$ and $1 + \hat\Psi_1(t) + \hat\Psi_2(t)$ at $(1,1)$. Thus the minimum value ρ is given by

$$\rho = \begin{cases} 0 & \text{if } \hat\Psi_1(t) > 0 \text{ and } \hat\Psi_2(t) > 0; \\ \hat\Psi_1(t) & \text{if } \hat\Psi_1(t) < 0,\ \hat\Psi_1(t) < \hat\Psi_2(t), \text{ and } \hat\Psi_2(t) > -1; \\ \hat\Psi_2(t) & \text{if } \hat\Psi_2(t) < 0,\ \hat\Psi_1(t) > \hat\Psi_2(t), \text{ and } \hat\Psi_1(t) > -1; \\ 1 + \hat\Psi_1(t) + \hat\Psi_2(t) & \text{if } \hat\Psi_1(t) < -1 \text{ and } \hat\Psi_2(t) < -1. \end{cases} \tag{57}$$

These inequalities define the open regions in (55). As the vector $(\hat\Psi_1(t), \hat\Psi_2(t))$ crosses one of the following four boundary segments,

$$\partial_1 = \{(\hat\Psi_1(t), \hat\Psi_2(t)) : \hat\Psi_1(t) < -1,\ \hat\Psi_2(t) = -1\}, \tag{58}$$

$$\partial_2 = \{(\hat\Psi_1(t), \hat\Psi_2(t)) : \hat\Psi_1(t) = -1,\ \hat\Psi_2(t) > -1\}, \tag{59}$$

$$\partial_3 = \{(\hat\Psi_1(t), \hat\Psi_2(t)) : \hat\Psi_1(t) > 0,\ \hat\Psi_2(t) = 0\}, \tag{60}$$

and

$$\partial_4 = \{(\hat\Psi_1(t), \hat\Psi_2(t)) : \hat\Psi_1(t) = 0,\ \hat\Psi_2(t) > 0\}, \tag{61}$$

the control v_1 remains constant as ∂_1 or ∂_3 are crossed and v_2 remains constant as ∂_2 or ∂_4 are crossed. Along the fifth boundary piece

$$\partial_5 = \{(\hat{\Psi}_1(t), \hat{\Psi}_2(t)) : \hat{\Psi}_1(t) = \hat{\Psi}_2(t),\ -1 < \hat{\Psi}_1(t) < 0\}, \tag{62}$$

both $v_* = (1, 0)$ or $v_* = (0, 1)$ are minimizing, but no other control is. □

Proposition 6 completely determines the controls in the open regions in Fig. 2. It does not, however, exclude more degenerate cases corresponding to singular controls. For example, if $(\hat{\Psi}_1(t), \hat{\Psi}_2(t)) \in \partial_1$, then the minimizing control satisfies $v_1^* = 1$, but no information about v_2 follows from the minimization condition and in principle this control could be arbitrary. If $(\hat{\Psi}_1(t), \hat{\Psi}_2(t)) \in \partial_1$ for t in some open interval I, then $v_1^* \equiv 1$ on I and, as before, a possible singular control v_2^* is determined by differentiation the defining relation, (that is $\Psi_2(t) + \Theta(t) \equiv 0$ in case of ∂_1,) twice with respect to t and then solving for v_2. If this control is admissible, it again needs to satisfy the generalized Legendre-Clebsch condition (27) in order to be optimal. In principle this analysis needs to be carried out for all boundary pieces ∂_i, $i = 1, \ldots, 5$. However, the main candidates will be bang-bang controls as the vector $(\hat{\Psi}_1(t), \hat{\Psi}_2(t))$ crosses these boundary segments transversally.

One important qualitative feature of the structure of optimal controls which follows from the geometry of the switching curves in Fig. 2 is that it is not optimal to directly switch between the controls $v_* = (0, 0)$ and $v_* = (1, 1)$. Thus it is never optimal to simultaneously withdraw or start administering both drugs at the same time. This, of course, does not exclude that both drugs may be given at the same time - and it may be beneficial to do so if the benefit of the combined cell kill outweighs the side effects. But drugs should be initiated respectively withdrawn one at a time. Intuitively this makes sense: in the absence of one drug one would like to administer the other in order to prevent a strong repopulation and hope that at the same time the resistance with respect to the first drug will decline in its absence. Unfortunately, over time the cumulative toxic side effects will build up and this may necessitate to withdraw them both. In fact, in all the simulations we ran, the compartment R of cells resistant to both drugs takes over even from the tiniest fraction of initial data and eventually forces the shut down of both drugs as the "optimal" solution.

4. **Simulations.** We include some simulations for the multi-drug model. The numerical values chosen are just for illustrative purposes and are not based on medical data. The data for the objective are the same for all runs and we simply picked all parameters arising in the objective as 1, i.e. $k = \ell = (1, 1, 1, 1)$ and $m = (1, 1)$. Also, for simplicity we simply take $u^1_{\max} = u^2_{\max} = 1$. As transition probabilities in the dynamics we chose $q_1 = .02$, $q_2 = .02$, $r_1 = .005$, $r_2 = .01$, $s_1 = .02$, and $s_2 = .02$. In the data for the cell-cycle parameters we fix $a = .4$, $b_1 = .35$, and $b_2 = .35$, but for some of the runs we vary the transit time through the compartment R of cells that are resistant to both drugs. Clearly these parameters strongly influence the structure of controls and here we only compare briefly runs for $c = .3$ and for $c = .8$. The value $c = .3$ corresponds to a situation when the transit times through the resistant compartments are somewhat slower than for the sensitive compartment (tumors that are responding to treatment) while $c = .8$ means that these doubly resistant cells duplicate on average twice as fast, a situation more reminiscent of malignant situations. In the simulations below the time horizon is always taken as the interval $[0, 10]$.

We compare an extremal control (i.e. one that satisfies the necessary conditions for optimality) with two reasonable ad hoc choices as reference controls. Reference control 1 applies both drugs simultaneously at full dose over the intervals $[0, 2]$, $[4, 6]$ and $[8, 10]$ with rest periods in between while reference control 2 alternates the drugs over these intervals with drug 1 given on $[0, 2]$, $[4, 6]$ and $[8, 10]$ and drug 2 given on $[2, 4]$ and $[6, 8]$ so that there is no rest-period over the therapy interval. Figs. 3 and 4 compare the response of the system for an initial condition given by $S(0) = .90$, $L_1(0) = .05$, $L_2(0) = .05$, and $R = 0$ for the case when $c = .3$. In all figures the solid graph represents the response of the sensitive cells S, the dashed curves give the responses of L_1 and L_2 and the dash-dot curve gives the response of the fully resistant compartment R. Note that the curves for L_1 and L_2 in Fig. 3 overlay because of the symmetries in the data. In this case it is evident that alternating the drugs is the better strategy. The reason simply lies in the fact that resistance is still very small and does not yet build up significantly over the therapy interval. Side effects have not yet become an issue for this initial condition.

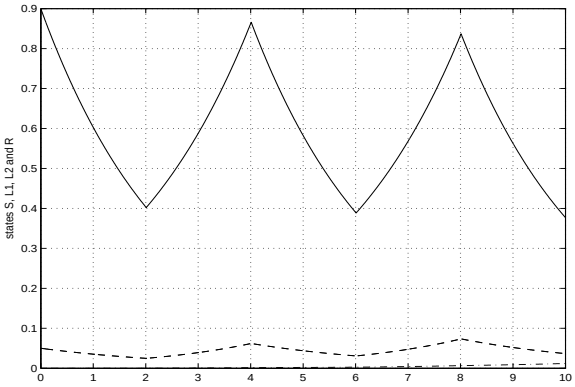

FIGURE 3. Response to reference control 1 for $c = .3$

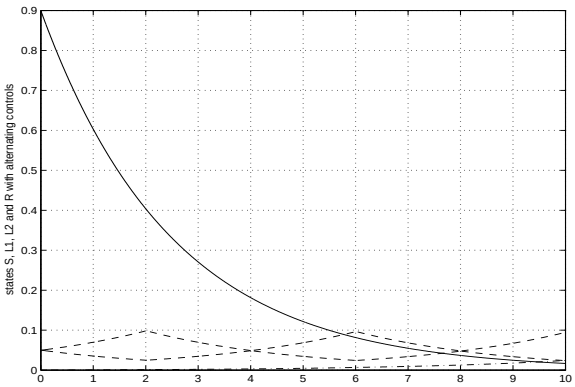

FIGURE 4. Response to reference control 2 for $c = .3$

On the other end of the spectrum of possibilities, Figs. 5 and 6 compare the response of the system for the same initial condition ($S(0) = .90$, $L_1(0) = .05$,

$L_2(0) = .05$, $R = 0$,) but now for the case when $c = .8$. In this case the strategy of alternating the drugs is drastically inferior. Comparing the total number of cancer cells that had been normalized to 1 at the initial time, reference control 1 leads to a reduction in the total number of cancer cells to 0.7348, but the fully resistant population R has grown to $R = .2826$, more than one third of the overall number of cancer cells. For the alternating strategy 2 the total number of cancer cells actually increases to 1.4957 and the fully resistant portion makes up 1.3467 of it, a horrendous outcome. The reason is that resistance, once established at any ever so small proportion, rapidly takes over. Hence the more drug can be applied initially, the better it seems to be. Fig. 8 gives the response to an extremal control that was computed by backward integration from the same terminal condition that was generated with the now better reference control 1. The corresponding control is identical $v_2^* = 1$ over $[0, 10]$ (i.e. the second drug is NOT used) and the first control v_1^* switches from $v = 0$ to $v = 1$ at $\tau = 6.11$. In this case, with the same number of cancer cells at the end of the therapy interval, initially the number of cancer cells is 1.0216; thus there is a comparable response in reducing the cancer cells, but it is achieved with roughly half the dose since only the first drug is given.

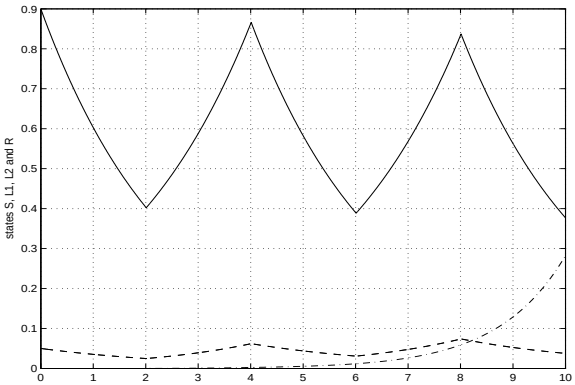

FIGURE 5. Response to reference control 1 for $c = .8$

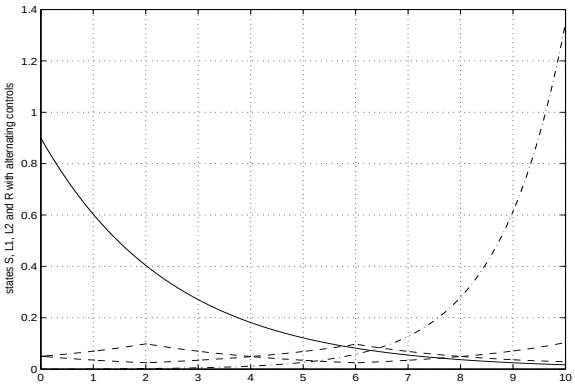

FIGURE 6. Response to reference control 2 for $c = .8$

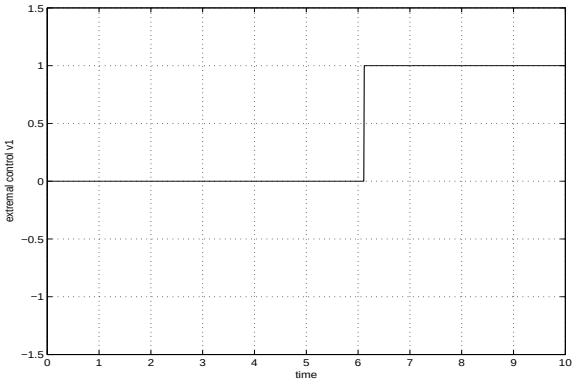

FIGURE 7. Extremal Control v_1^*

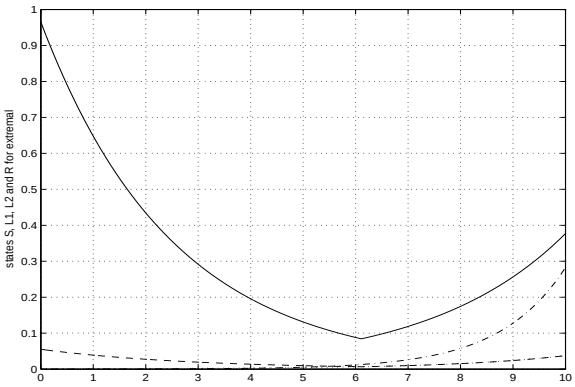

FIGURE 8. Response to extremal control

Figs. 9 and 10 compare the response of the system for a different initial condition given by $S(0) = .8$, $L_1(0) = 0$, $L_2(0) = .2$, and $R = 0$, and again for $c = .8$. As above the strategy of alternating the drugs is inferior. Comparing the total number of cancer cells that had been normalized to 1 at the initial time, reference control 1 now only leads to a minimal reduction in the total number of cancer cells to 0.9883 with the fully resistant population R growing to $R = .5309$, more than half of the overall number of cancer cells. The alternating strategy 2 is disastrous with the total number of cancer cells multiplying more than five-fold to 5.3292 and the doubly resistant portion making up 4.8843. The reason for the much shorter lead time until resistance builds up of course is that we already have 20% resistant cells, although only resistant to drug 1, at the beginning. Nevertheless, through the transitions to R this causes a resistant population to develop faster and then quickly to become dominant. Fig. 12 again gives the response to an extremal control that was computed by backward integration from the same terminal condition that was generated with the now better reference control 1. The corresponding control now is identical $v_1^* = 1$ over $[0, 10]$ (i.e. the first drug is NOT used consistent with the existing resistance to drug 1 of some of the cells) and the second control v_2^* switches from $v = 0$ to $v = 1$ at $\tau = 6.75$. In this case, however, with the same number of

cancer cells at the end of the therapy interval, initially the number of cancer cells is 1.7410 and thus giving a much better response in reducing the cancer cells which again is achieved with roughly half the dose since only the second drug is given.

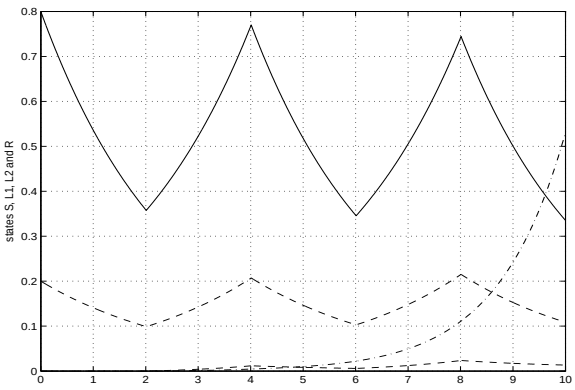

FIGURE 9. Response to reference control 1

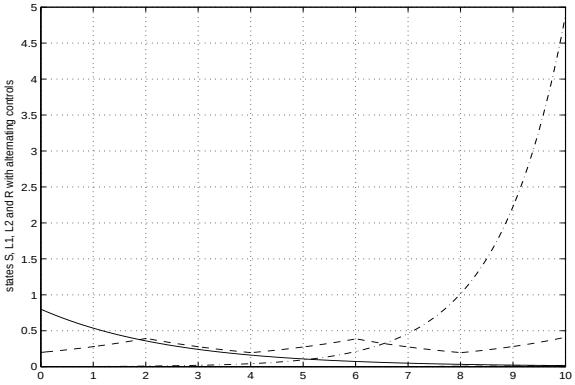

FIGURE 10. Response to reference control 2

5. **Conclusion.** The emergence of resistant clones is a universal problem of chemotherapy and one of the main, although not the only obstacle to effective treatments. The hope is that improvements in scheduling chemotherapy sessions may delay the onset of drug resistance and thus give a higher life expectancy. In this paper we presented a formulation and some preliminary analysis for two finite-dimensional models for cancer chemotherapy taking into account drug resistance with respect to single and multiple killing agents. For both systems we established invariance properties for the states and adjoint variables which enables a further analysis of the candidates for optimal protocols. Two different classes of controls representing such protocols result from the Maximum Principle: bang-bang controls, which correspond to administering full doses with rest periods in between, and singular controls representing time-varying partial doses. Conditions for optimality of singular controls in terms of the size of the resistant versus sensitive population are

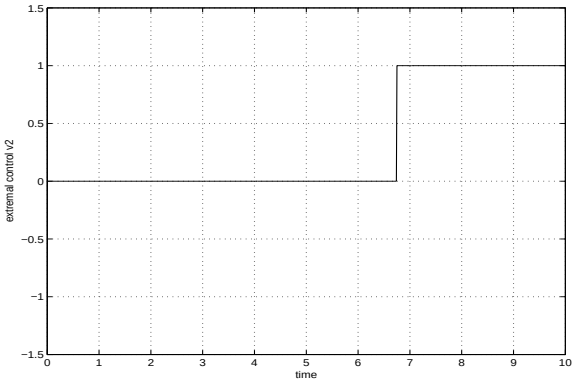

FIGURE 11. Extremal control v_2

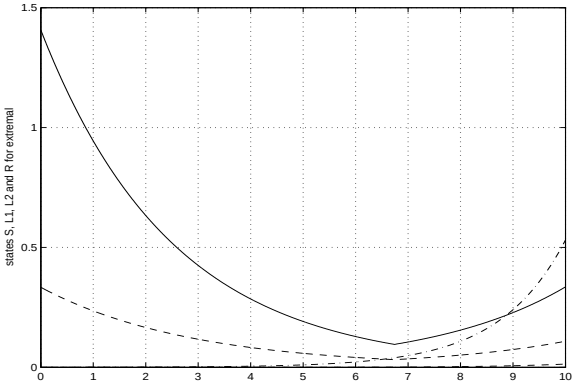

FIGURE 12. Response to extremal control

given for a single drug model. This condition indicates that if the resistant population becomes too large, then bang-bang controls may no longer be optimal since in this case the damage caused by a full dose to healthy cells outweighs the benefits of killing the cancer cells. In this situation we cannot help the patient any more with treatment with this drug and the natural choice become combination treatments involving other drugs. An example of a model for such a treatment involving two drugs is presented in the second part of the paper. Mathematically it has a different structure than the previous model since the dynamics is quadratic in the control. Our initial results show that in scheduling the therapy it is not optimal to simultaneously withdraw or initiate the treatment of both drugs.

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