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Control structures of drug resistance in cancer chemotherapy

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Abstract— **The primary factor limiting the success of chemotherapy in cancer treatment is the phenomenon of drug resistance. Resistance manifests through a diverse set of molecular mechanisms, such as the upregulation of efflux transporters on the cell membrane, enhanced DNA damage repair mechanisms, and/or the presence of cancer stem cells. Classically, these mechanisms are understood as conferred to the cell by random genetic mutations, from which clonal expansion occurs via Darwian evolution. However, the recent experimental discovery of epigenetics and phenotype plasticity complicates this hypothesis. It is now believed that chemotherapy can produce drug-resistant clones. In this work, we study a previously introduced framework of drug-induced resistance, which incorporates both random and drug induced effects. A time-optimal control problem is then presented and analyzed utilizing differential-geometric techniques. Specifically, we seek the treatment protocol which prolongs patients life by maximizing the time of treatment until a critical tumor size is reached. The general optimal control structure is determined as a combination of both bang-bang and path-constrained arcs. Numerical results are presented which demonstrate decreasing treatment efficacy as a function of the ability of the drug to induce resistance. Thus, drug-induced resistance may dramatically effect the outcome of chemotherapy, implying that factors besides cytotoxicity should be considered when designing treatment regimens.**

I. INTRODUCTION

Drug resistance is a major factor limiting the success of cancer chemotherapy. A diverse set of molecular and environmental mechanisms by which resistance manifests have been identified in the past thirty years, and our current understanding of the phenomenon remains incomplete [1]. For example, the alteration of drug targets, upregulation of efflux transporters on the cell membrane, irregular tumor vascular structure, increased microenvironmental acidity, and tumor-stroma interactions have all been shown to decrease treatment efficacy. Clinical as well as mathematical investigations continue to be an active area of current research. For a review of the mathematical literature, see [2].

As mentioned, the mechanisms by which drug resistance presents are extraordinarily diverse. However, a more fundamental question relates to the method by which these resistance-inducing traits arise in a clonal population. In general, resistance can be classified as either *pre-existing* or *acquired* [1]. Pre-existing (or intrinsic) denotes the case when resistant subpopulations exist prior to treatment, and are subsequently selected in a classic Darwinian manner after treatment is applied. Acquired resistance denotes the converse: resistant clones are generated during the course of therapy. But this latter phenomenon is more complicated, as the resistance mechanism may be *randomly acquired* due to genetic mutations and/or epigenetic phenotype-switching [3], or may be *induced* by the presence of the drug itself [4], [5], [6], [3]. For example, Pisco and colleagues have measured the relative contribution of resistance selection (pre-existing and randomly acquired) versus drug-induced resistance in HL60 leukemic cells [3]. Both pre-existing and randomly acquired resistance have been well studied mathematically. It is the latter form, *drug-induced resistance*, which is more recently discovered and lacks substantial theoretical analysis.

In a previous work we have developed a mathematical framework to distinguish between the three forms of resistance discussed above [7]. Specifically, we have formulated a minimal model of two ordinary differential equations and a single control representing the chemotherapeutic agent which may or may not be able to induce drug resistance in a dose-dependent manner. Our initial investigation was related to structural and practical identifiability questions, where we posited novel *in vitro* methods that could be utilized to measure a treatment's induction rate without *a priori* knowledge of the resistance mechanisms.

As our previous work demonstrated our model as fully identifiable, a natural extension is then to consider the control structure based on parameter values. More precisely, we are interested in understanding how the drug-induced rate of resistance impacts the overall control structure from both mathematical and clinical perspectives. An important question is then how chemotherapy should be scheduled, given a measured induction rate. Similarly, does this rate have an effect on treatment outcome? We formulate an optimal control problem, and utilize both the Pontryagin Maximum Principle and differential-geometric techniques to characterize solutions that maximize the time until treatment failure. The necessary conditions then imply that the optimal control can be synthesized as a combination of bang-bang and path-constraint arcs. Numerical results are also provided which support the computed control structure. We then investigate the dependence of the control structure and treatment efficacy as a function of both the chemotherapeutic cytotoxicity (a classical measure of the effectiveness of treatment) and the rate at which resistance is induced by the drug. Our results suggest that the latter may significantly alter the outcome of treatment, and may in fact be more important than drug toxicity in certain parameter ranges. Hence, the propensity of a treatment to promote resistance is clinically significant, demonstrating the need for further experimental

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and mathematical research.

II. MATHEMATICAL MODELING OF INDUCED DRUG RESISTANCE

We briefly review the simplified model presented in [7]. In that work, we have constructed a dynamical model which describes the evolution of drug resistance through both drug-independent (e.g. random point mutations, gene amplification) and drug-dependent (e.g. mutagenicity, epigenetic modifications) mechanisms. To our knowledge, this is the first theoretical study of the phenomena of drug-induced resistance, which although experimentally observed (see Section I) remains poorly understood. It is our hope that a mathematical analysis will provide mechanistic insight and produce a more complete understanding of this process by which cancer cells inhibit treatment efficacy.

Specifically, we assume that the cancer population is composed of two types of cells: sensitive (S) and resistant (R). For simplicity, the drug is taken as completely ineffective against the resistant population, while the log-kill hypothesis is assumed for the sensitive cells. Complete resistance is of course unrealistic, but can serve as a reasonable approximation, especially when toxicity constraints are considered, and hence limit the total amount of drug that may be administered. Furthermore, this assumption permits a natural metric on treatment efficacy that may not be present otherwise (see Section III-A). The effect of treatment is considered as a control agent $u(t)$, which we assume is a locally bounded Lebesgue measurable function taking values in $\mathbb{R}_+$. Here $u(t)$ is directly related to the applied drug dosage $D(t)$, and in the present work we assume that we have explicit control over $u(t)$. Later, during the formulation of the optimal control problem (Section III), we will make precise specifications on the control set U such that $u(t) \in U$.

Sensitive and resistant cells are assumed to compete for resources in the tumor microenvironment; this is modeled via a joint carrying capacity, which we have scaled to one. Furthermore, cells are allowed to transition between the two phenotypes in both a drug-independent and drug-dependent manner. All random transitions to the resistant phenotype are modeled utilizing a common term, ϵS, which accounts for both genetic mutations and epigenetic events occurring independently of the application of treatment. Drug-induced transitions are assumed of the form $\alpha u(t) S$, which implies that the per-capita drug-induced transition rate is directly proportional to the dosage (as we assume full control on $u(t)$, i.e. pharmacokinetics are ignored). Of course, other functional relationships may exist, but since the problem is not well-studied, we consider it reasonable to begin our analysis in this simple framework. The above assumptions then yield the following system of ordinary differential equations (ODEs):

$$\begin{aligned} \frac{dS}{dt} &= (1 - (S + R))\, S - (\epsilon + \alpha u(t))S - d u(t) S \\ \frac{dR}{dt} &= p_r\, (1 - (S + R))\, R + (\epsilon + \alpha u(t))S. \end{aligned} \tag{1}$$

All parameters are taken as non-negative, and $0 \leq p_r < 1$. The restriction on p_r emerges due to (1) already being non-dimensionalized, as p_r represents the relative growth rate of the resistant population with respect to that of the sensitive cells. The condition $p_r < 1$ thus assumes that the resistant cells divide more slowly than their sensitive counterparts, which is both observed experimentally [8], [9], [10], and necessary for our mathematical framework. Indeed, the condition $p_r \geq 1$ would imply that $u(t) \equiv 0$ is optimal under any clinically realistic objective.

As mentioned previously, many simplifying assumptions are made in system (1). Specifically, both types of resistance (random genetic and phenotypic) are modeled as dynamically equivalent; both possess the same division rate p_r and spontaneous (i.e. drug-independent) transition rate ϵ. Thus, the resistant compartment R denotes the total resistant subpopulation, both genetic and phenotypic.

The region $\Omega = \{(S, R) \,|\, 0 \leq S + R \leq 1\}$ in the first quadrant is forward invariant for any locally bounded Lebesgue measurable treatment function $u(t)$ taking values in $\mathbb{R}_+$. Furthermore, if $\epsilon > 0$, the population of (1) becomes asymptotically resistant: $(S(t), R(t)) \xrightarrow{t \to \infty} (0, 1)$. For a proof, see Theorem 2 in SI A in [7]. Thus, in our model, the phenomenon of drug resistance is inevitable. However, we may still implement control strategies which, for example, may increase patient survival time. Such aspects will inform the objective introduced later in this work (Section III). For more details on the formulation and dynamics of system (1), we refer the reader to [7].

III. OPTIMAL CONTROL

We focus on control structures based on the presence of drug-induced resistance. Thus, we rely on the ability to determine whether, and to what degree, the specific chemotherapeutic treatment is generating resistance. Ideally, we envision a clinical scenario in which cancer cells from a patient are cultured in an *ex vivo* assay (for example, see [11]) prior to treatment. Parameter values are then calculated from treatment response dynamics in the assay, and an optimal therapy regime is implemented based on theoretical work such as that described in this section. Thus, identifying patient-specific model parameters, specially the induced-resistance rate α, is a necessary step in determining control structures to apply. In [12], we address this issue, and prove that all parameters are structurally identifiable, as well as demonstrate a specific set of controls that may be utilized to determine α. Hence, for the remainder of this work, we assume that prior to the onset of treatment, all patient-specific parameters are known. We now analyze behavior and response of system (1) to applied treatment strategies $u(t)$ utilizing geometric methods. The subsequent analysis is strongly influenced by the Lie-derivative techniques introduced by Sussmann [13], [14], [15], [16]. For an excellent source on both the general theory and applications to cancer biology, see the textbooks by Schättler and Ledzewicz [17], [18].

A. Formulation

As discussed in Section II, all treatment strategies $u(t)$ result in an entirely resistant tumor: $(S_*, R_*) = (0, 1)$ is globally asymptotically stable for all initial conditions in region Ω. Thus, any chemotherapeutic protocol will eventually fail, and a new drug must be introduced (not modeled in this work, but the subject of future study). Therefore, selecting an objective which minimizes tumor volume $(S + R)$ or resistant fraction $(R/(S+R))$ at a fixed time horizon would be specious for our modeling framework. However, one can still combine therapeutic efficacy and clonal competition to influence transient dynamics and possibly prolong patient life, as has been shown clinically utilizing real-time patient data [19]. Motivated by this observation, we define an objective based on maximizing time until treatment failure, as described below.

Let $V_c \in (0, 1-\epsilon)$ be a *critical tumor volume* at which treatment, by definition, has failed. The upper bound is a technical constraint that will be needed in Section III-D; note that this is not prohibitive, as the genetic mutation rate ϵ is generally small [20]. Recall that populations have been normalized to lie in $[0, 1]$. Our interpretation is that a tumor volume larger than V_c interferes with normal biological function, while $S + R \leq V_c$ indicates a clinically acceptable state. Different diseases will have different V_c values. Define t_c as the time at which the tumor increases above size V_c for the first time. To be precise, t_c is the maximal time for which $S + R \leq V_c$. Since all treatments approach the state $(0, 1)$, t_c is well defined for each $u(t) : t_c = t_c(u(t))$. Time t_c is then a measure of treatment efficacy, and our goal is then to determine $u_*(t)$ which maximizes $t_c(u(t))$.

Toxicity as well as pharmacokinetic constraints limit the amount of drug to be applied at any given instant. Thus, we assume that there exists $M > 0$ such that $u(t) \leq M$ for all $t \geq 0$. Any other Lebesgue measurable treatment regime $u(t)$ is then considered, so that the control set $U = [0, M]$ and the set of admissible controls $\mathcal{U}$ is

$$\mathcal{U} = \{u : [0, T] \to [0, M] \,|\, T > 0, u \text{ is Lebesgue measurable}\}.$$

We are thus seeking a control $u_*(t) \in \mathcal{U}$ which *maximizes* t_c, i.e. solves the time-optimal minimization problem with Lagrangian $L(t, x, u) = -1$, restricted to the dynamic state equations given by the system described previously:

$$\begin{aligned} \dot{x}(t) &= f(x(t)) + u(t)g(x(t)), \\ x(0) &= x_0, \end{aligned} \tag{2}$$

where f and g are

$$f(x) = \begin{pmatrix} (1 - (x_1 + x_2))x_1 - \epsilon x_1 \\ p_r(1 - (x_1 + x_2))x_2 + \epsilon x_1 \end{pmatrix}, \tag{3}$$

$$g(x) = \begin{pmatrix} -(\alpha + d) \\ \alpha \end{pmatrix} x_1, \tag{4}$$

and $x(t) = (S(t), R(t))$. Note that the above is formulated as a *minimization* problem to be consistent with previous literature and results related to the Pontryagin Maximum Principle (PMP) [17]. Note however that maximization is still utilized in Section III-B since the explicit necessary conditions are not needed.

The initial state $x_0 = (S_0, 0)$ is assumed to lie in Ω, and the time t_c must satisfy the terminal condition $(t_c, x(t_c)) \in N$, where N is the line $S + R = V_c$ in Ω, i.e. $N = \psi^{-1}(0) \cap \Omega$, where $\psi(S, R) := S + R - V_c$. Furthermore, the path-constraint

$$\psi(S(t), R(t)) \leq 0 \tag{5}$$

must also hold for $0 \leq t \leq t_c$. Equation (5) ensures that the tumor remains below critical volume V_c for the duration of treatment.

B. Elimination of Path Constraints

We begin our analysis by separating interior controls from those determined by the path-constraint (5). It can be shown (see [12]) that an optimal control to the problem presented in Section III-A exists. The following theorem implies that outside of the manifold N, the optimal pair (x_*, u_*) solves the same local optimization problem without the path and terminal constraints. More precisely, the necessary conditions of the PMP (see Section III-C) at states not on N are exactly the conditions of the corresponding maximization problem with no path or terminal constraints.

THEOREM 1. *Suppose that x_* is an optimal trajectory. Let T be the first time such that $x(t) \in N$. Fix $\epsilon > 0$ such that $T - \epsilon > 0$, and $\xi = x(T - \epsilon)$. Define $z(t) := x_*(t)|_{t \in [0, T-\epsilon]}$. Then the trajectory z is a local solution of the corresponding time maximization problem t_f with boundary conditions $x(0) = x_0$, $x(t_f) = \xi$, and no additional path constraints. Hence at all times t, z (together with the corresponding control and adjoint) must satisfy the corresponding unconstrained Pontryagin Maximum Principle.*

Proof. See [12]. □

Theorem 1 then tells us that for states $x = (S, R)$ such that $S + R < V_c$, the corresponding unconstrained PMP must be satisfied by any extremal lift of the original problem. Furthermore, there exists a unique feedback law for trajectories to remain on the boundary $V = V_c$:

$$u_p(S, R) = \frac{1}{d} \frac{(1 - (S + R))(S + p_r R)}{S}. \tag{6}$$

Equation (6) is only feasible on regions of phase space where $0 \leq u_p(S, R) \leq M$, and one can show that there exists a resistant state $R_c \in [0, 1)$ such that $u_p > M$ if $R > R_c$.

We have shown that the optimal control consists of concatenations of controls obtained from the unconstrained necessary conditions and controls of the form (6). In the next section, we analyze the Maximum Principle in the region $S + R < V_c$.

C. Maximum Principle and Necessary Conditions

Necessary conditions for the optimization problem discussed in Section III-A without path or terminal constraints

are derived from the PMP. The corresponding Hamiltonian function H is defined as

$$H(\lambda_0, \lambda, x, u) = -\lambda_0 + \langle \lambda, f(x) \rangle + u\Phi(x), \tag{7}$$

where $\lambda_0 \geq 0$ and $\lambda \in \mathbb{R}^2$. Here $\langle \cdot, \cdot \rangle$ denotes the standard inner product on $\mathbb{R}^2$ and, since the dynamics are affine in the control u, $\Phi(x, \lambda)$ is the switching function:

$$\Phi(x, \lambda) = \langle \lambda, g(x) \rangle. \tag{8}$$

The Maximum Principle then yields the following theorem:

THEOREM 2. *If the extremal (x_*, u_*) is optimal, there exists $\lambda_0 \geq 0$ and a covector (adjoint) $\lambda : [0, t_c] \to (\mathbb{R}^2)^*$, such that the following hold:*

1. *$(\lambda_0, \lambda(t)) \neq 0$ for all $t \in [0, t_c]$.*
2. *$\lambda(t) = (\lambda_S(t), \lambda_R(t))$ satisfies the second-order differential equation*

$$\dot{\lambda}(t) = \begin{pmatrix} 2S + R + \epsilon - 1 & p_r R - \epsilon \\ S & p_r(2R + S - 1) \end{pmatrix} \lambda(t) + u(t) \begin{pmatrix} \alpha + d & -\alpha \\ 0 & 0 \end{pmatrix} \lambda(t)$$

3. *$u_*(t)$ minimizes H pointwise over the control set U:*

$$H(\lambda_0, \lambda, x_*(t), u_*(t)) = \min_{v \in U} H(\lambda_0, \lambda, x_*(t), v).$$

Thus, the control $u_*(t)$ must satisfy

$$u_*(t) = \begin{cases} 0 & \Phi(t) > 0, \\ M & \Phi(t) < 0. \end{cases} \tag{9}$$

where

$$\Phi(t) := \Phi(x_*(t), \lambda(t)). \tag{10}$$

4. *The Hamiltonian H is identically zero along the extremal lift $(x_*(t), u_*(t), \lambda(t))$:*

$$H(\lambda_0, \lambda(t), x_*(t), u_*(t)) \equiv 0. \tag{11}$$

Proof. See [12]. □

D. Geometric Properties and Singular Arcs

We now undertake a geometric analysis of the optimal control problem utilizing the affine structure of system (2) for interior states (i.e. controls which satisfy Theorem 2). We call such controls *interior extremals*, and all extremals in this section are assumed to be interior. The following results depend on the independence of the vector fields f and g, which we use to both classify the control structure for abnormal extremal lifts (extremal lifts with $\lambda_0 = 0$), as well as characterize the switching function dynamics via the Lie bracket.

Proposition 3. *For all $S \in \Omega, S > 0$, the vector fields $f(x)$ and $g(x)$ are linearly independent.*

Proof. See [12]. □

The line $S = 0$ is invariant in Ω, and furthermore the dynamics in the set are independent of the control $u(t)$. Conversely, $S_0 > 0$ implies that $S(t) > 0$ for all $t \geq 0$. We concern our analysis only in this latter case, and so without loss of generality, $f(x)$ and $g(x)$ are linearly independent in the region of interest.

The interior control structure corresponding to abnormal extremal lifts (i.e. $\lambda_0 = 0$) is easily characterized: $u_*(t) \equiv M$. For a proof, see [12]. To understand normal extremal lifts ($\lambda_0 > 0$), without loss of generality we assume that $\lambda_0 = 1$. The Hamiltonian $H(t)$ evaluated along $(\lambda(t), x_*(t), u_*(t))$ is then of the form

$$H(t) = -1 + \langle \lambda(t), f(x_*(t)) \rangle + u_*(t)\Phi(t) \equiv 0. \tag{12}$$

As f and g are linearly independent in Ω, there exist $\gamma, \beta \in C^\infty(\Omega)$ such that

$$[f, g](x) = \gamma(x)f(x) + \beta(x)g(x), \tag{13}$$

for all $x \in \Omega$. In fact, we can compute γ and β explicitly:

$$\gamma(x) = -\frac{(\alpha + d)S^2}{\det A(x)} \left(aS + bR - c\right), \tag{14}$$

$$\beta(x) = \frac{S^2}{\det A(x)} \Big(\alpha(1 - p_r)\kappa(x)(\kappa(x) - \epsilon) + \epsilon d(S + p_r R + \kappa(x) - \epsilon) \Big), \tag{15}$$

where

$$a = \alpha \left((1 - p_r) + \frac{d}{\alpha + d} \right), \tag{16}$$

$$b = \alpha(1 - p_r) + dp_r, \tag{17}$$

$$c = \alpha(1 - p_r) + \epsilon d. \tag{18}$$

Clearly, for parameter values of interest, $a, b, c > 0$. The assumption $V_c < 1 - \epsilon$ guarantees that $\beta(x) > 0$ that on $0 < S + R \leq V_c$.

From (9), the sign of the switching function Φ determines the value of the control u_*. As λ and x_* are solutions of differential equations, Φ is differentiable. The dynamics of Φ can be understood in terms of the Lie bracket $[f, g]$:

$$\dot{\Phi}(t) = \gamma(x_*(t))\langle \lambda(t), f(x_*(t)) \rangle + \beta(x_*(t))\Phi(t). \tag{19}$$

Equation (19) follow from (13) as well as the linearity of the inner product. We are then able to derive an ODE system for x_* and Φ. Equation (12) allows us to solve for $\langle \lambda(t), f(x_*(t)) \rangle = 1 - u_*(t)\Phi(t)$. Substituting the above into (19) then yields the following ODE for $\Phi(t)$, which we view as coupled to system (2) via (9):

$$\dot{\Phi}(t) = \gamma(x_*(t)) + \Big(\beta(x_*(t)) - u_*(t)\gamma(x_*(t)) \Big)\Phi(t). \tag{20}$$

The structure of the optimal control may now be characterized as a combination of bang-bang and singular arcs. We recall that the control (or, more precisely, the extremal lift) u_* is singular on an open interval $I \subset [0, t_c]$ if the switching function $\Phi(t)$ and all its derivatives are identically zero on I. On such intervals, equation (9) does not determine the value of u_*, and a higher-order analysis of the zero set of $\Phi(t)$ is necessary. Indeed, for a problem such as ours, singular arcs are the only candidates for interior optimal controls that may

take values outside of the set $\{0, M\}$. Equation (20) allows us to completely characterize the regions in the (S, R) plane where singular arcs are attainable, as demonstrated in the following proposition.

Proposition 4. *Singular arcs are only possible in regions of the (S, R) plane where $\gamma(x) = 0$. Furthermore, as $S(t) > 0$ for all $t \geq 0$, the region $\left\{x \in \mathbb{R}^2 | \gamma(x) = 0\right\} \cap \Omega$ is the line*

$$aS + bR - c = 0, \tag{21}$$

where a, b, c are defined in (16)-(18).

Proof. See [12]. □

Proposition 4 implies that singular solutions can only occur along the line $aS + bR - c = 0$. Thus, define regions in the first quadrant as follows: $\Omega_0 := \left\{x \in \mathbb{R}^2 \,|\, R, S \geq 0, R + S \leq V_c\right\}$, $\Omega_0^+ := \left\{x \in \Omega_0 \,|\, \gamma(x) > 0\right\}$, $\Omega_0^- := \left\{x \in \Omega_0 \,|\, \gamma(x) < 0\right\}$, and $\mathcal{L} = \left\{x \in \Omega_0 \,|\, \gamma(x) = 0\right\}$. Note that Ω_0 is simply the region in Ω prior to treatment failure, i.e. $0 \leq V \leq V_c$.

If the maximal tolerable dose M is large enough, there exists a subset $\bar{\mathcal{L}} \subset \mathcal{L}$ that is a feasible singular arc (for $X := f, Y := f + Mg$, $\bar{\mathcal{L}}$ is precisely the subset of $\mathcal{L}$ where $L_Y \gamma < 0$). It can be shown that the singular arc is of order one. From the above, we know that optimal control consists of a concatenation of bang-bang and singular arcs. The following theorem characterizes the interior extremals precisely.

Theorem 5. *The singular arc $\bar{\mathcal{L}}$ is not optimal. The interior extremals consist of a finite number of bang-bang arcs, where at most one switch may occur in the regions $\gamma > 0, \gamma < 0$. In the regions, the switching structure must take the form YX if $\gamma > 0$, and XY if $\gamma < 0$. Thus, multiple switchings may only occur across $\bar{\mathcal{L}}$.*

Proof. See [12]. □

For a visualization of the partition of Ω and the corresponding control structure, see Figure 1.

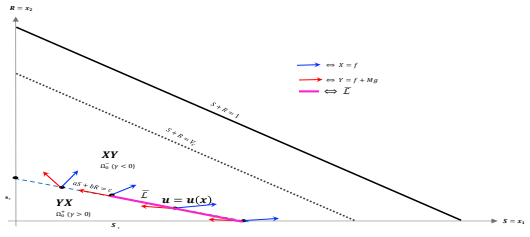

Fig. 1: Geometry of interior control structure. YX denotes a local control structure of a Y arc followed by an X arc. Note that only one switch is allowed for trajectories remaining in each of Ω_0^+ and Ω_0^-; additional switches must occur across the singular arc $\bar{\mathcal{L}}$.

E. Optimal Synthesis

We now state our main theorem, which synthesizes the features of the interior and path-constraint optimal controls in the (S, R) plane.

Theorem 6. *For any $\alpha \geq 0$, the optimal control to maximize the time to reach a critical time is a concatenation of bang-bang and path-constraint controls. In fact, the general control structure takes the form*

$$(YX)^n (u_p Y)^m, \tag{22}$$

where $(YX)^n := (YX)^{n-1} YX$ and similarly for $(u_p Y)^m$, for $n, m \in \mathbb{N}$, and the order should be read left to right. Here u_p is defined in (6).

Proof. See [12]. □

IV. Numerical Results

To investigate the precise control structure as a function of parameter values, we utilize the GPOPS-II software package [21]. We begin by fixing values as they appear in [7] for a resistance-inducing drug ($\alpha = 10^{-2}$). The results are shown in Figure 2.

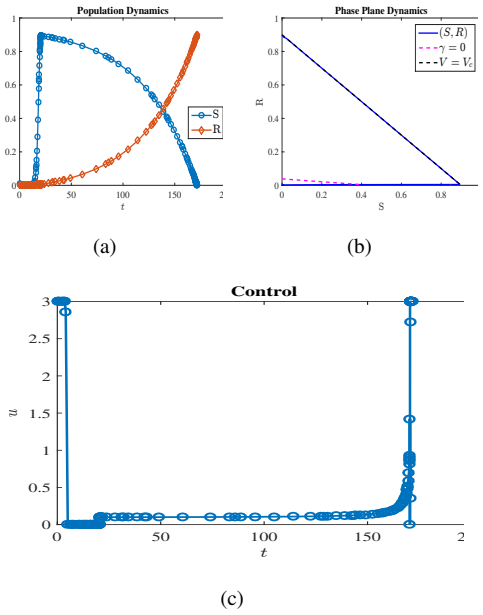

Fig. 2: Numerical solution of optimal control problem introduced in Section III-A. Parameter values are given by $S(0) = 0.01, R(0) = 0, p_r = 0.2, \epsilon = 10^{-6}, \alpha = 10^{-2}, M = 3$, and $V_c = 0.9$. (a) Sensitive and resistant populations. (b) Corresponding phase plane dynamics. (c) Optimal control u_*.

Note that u_* is of the form $u_* = YXu_pY$, consistent with the results of Theorem 6. A comparison of the computed path-constraint control and equation (6) is provided in Figure 3. Note the close agreement for most time points. Furthermore, the switching structure for the bang arcs is YX in the region $\gamma > 0$, which also agrees with Theorem 5.

We now investigate the dependence on parameter α, the degree to which the drug induces resistance. Parameters are fixed as in Figure 2, unless explicitly stated otherwise. Numerical results suggest optimal controls all possess the same qualitative structure over a range of α parameters. However, the overall success of therapy t_c varies dramatically with parameter α. In general, it appears that therapies become

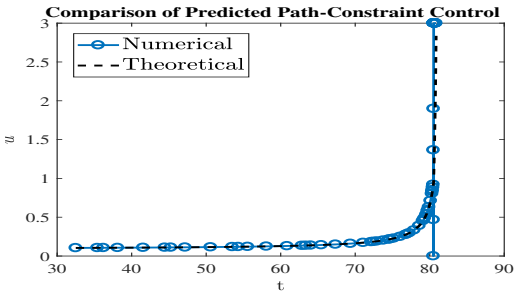

Fig. 3: Comparison of GPOPS-II output and predicted formula (6) along line $V = V_c$. The numerically computed states S and R were substituted into (6) find the control as a function of time t.

less successful for increasing values resistance induction. For example, $\alpha = 0$ has a critical time $t_c(\alpha = 0) = 525$, while $\alpha = 10^{-2}$ has a corresponding $t_c(\alpha = 10^{-2}) = 171$. This is intuitive, but the mathematical model allows us to quantity the outcomes of optimal therapies precisely.

A study of the tradeoff between cytotoxicity and resistance-induction is also analyzed. Recall that parameter d measures the overall cytotoxic potential of the therapy. One might assume that therapies with larger values of d are always preferable. Computing numerically we find that $t_c(d = 0.5, \alpha = 10^{-2}) = 139$ as compared to $t_c(d = 1, \alpha = 10^{-1}) = 81$. Ignoring the effect of drug-induced resistance, one might conclude that the latter therapy will be more effective, as it has an increased ability to eliminate cancerous cells. However, the ability to promote resistance dominates in this instance, and we see that the less cytotoxic, less mutagenic therapy is actually superior.

V. CONCLUSIONS AND FUTURE WORK

In this work, we have analyzed the mathematical model (1) introduced in [7] that describes both the traditional genetic origin of resistance, as well as drug induced resistance that can occur at both the genetic and epigenetic level. Using the Maximum Principle and differential-geometric techniques we have analyzed the structure of the zero set of Φ, and analyzed the overall structure of the optimal control. Numerical results suggest that drugs which promote resistance have less clinical potential. Furthermore, cytotoxicity and induction need to be considered simultaneously when designing therapies for maximally effective clinical results.

The present work provides candidates for the optimal control which maximizes time until treatment failure. We are currently exploring the precise dependence of treatment success on cytotoxicity and induction, as well as to extend the model to include both reversible drug-induced resistance and controls problems related to multiple chemotherapeutic agents targeting both cell populations. For complete proofs of presented theorems and the discussed extensions, see [12].

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AUTHOR CONTRIBUTIONS

All authors contributed equally to this work.

CONFLICT OF INTEREST

None declared.

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