Mathematical Details on a Cancer Resistance Model

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Abstract

The primary factor limiting the success of chemotherapy in cancer treatment is the phenomenon of drug resistance. We have recently introduced a framework for quantifying the effects of induced and non-induced resistance to cancer chemotherapy [8, 7]. In this work, we expound on the details relating to an optimal control problem outlined in [7]. The control structure is precisely characterized as a concatenation of bang-bang and path-constrained arcs via the Pontryagin Maximum Principle and differential Lie techniques. A structural identifiability analysis is also presented, demonstrating that patient-specific parameters may be measured and thus utilized in the design of optimal therapies prior to the commencement of therapy. For completeness, a detailed analysis of existence results is also included.

Keywords. Drug resistance | Chemotherapy | Phenotype | Optimal Control Theory | Singular Controls

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1 Mathematical Modeling of Induced Drug Resistance

We briefly review the model presented in [8] and analyzed in [7]. In that work, we have constructed a simple 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 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 [25] 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 3). 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 3), we will make precise specifications on the control set U. Obviously, an arbitrary function of time is unrealistic as a treatment strategy, due to practical constraints. Our objective, however, is not quantitatively precise modeling, but rather an analysis of the fundamental mathematical questions associated to drug-induced resistance.

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):

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

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 [11, 16, 3], 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 epigenetic) 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 epigenetic.

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:

$$\begin{pmatrix} S(t) \\ R(t) \end{pmatrix} \xrightarrow{t\to\infty} \begin{pmatrix} 0 \\ 1 \end{pmatrix}. \tag{2}$$

For a proof, see Theorem 2 in SI A in [8]. 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 in the following section. For more details on the formulation and dynamics of system (1), we refer the reader to [8].

2 Structural Identifiability

Before beginning a discussion of the optimal control problem, we first discuss the identifiability of system (1). Our focus in the remainder of the work is on control structures based on the presence of drug-induced resistance, and thus relies 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 [17]) prior to treatment. Parameter values are then calculated from treatment response dynamics in the assay, and an optimal therapy regime is implemented based on the theoretical work described below. Thus, identifying patient-specific model parameters, specially the induced-resistance rate α, is a necessary step in determining control structures to apply. In this section, 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. A self-contained discussion is presented; for more details on theoretical aspects, see [19] and the references therein. Other recent works related to identifiability in the biological sciences (as well as *practical identifiability*) can be found in [4, 26].

We first formulate our dynamical system, and specify the input and output variables. Clearly, the treatment $u(t)$ is the sole input. Furthermore, we assume that the only clinically observable output is the entire tumor volume $V(t)$:

$$V(t) := S(t) + R(t). \tag{3}$$

That is, we do not assume real-time measurements of the individual sensitive and resistant sub-populations. We note that in some instances, such measurements may be possible; however for a general chemotherapy, the precise resistance mechanism may be unknown *a priori*, and hence no biomarker with the ability to differentiate cell types may be available.

Treatment is initiated at time $t = 0$, at which we assume an entirely sensitive population:

$$S(0) = S_0, \qquad R(0) = 0. \tag{4}$$

Here $0 < S_0 < 1$, so that $(S(t), R(t)) \in \Omega$ for all $t \geq 0$. We note that $R(0) = 0$ is not restrictive, and similar results may derived under the more general assumption $0 \leq R_0 < 1$. The condition $R(0) = 0$ is utilized both for computational simplicity and since $R(0)$ is generally small (assuming a non-zero detection time, and small random mutation parameter ϵ; see [8] for a discussion).

The above then allows us to formulate our system (1) in input/output form, where the input $u(t)$ appears affinely:

$$\begin{aligned} \dot{x}(t) &= f(x(t)) + u(t)g(x(t)), \\ x(0) &= x_0, \end{aligned} \tag{5}$$

where f and g are

$$f(x) = \begin{pmatrix} (1-(x_1+x_2))x_1 - \epsilon x_1 \\ p_r(1-(x_1+x_2))x_2 + \epsilon x_1 \end{pmatrix}, \tag{6}$$

$$g(x) = \begin{pmatrix} -(\alpha+d) \\ \alpha \end{pmatrix} x_1, \tag{7}$$

and $x(t) = (S(t), R(t))$. As is standard in control theory, the output is denoted by the variable y, which in this work corresponds to the total tumor volume. A system in form (5) is said to be *uniquely structurally identifiable* if the map $p \mapsto (u(t), x(t,p))$ is injective almost everywhere [4, 13]. *Local identifiability* and *non-identifiability* correspond to the map being finite-to-one and infinite-to-one, respectively. Our objective is then to demonstrate unique structural identifiability for model system (5) (or equivalently (1)), and hence recover all parameter values p from only measurements of the tumor volume y. We also note that the notion of identifiability is closely related to that of *observability*; for details [1, 18] are a good reference.

To analyze identifiability, we utilize results appearing in [9, 27, 20], and hence frame the issue from a differential-geometric perspective. Our hypothesis is that perfect (hence noise-free) input-output data is available in the form of y and its derivatives on any interval of time. We thus, for example, make measurements of

$$\begin{aligned} y(0) &= h(x(0)), \\ \dot{y}(0) &= \left.\frac{d}{dt}\right|_{t=0} h(x(t)) \end{aligned} \tag{8}$$

and relate their values to the unknown parameter values p. If there exist inputs $u(t)$ such that the above system of equations may be solved for p, the system is identifiable. The right-hand sides of (8) may be computed in terms of the Lie derivatives of the vector fields f and g in system (5). We recall that Lie differentiation $L_X H$ of a C^ω function H by a C^ω vector field X:

$$L_X H(x) := \nabla H(x) \cdot X(x). \tag{9}$$

Here the domain of both X and H is the first-quadrant triangular region Ω, seen as a subset of the plane, and the vector fields and output function are C^ω on an open set containing Ω (in fact, they are given by polynomials, so they extend as analytic functions to the entire plane). Recall that set C^ω consists of all analytic functions. Iterated Lie derivatives are well-defined, and should be interpreted as function composition, so that for example $L_Y L_X H = L_Y(L_X H)$, and $L_X^2 H = L_X(L_X H)$.

More formally, defining observable quantities as the zero-time derivatives of the output $y = h(x)$,

$$Y(x_0, U) = \left.\frac{d^k}{dt^k}\right|_{t=0} h(x(t)), \tag{10}$$

where $U \in R^k$ is the value of the control $u(t)$ and its derivatives evaluated at $t = 0$: $U = \left(u(0), u'(0), ..., u^{(k-1)}(0)\right)$. Here $k \geq 0$, indicating that the k^{th}-order derivative Y may expressed as a polynomial in the components of U [20]. The initial conditions x_0 appear due to evaluation at $t = 0$. The observation space is then defined as the span of the $Y(x_0, U)$ elements: $F_1 := \text{span}_{\mathbb{R}} \left\{ Y(x_0, U) \,|\, U \in \mathbb{R}^k, k \geq 0 \right\}$. Conversely, we also define span of iterated Lie derivatives with respect to the output h and vector fields $f(x)$ and $g(x)$: $F_2 := \text{span}_{\mathbb{R}} \left\{ L_{i_1} \ldots L_{i_k} h(x_0) \,|\, (i_1, \ldots i_k) \in \{g, f\}^k, k \geq 0 \right\}$. Wang and Sontag [27] proved that $F_1 = F_2$, so that the set of "elementary observables" may be considered as the set of all iterated Lie derivatives F_2. Hence, identifiability may be formulated in terms of the reconstruction of parameters p from elements in F_2. Parameters p are then identifiable if the map

$$p \mapsto \left(L_{i_1} \ldots L_{i_k} h(x_0) \,|\, (i_1, \ldots i_k) \in \{g, f\}^k, k \geq 0 \right) \tag{11}$$

is one-to-one. For the remainder of this section, we investigate the mapping defined in (11).

Computing the Lie derivatives and recalling that $x_0 = (S_0, 0)$ we can recursively determine the parameters p:

$$\begin{aligned}
S_0 &= h(x_0), \\
d &= -\frac{L_g h(x_0)}{S_0}, \\
\alpha &= \frac{L_g^2 h(x_0)}{d S_0} - d, \\
\epsilon &= \frac{L_f L_g h(x_0)}{d S_0} + 1 - S_0, \\
p_r &= \frac{S_0}{1 - S_0} + \frac{L_g L_f h(x_0)}{\alpha S_0 (1 - S_0)} - \left(1 + \frac{d}{\alpha}\right)\left(1 - \frac{S_0}{1 - S_0}\right).
\end{aligned} \tag{12}$$

Since $F_1 = F_2$, all of the above Lie derivatives are observable via appropriate treatment protocols. For an explicit set of controls and corresponding relations to measurable quantities (elements of the form (10)), see [8]. Thus, we conclude that all parameters in system (1) are identifiable, which allows us to investigate optimal therapies dependent upon *a priori* knowledge of the drug-induced resistance rate α.

3 Optimal Control Formulation

As discussed in Section 1, 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 [6]. Motivated by this observation, we define an objective based on maximizing time until treatment failure, as described below.

Let

$$V_c \in (0, 1-\epsilon) \tag{13}$$

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 6; note that this is not prohibitive, as the genetic mutation rate ϵ is generally small [12], and our interest is on the impact of induced resistance. 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 $u(t) : t_c = t_c(u)$. Time t_c is then a measure of treatment efficacy, and our goal is then to determine u_* which maximizes $t_c(u)$.

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

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

We are thus seeking a control $u_*(t) \in \mathcal{U}$ which *maximizes* t_c, i.e. solves the time-optimal minimization problem

$$\min_{u \in \mathcal{U}} \{J(u)\} = \min_{u \in \mathcal{U}} \left\{ -\int_0^{t_c} 1 \, dt \right\}, \tag{14}$$

restricted to the dynamic state equations given by the system described previously in (5). 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) [10]. Note that maximization is still utilized in Sections 4 and 5.1, and we believe that the objective will be clear from context.

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

$$\psi(S(t), R(t)) \leq 0 \tag{15}$$

must also hold for $0 \leq t \leq t_c$. Equation (15) ensures that the tumor remains below critical volume V_c for the duration of treatment. Equivalently, the dynamics are restricted to lie in the set $\Omega_c \subseteq \Omega$, where

$$\Omega_c := \{(S, R) \,|\, 0 \leq S + R \leq V_c\}, \tag{16}$$

for times t such that $t \in [0, t_c]$. The initial state

$$x_0 = (S_0, R_0) \tag{17}$$

is also assumed to lie in Ω_c. We not longer restrict to the case $R_0 = 0$ as was assumed for simplicity in Section 2.

4 Existence Results

Before characterizing the structure of the desired optimal control for the problem presented in Section 3, we must first verify that the supremum of times $t_c(u)$ for $u \in \mathcal{U}$ is obtained by some $u_* \in \mathcal{U}$, i.e. that the optimal control exists. This involves two distinct steps: proving that the supremum is both finite and that it is obtained by at least one admissible control. The following two subsections verify these claims.

4.1 Finiteness of the Supremum

We prove that

$$\sup_{u \in \mathcal{U}} t_c(u) < \infty \tag{18}$$

for a more general control system. The result depends crucially on (2), and the fact that asymptotically stable state $(0, 1)$ is disjoint from the dynamic constraint $x \in \Omega_c$ (see equation (15)). That is, $V_c < 1$ is necessary for the following subsequent result to hold, and generally an optimal control will not exist if $V_c = 1$ or the path constraint is removed.

Consider a control system of the form

$$\dot{x} = \tilde{f}(t, x, u), \tag{19}$$

where $x \in \Omega, u \in \mathcal{U} := \{u : \mathbb{R}_+ \to U \,|\, u \text{ measurable}\}$, and $\tilde{f} : \mathbb{R} \times \Omega \times U \to \Omega$, where Ω is an open subset of $\mathbb{R}^n$, $U \subseteq \mathbb{R}$. Fix the initial conditions

$$x(0) = x_0, \tag{20}$$

with $x_0 \in \Omega$, and assume that all solutions of (19) and (20) approach a fixed point $\bar{x} \in \Omega$. That is, for all $u \in \mathcal{U}$,

$$x_u(t) \xrightarrow{t \to \infty} \bar{x}. \tag{21}$$

Note that we explicitly denote the dependence of the trajectory on the control u, and the above point $\bar{x}$ is independent of the control u.

Fix a closed subset L of Ω such that $x_0 \in L, \bar{x} \notin L$. Associate to each control (and hence corresponding trajectory) a time $t_c(u)$ such that

$$t_c(u) = \min\{T \,|\, x_u(t) \notin L \text{ for all } t > T\}. \tag{22}$$

Note that the above is well-defined (as a minimum) for each control u, since by assumption $x_0 \in L$ and each trajectory asymptotically approaches $\bar{x} \notin L$.

Theorem 1. *Define*

$$T_* = \sup_{u \in \mathcal{U}} t_c(u). \tag{23}$$

With the above construction, T_* is finite.

Proof. Fix an open set K of Ω containing $\bar{x}$ such that $K \cap \Omega = \emptyset$. Note that this is possible, as L is closed and $\bar{x} \notin L$. Suppose, by contradiction, that $T_* = \infty$. We construct a trajectory that remains in L for all time t, thus contradicting the fact that every trajectory must eventually enter K. By definition of the supremum, there exists a sequence of controls $u_n \in \mathcal{U}$ such that $x_{u_n} \in L$ for $t \in [0, t_n]$, with $t_n \xrightarrow{n \to \infty} \infty$. By taking a subsequence, we assume that t_n is increasing. Note that each u_n is defined on $[0, \infty)$, and the initial condition (20) is fixed for all pairs (x_{u_n}, u_n).

We construct a new control u_* inductively as follows. Define a sequence of controls on $[0, t_1]$:

$$u_{n,1} = \{u_n|_{[0,t_1]}\}_{n=1}^{\infty}. \tag{24}$$

Since the time interval $[0, t_1]$ is compact, there exists a convergence subsequence $\{u_{n_k,1}\} \xrightarrow{n_k \to \infty} u_{*,1}$ in the weak topology. As a subsequence, the corresponding trajectory $x_{*,1}$ remains in L for $t \in [0, t_1]$. Similarly, define subsequence $u_{n,2}$ on $[t_1, t_2]$ as

$$u_{n,2} = \{u_{n_k,1}|_{[t_1,t_2]}\}, \tag{25}$$

where we begin the sequence at the maximum of n_1 and 2, to ensure that all controls in the sequence correspond to trajectories entirely inside of L. Again, since the interval is compact, there exists a convergence subsequence (in the weak topology) of $u_{n,2}$, say $u_{*,2}$, with, by continuity of the state with respect to the control, the corresponding trajectory lies entirely in L. Continue in this manner, constructing a sequence of controls $u_{*,i}, i = 1, 2, ...$, where $u_{*,i}$ is defined on $[t_{i-1}, t_i]$, with $t_0 = 0$. Define u_* on $[0, \infty)$ as the concatenation of the $u_{*,i}$:

$$u_* = u_{1,*} * u_{2,*} * \cdots \tag{26}$$

As the pointwise limit of measurable functions, u_* is measurable. Clearly, $u \in U$ by construction, so that $u \in \mathcal{U}$. The corresponding trajectory x_{u_*} thus lies entirely in L for $t \in [0, \infty)$, and hence never enters K. This the desired contradiction, so that T_* must be finite, as desired. □

For the system and control problem defined in Sections 1 and 3, the above theorem implies that $\sup_{u \in \mathcal{U}} t_c(u)$ is finite by taking $L = \Omega_c$.

4.2 Supremum as a Maximum

Here we provide a general proof for the existence of optimal controls for systems of our form, assuming the set of maximal times is bounded above, which has been proven in Section 4.1. For convenience, we make the proof as self-contained as possible (one well-known result of Filippov will be cited), and state the results in generality which I will later apply to the model of induced resistance. Arguments are adapted primarily from the textbook of Bressan and Piccoli [2].

Consider again general control systems as in Section 4.1. Solutions (or trajectories) of (19) will be defined as absolutely continuous functions for which a control $u \in \mathcal{U}$ exists such that $(x(t), u(t))$ satisfy (19) a.e. in their (common) domain $[a, b]$.

It is easier and classical to formulate existence with respect to differential inclusions. That is, define the multi-function

$$F(t, x) = \{\tilde{f}(t, x, \omega) \,|\, \omega \in U\}. \tag{27}$$

Thus, the control system (19) is clearly related to the inclusion

$$\dot{x} \in F(t, x). \tag{28}$$

The following theorem (see [5]) makes this relationship precise.

Theorem 2. *An absolutely continuous function $x : [a, b] \mapsto \mathbb{R}^n$ is a solution of* (19) *if and only if it satisfies* (28) *almost everywhere.*

We first prove a lemma demonstrating that the set of trajectories is closed w.r.t. to the sup-norm $||\cdot||_\infty$ if the set of velocities $F(t, x)$ are all convex.

Lemma 3. *Let x_k be a sequence of solutions of* (19) *converging to x uniformly on $[0, T]$. If the graph of $(t, x(t))$ is entirely contained in Ω, and the $F(t, x)$ are all convex, then x is also a solution of* (19)*.*

Proof. By the assumptions on $\tilde{f}$, the sets $F(t, x)$ are uniformly bounded as (t, x) range in a compact domain, so that x_k are uniformly Lipschitz, and hence x is Lipschitz as the uniform limit. Thus x is differentiable a.e., and by Theorem 2, it is enough to show that

$$\dot{x}(t) \in F(t, x(t)) \tag{29}$$

for all t such that the derivative exists.

Assume not, i.e. that the derivative exists at some τ, but $\dot{x}(\tau) \notin F(\tau, x(\tau))$. Since $F(\tau, x(\tau))$ is compact and convex, and $\dot{x}(\tau)$ is closed, the Hyperplane Separation Theorem implies that there exists a hyperplane separating $F(\tau, x(\tau))$ and $\dot{x}(\tau)$. That is, there exists an $\epsilon > 0$ and a (WLOG) unit-vector $p \in \mathbb{R}^n$ such that

$$\langle p, y \rangle \leq \langle p, \dot{x}(\tau) \rangle - 3\epsilon, \tag{30}$$

for all $y \in F(\tau, x(\tau))$. By continuity, there exists $\delta > 0$ such that for $|t - t'| \leq \delta, |x' - x(\tau)| \leq \delta$

$$\langle p, y \rangle \leq \langle p, \dot{x}(\tau) \rangle - 2\epsilon, \tag{31}$$

for all $y \in F(\tau, x')$. Since x is differentiable at τ, we can choose $\tau' \in (\tau, \tau + \delta]$ such that

$$\begin{aligned} \left| \frac{x(\tau') - x(\tau)}{\tau' - \tau} - \dot{x}(\tau) \right| &< \epsilon, \\ |x(t) - x(\tau)| &< \delta, \end{aligned} \tag{32}$$

for all $t \in [\tau, \tau']$. Equation (32) and uniform convergence then implies that

$$\begin{aligned} \left\langle p, \frac{x_k(\tau') - x_k(\tau)}{\tau' - \tau} \right\rangle \xrightarrow{k\to\infty} &= \left\langle p, \frac{x(\tau') - x(\tau)}{\tau' - \tau} \right\rangle \\ &> \langle p, \dot{x}(\tau) \rangle - \epsilon. \end{aligned} \tag{33}$$

On the other hand, since $\dot{x} \in F(t, x')$ for $t \in [\tau, \tau']$, equation (31) implies that for k sufficiently large,

$$\begin{aligned} \left\langle p, \frac{x_k(\tau') - x_k(\tau)}{\tau' - \tau} \right\rangle &= \frac{1}{\tau' - \tau} \int_{\tau}^{\tau'} \langle p, \dot{x}(t) \rangle \, \mathrm{d}t \\ &\leq \langle p, \dot{x}(\tau) \rangle - 2\epsilon. \end{aligned} \tag{34}$$

Clearly, (33) and (34) contradict one another, so that (29) must be true, as desired. □

An optimal control problem associated to (19) may now be formulated. Suppose $x_0 \in \Omega$ is an initial condition for the corresponding system, so that

$$x(0) = x_0. \tag{35}$$

Let S denote the set of admissible terminal conditions, $S \subset \mathbb{R} \times \mathbb{R}^n$, and $\phi : \mathbb{R} \times \mathbb{R}^n \mapsto \mathbb{R}$ a cost function. We would like to maximize $\phi(T, x(T))$ over admissible controls with initial and terminal constraints:

$$\begin{aligned} &\max_{u \in \mathcal{U}, T \geq 0} \phi(T, x(T, u)), \\ &x(0) = x_0, \, (T, x(T)) \in S. \end{aligned} \tag{36}$$

We now state sufficient conditions for such an optimal control to exist.

Theorem 4. *Consider the control system* (19) *and corresponding optimal control problem* (36)*. Assume the following:*

1. *The objective ϕ is continuous.*
2. *The sets of velocities $F(t, x)$ are convex.*
3. *The trajectories x remain uniformly bounded.*
4. *The target set S is closed.*
5. *A trajectory satisfying the constraints in* (36) *exists.*
6. *S is contained in some strip $[0, T] \times \mathbb{R}^n$, i.e. the set of final times (for free-endpoint problems) can be uniformly bounded.*

If the above items are all satisfied, an optimal control exists.

Proof. By assumption, there is at least one admissible trajectory reaching the target set S. Thus, we can construct a sequence of controls $u_k : [0, T_k] \mapsto U$ whose corresponding trajectories x_k satisfy

$$\begin{aligned} x_k(0) &= x_0, \\ (T_k, x_k(T_k)) &\in S, \\ \phi(T_k, x(T_k)) &\xrightarrow{k\to\infty} \sup_{u\in\mathcal{U},\bar{T}\geq 0} \phi(\bar{T}, x(\bar{T}, u)). \end{aligned} \tag{37}$$

Since $S \subset [0, T] \times \mathbb{R}^n$, we know that $T_k \leq T$ for all k. Each function x_k can then be extended to the entire interval $[0, T]$ by setting $x_k(t) = x_k(T_k)$ for $t \in [T_k, T]$.

The sequence x_k is uniformly Lipschitz continuous, as f is uniformly bounded on bounded sets. This then implies equicontinuity of $\{x_k\}_{k=1}^{\infty}$. By the Arzela-Ascoli Theorem, there exists a subsequence x_{n_k} such that $T_{n_k} \to T_*$, $T_* \leq T$, and $x_{n_k} \to x_*$ uniformly on $[0, T_*]$.

Lemma 3 implies that x_* is admissible, so that there exists a control $u_* : [0, T_*] \mapsto U$ such that

$$\dot{x}_*(t) = f(t, x_*(t), u_*(t)) \tag{38}$$

for almost all $t \in [0, T_*]$. Equations (37) imply that

$$\begin{aligned} x_*(0) &= x_0 \\ (T_*, x_*(T_*)) &= \lim_{n_k\to\infty} \phi(T_{n_k}, x_{n_k}(T_{n_k})) \in S. \end{aligned} \tag{39}$$

Note that the second of (39) relies on S being closed. Continuity of ϕ and (37) implies that

$$\phi(T_*, x_*(T_*)) = \lim_{n_k\to\infty} \phi(T_{n_k}, x_{n_k}(T_{n_k})) = \sup_{u\in\mathcal{U},T_*\geq 0} \phi(T_*, x(T_*, u)). \tag{40}$$

Thus, u_* is optimal, as desired. □

For the model of drug-induced resistance, the right-hand side $\tilde{f}$ takes the form (5) where f and g are smooth on the domain Ω. Here the control set U is the compact set $U = [0, M]$, and for such control-affine systems, convexity of $F(t, x)$ is implied by the convexity of U. Existence of a trajectory satisfying the constraints is clear; for example, take $u(t) \equiv 0$. Our objective is to maximize the time to reach the critical tumor volume $S = N$. Note that N is a closed subset of $\mathbb{R}^2$, and that

$$\phi(\bar{T}, x(\bar{T}, u)) = \bar{T}. \tag{41}$$

is continuous. Lastly, we have seen that all solutions remain in the closure $\bar{\Omega}$, so that $|x(t)| \leq 1$ for all $u \in \mathcal{U}$ and hence solutions are uniformly bounded. Existence is then reduced to Item 6 in the previous theorem. Since the supremum was shown to be finite, an Theorem 4 together with Theorem 1 imply that the optimal control for the problem presented in Section 3 exists.

5 Maximum Principle

The results of Section 4 imply that the optimal control problem introduced in Section 3 has at least one solution $u_* \in \mathcal{U}$. We now characterize this control utilizing the Pontryagin Maximum Principle (PMP). We envision a clinical scenario in which cancer cells from a patient are cultured in an *ex vivo* assay (for example, see [17]) prior to treatment. Parameter values are then calculated from treatment response dynamics in the assay, and an optimal therapy regime is implemented based on the theoretical work of this section. Thus, identifying patient-specific model parameters, specially the induced-resistance rate α, is a necessary step in determining control structures to apply. This issue was addressed partially in Section 2; for further *in vitro* results, see [8]. 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 [21, 23, 22, 24]. For an excellent source on both the general theory and applications to cancer biology, see the textbooks by Schättler and Ledzewicz [10, 15].

5.1 Elimination of Path Constraints

We begin our analysis by separating interior controls from those determined by the path-constraint (15) (equivalently, $x \in \Omega_c$). 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 5.2) at states not on N are exactly the conditions of the corresponding maximization problem with no path or terminal constraints.

Theorem 5. *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*

$$\xi = x(T - \epsilon). \tag{42}$$

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. We first claim that z satisfies the path-constrained maximization problem with boundary conditions $x(0) = x_0, x(t_f) = \xi$. Otherwise, if there exists a trajectory $\bar{z}$ such that $\bar{z}(\tau) = \xi$, $\tau > T-\epsilon$, concatenate $\bar{z}$ with x_* at $t = \tau$ to obtain a feasible trajectory satisfying all constraints. This trajectory then has total time $\tau + \epsilon + t_c - T > t_c$, contradicting the global optimality of x_*.

Recall that T was the first time that $x_*(t) \in N$. Since z is compact, we can find a neighborhood of z that lies entirely in $\{x \,|\, x \notin N\}$. As the Maximum Principle is a local condition with respect to the state, this completes the proof. □

Theorem 5 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 of (42):

$$u_p(S,R) = \frac{1}{d}\frac{(1-(S+R))(S+p_rR)}{S}. \tag{43}$$

Thus, we have shown that the optimal control consists of concatenations of controls obtained from the unconstrained necessary conditions and controls of the form (43). In the next section, we analyze the Maximum Principle in the region $S+R<V_c$.

5.2 Maximum Principle and Necessary Conditions at Interior Points

Necessary conditions for the optimization problem discussed in Section 3 without path or terminal constraints are derived from the Pontryagin Maximum Principle [14, 10]. The corresponding Hamiltonian function H is defined as

$$H(\lambda_0,\lambda,x,u) = -\lambda_0 + \langle \lambda, f(x)\rangle + u\Phi(x), \tag{44}$$

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:

$$\Phi(x,\lambda) = \langle \lambda, g(x)\rangle. \tag{45}$$

The Maximum Principle then yields the following theorem:

Theorem 6. *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*

$$\begin{aligned}\dot{\lambda}(t) = &\begin{pmatrix} 2S+R+\epsilon-1 & p_rR-\epsilon \\ S & p_r(2R+S-1)\end{pmatrix}\lambda(t) \\ &+ u(t)\begin{pmatrix}\alpha+d & -\alpha \\ 0 & 0\end{pmatrix}\lambda(t)\end{aligned} \tag{46}$$

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

$$u_*(t) = \begin{cases} 0 & \Phi(t) > 0, \\ M & \Phi(t) < 0.\end{cases} \tag{47}$$

where

$$\Phi(t) := \Phi(x_*(t),\lambda(t)). \tag{48}$$

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

$$H(\lambda_0, \lambda(t), x_*(t), u_*(t)) \equiv 0. \tag{49}$$

Proof. Most statements of Theorem 6 follow directly from the Maximum Principle, so proofs are omitted. In particular, items (1), (2) and the first part of (3) are immediate consequences [10]. Equation (47) follows directly since we minimize the function H, which is affine in u (see equation (44)). The Hamiltonian vanishes along $(x_*(t), u_*(t), \lambda(t))$ since it is independent of an explicit time t dependence and the final time t_c is free, the latter being part of the transversality condition. □

For completeness, we state the following proposition.

Proposition 7. *For all $t \in [0, t_c]$, the adjoint $\lambda(t)$ corresponding to the extremal lift $(x_*(t), u_*(t), \lambda(t))$ is nonzero.*

Proof. This is a general result relating to free end time problems. We include a proof here for completeness. Suppose that there exists a time $t \in [0, t_c]$ such that $\lambda(t) = 0$. By (44), the corresponding value of the Hamiltonian is $H(\lambda_0, \lambda(t), x_*(t), u_*(t)) = -\lambda_0$. By item (4) in Theorem 6, $H \equiv 0$, which implies that $\lambda_0 = 0$. This contradicts item (1) in Theorem 6. Hence, $\lambda(t) \neq 0$ on $[0, t_c]$. □

5.3 Geometric Properties and Existence of Singular Arcs

We now undertake a geometric analysis of the optimal control problem utilizing the affine structure of system (5) for interior states (i.e. controls which satisfy Theorem 6). 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 8. *For all $S \in \Omega, S > 0$, the vector fields $f(x)$ and $g(x)$ are linearly independent.*

Proof. Define $A(x) = A(S, R)$ to be the matrix

$$\begin{aligned} A(S,R) &= \begin{pmatrix} f(x) & g(x) \end{pmatrix} \\ &= \begin{pmatrix} (1-(S+R)-\epsilon)S & -(\alpha+d)S \\ p_r(1-(S+R))R+\epsilon S & \alpha S \end{pmatrix}. \end{aligned} \tag{50}$$

The determinant of A can calculated as

$$\det A(x) = \alpha S^2 \kappa(x) + p_r(\alpha+d) RS\kappa(x) + \epsilon d S^2 \tag{51}$$

where

$$\kappa(x) := 1 - (S+R). \tag{52}$$

As $S(t) + R(t) \leq 1$ for all $t \geq 0$, $\kappa(x(t)) \geq 0$, and we see that $\det A(x) = 0$ in Ω if and only if $S = 0$, completing the proof. □

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, **$\mathbf{f}(\mathbf{x})$ and $\mathbf{g}(\mathbf{x})$ are linearly independent in the region of interest $\boldsymbol{\Omega}_\mathbf{c}$.**

We begin by showing that abnormal extremal lifts are easily characterized. We recall that an extremal lift is abnormal if $\lambda_0 = 0$, i.e. if the Hamiltonian is independent of the objective.

Theorem 9. *Abnormal extremal lifts at interior points, i.e. extremal lifts corresponding to $\lambda_0 = 0$, are constant and given by the maximal (M) or minimal (0) dosage.*

Proof. Assume that u_* switches values at some time t. From (47), we must have that $\Phi(t) = 0$. Since $\lambda_0 = 0$ and $\Phi(t) = \langle \lambda(t), g(x_*(t))\rangle$, equation (44) reduces to

$$H(t) = \langle \lambda(t), f(x_*(t))\rangle = 0. \tag{53}$$

Thus, $\lambda(t)$ is orthogonal to both $f(x_*(t))$ and $g(x_*(t))$. Since f and g are linearly independent (Proposition 8), this implies that $\lambda(t) = 0$. But this contradicts Proposition 7. Hence, no such time t exists, and $u_*(t)$ is constant. The constant sign of Φ thus corresponds to $u = 0$ or $u = M$ (see equation (47)). □

The control structure for abnormal extremal lifts is then completely understood via Theorem 9. To analyze the corresponding behavior for normal extremal lifts, without loss of generality we assume that $\lambda_0 = 1$. Indeed, $\lambda(t)$ may be rescaled by $\lambda_0 > 0$ to yield an equivalent version of Theorem 6. We thus assume that the Hamiltonian $H(t)$ evaluated along $(\lambda(t), x_*(t), u_*(t))$ is of the form

$$H(t) = -1 + \langle \lambda(t), f(x_*(t))\rangle + u_*(t)\Phi(t) \equiv 0. \tag{54}$$

We recall the Lie bracket as the first-order differential operator between two vector fields X_1 and X_2:

$$[X_1, X_2](z) = DX_2(z)X_1(z) - DX_1(z)X_2(z), \tag{55}$$

where, for example, $DX_2(z)$ denotes the Jacobian of X_2 evaluated at z. As f and g are linearly independent in Ω, there exist $\gamma, \beta \in C^\infty(\Omega)$ such that

$$[f, g](x) = \gamma(x)f(x) + \beta(x)g(x), \tag{56}$$

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

$$\gamma(x) = -\frac{(\alpha + d)S^2}{\det A(x)}\left(aS + bR - c\right), \tag{57}$$

$$\beta(x) = \frac{S^2}{\det A(x)}\Big(\alpha(1 - p_r)\kappa(x)(\kappa(x) - \epsilon) + \epsilon d(S + p_r R + \kappa(x) - \epsilon)\Big), \tag{58}$$

where

$$a = \alpha\left((1 - p_r) + \frac{d}{\alpha + d}\right), \tag{59}$$

$$b = \alpha(1 - p_r) + dp_r, \tag{60}$$

$$c = \alpha(1 - p_r) + \epsilon d. \tag{61}$$

Clearly, for parameter values of interest, $a, b, c > 0$. The assumption (13) guarantees that $\beta(x) > 0$ on $0 < S + R < V_c$.

From (47), 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 $[f, g]$:

$$\dot{\Phi}(t) = \frac{d}{dt}\langle \lambda(t), g(x_*(t))\rangle \tag{62}$$

$$= \gamma(x_*(t))\langle \lambda(t), f(x_*(t))\rangle + \beta(x_*(t))\Phi(t). \tag{63}$$

The last lines of the above follow from (56) as well as the linearity of the inner product. We are then able to derive an ODE system for x_* and Φ. Equation (54) allows us to solve for $\langle \lambda(t), f(x_*(t))\rangle$:

$$\langle \lambda(t), f(x_*(t))\rangle = 1 - u_*(t)\Phi(t). \tag{64}$$

Substituting the above into (63) then yields the following ODE for $\Phi(t)$, which we view as coupled to system (5) via (47):

$$\dot{\Phi}(t) = \gamma(x_*(t)) + \Big(\beta(x_*(t)) - u_*(t)\gamma(x_*(t))\Big)\Phi(t). \tag{65}$$

The structure of the optimal control at interior points 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 (47) does not determine the value of u_*, and a more thorough analysis of the zero set of $\Phi(t)$ is necessary. Indeed, for a problem such as ours, singular arcs are the only candidates for optimal controls that may take values outside of the set $\{0, M\}$. Conversely, times t where $\Phi(t) = 0$ but $\Phi^{(n)}(t) \neq 0$ for some $n \geq 1$ denote candidate bang-bang junctions, where the control may switch between the vertices 0 and M of the control set U. Note that the parity of the smallest such n determines whether a switch actually occurs: n odd implies a switch, while for n even u_* remains constant. Equation (65) allows us to completely characterize the regions in the (S, R) plane where singular arcs are attainable, as demonstrated in the following proposition.

Proposition 10. *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 $\{x \in \mathbb{R}^2 \,|\, \gamma(x) = 0\} \cap \Omega$ is the line*

$$aS + bR - c = 0, \tag{66}$$

where a, b, c are defined in (59)-(61).

Proof. As discussed prior to the statement of Proposition 10, a singular arc must occur on a region where both $\Phi(t)$ and $\dot{\Phi}(t)$ are identically zero (as well as all higher-order derivatives). Denoting by $x_*(t)$ the corresponding trajectory in the (S, R) phase plane, we may calculate $\dot{\Phi}(t)$ from equation (65):

$$\dot{\Phi}(t) = \gamma(x_*(t)). \tag{67}$$

Note we have substituted the assumption $\Phi(t) = 0$. Clearly we must also have that $\gamma(x_*(t)) = 0$, thus implying that $x_*(t) \in \gamma^{-1}(0)$, as desired. The last statement of the proposition follows immediately from equation (57). □

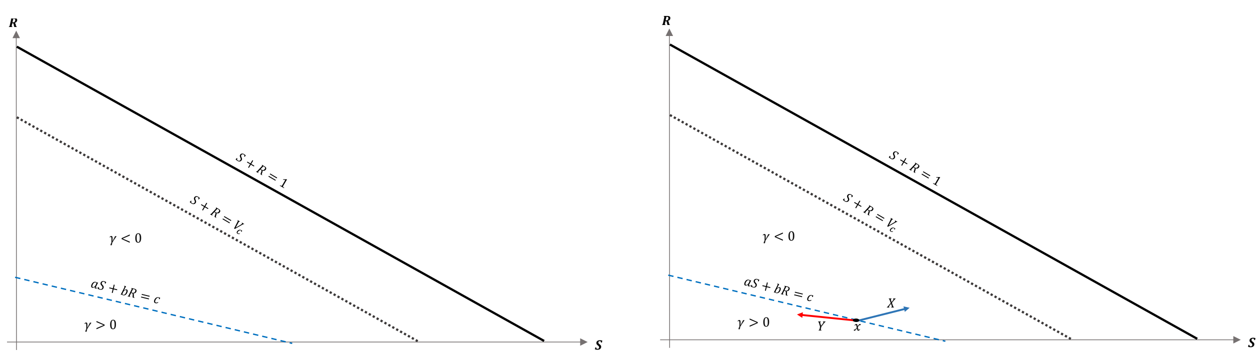
Proposition 10 implies that singular solutions can only occur along the line $aS + bR - c = 0$. Thus, define regions in the first quadrant as follows:

$$\Omega_c^+ := \{x \in \Omega \,|\, \gamma(x) > 0\}\,, \tag{68}$$
$$\Omega_c^- := \{x \in \Omega \,|\, \gamma(x) < 0\}\,, \tag{69}$$
$$\mathcal{L} = \{x \in \Omega \,|\, \gamma(x) = 0\}\,. \tag{70}$$

Recall that Ω_c is simply the region in Ω prior to treatment failure, i.e. $0 \le V \le V_c$. From (57), Ω_c is partitioned as in Figure 1(a). From (57) and (59)-(61), $\mathcal{L}$ is a line with negative slope $-b/a$. Furthermore, necessary and sufficient conditions for $\mathcal{L}$ to lie interior to Ω_0 are $\frac{c}{a}, \frac{c}{b} \le V_c$. From (59)-(61), this occurs if and only if

$$\epsilon \le \min\left\{\frac{\alpha}{\alpha + d} - \frac{1 - V_c}{d}\left(\alpha(1 - p_r) + \frac{\alpha d}{\alpha + d}\right), p_r - \frac{1 - V_c}{d}\Big(\alpha(1 - p_r) + dp_r\Big)\right\}. \tag{71}$$

As ϵ is generally assumed small (recall that it represents the drug-independent mutation rate) and $V_c \approx 1$, this inequality is not restrictive, and we assume it is satisfied for the remainder of the work. We note an important exception below: when $\alpha = 0$ the inequality is never satisfied with $\epsilon > 0$; for such parameter values, line $\mathcal{L}$ is horizontal. We note that this does not change the qualitative results presented below. Of course, other configurations of the line $aS + bR = c$ and hence precise optimal syntheses may exist, but we believe the situation illustrated in Figure 1(a) is sufficiently generic for present purposes.



(a) (b)

Figure 1: Domain in (S, R) plane. (a) Region where γ changes sign. We see that inside the triangular region $S + R \le 1$ of the first quadrant, γ changes sign only along the line $aS + bR - c = 0$. For this line to be interior to Ω_c as depicted, we must be in the parameter regime indicated in (71). (b) X and Y vector fields corresponding to vertices of control set U. For singular controls to lie in U, X and Y must point to opposite sides along $\mathcal{L}$.

With the existence of singular arcs restricted to the line $\gamma = 0$ by Proposition 66, we now investigate the feasibility of such solutions. Recall that the treatment $u(t)$ must lie in the control set $U = [0, M]$, for some $M > 0$ corresponding to the maximally tolerated applied dosage. Defining the vector field $X(x)$ and $Y(x)$ as the vector fields corresponding to the vertices of U,

$$\begin{aligned} X(x) &= f(x), \\ Y(x) &= f(x) + Mg(x), \end{aligned} \tag{72}$$

a singular control takes values in U at $x \in \mathcal{L}$ if and only if $X(x)$ and $Y(y)$ point in different directions along $\mathcal{L}$. More precisely, the corresponding Lie derivatives $L_X\gamma(x)$ and $L_Y\gamma(x)$ must have opposite signs; see Figure 1(b). The following proposition determines parameter values where this occurs.

Proposition 11. *Suppose that $\alpha > 0$, so that drug has the potential to induce drug resistance. Also, let the maximally tolerated dosage M satisfy*

$$M > \frac{\alpha + d}{\alpha(\alpha + d) + \alpha d}\left(d\left(\frac{\alpha}{\alpha + d} - \epsilon\right) + \epsilon d(p_r - \alpha) - 2\alpha d(1 - p_r)\right). \tag{73}$$

Then the following hold along $\mathcal{L}$:

1. *$L_X\gamma < 0$,*
2. *$L_Y\gamma < 0$ as $(S, R) \to \left(0, \frac{c}{b}\right)$ in Ω_0,*
3. *$L_Y\gamma > 0$ at $(S, R) = \left(\frac{c}{a}, 0\right)$, and*
4. *$L_Y\gamma$ is monotonically decreasing as a function of S.*

Thus, $\mathcal{L}$ contains a segment $\bar{\mathcal{L}} \subset \mathcal{L}$ which is a singular arc. Note that $\bar{\mathcal{L}}$ is precisely the region in $\mathcal{L}$ where $L_Y\gamma$ is negative.

Proof. The proof is purely computational. □

The geometry of Proposition 11 is illustrated in Figure 2. Thus, assuming $\alpha > 0$ and M as in (73), singular arcs exist along the segment $\bar{\mathcal{L}} \subset \mathcal{L}$. Furthermore, the corresponding control has a unique solution u_s, which may be computed explicitly. Indeed, as the solution must remain on the line $\mathcal{L}$, or equivalently, $aS + bR = c$, taking the time derivative of this equation yields $a\dot{S} + b\dot{R} = 0$, and substituting the expressions (1) we compute u_s as

$$u_s(t) = \frac{\kappa\big(x(t)\big)\Big(aS(t) + p_r bR(t)\Big) + \epsilon(b - a)S(t)}{2\alpha(1 - p_r)dS(t)}, \tag{74}$$

where a, b, c are given by (59)-(61) and R and S satisfy $aS + bR = c$. As discussed previously, $S(t) > 0$ for $S_0 > 0$, so this formula is well-defined. Proposition 11 implies that it is possible to simplify equation (74) as a function of S (i.e. as a *feedback law*) for $S \in \left(\bar{S}, \frac{c}{a}\right)$, for some $\bar{S} > 0$, but since its value will not be needed, we do not provide its explicit form. Note that the maximal dose M is achieved precisely at $S = \bar{S}$ where vector field Y is parallel to $\mathcal{L}$. Thus, at this $\bar{S}$, the trajectory must leave the singular arc, and enter the region Ω_0^+. As $\dot{R} \geq 0$, trajectories must follow $\mathcal{L}$ in the direction of decreasing S; see Figure 2. We summarize these results in the following theorem.

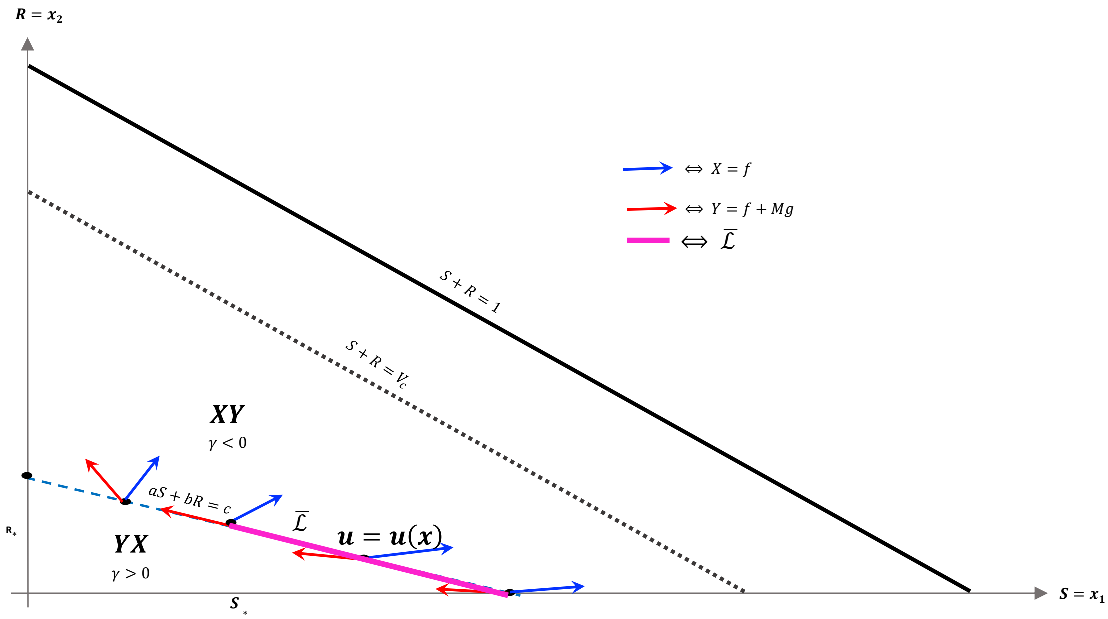


Figure 2: Geometry of vector fields X and Y with $\alpha > 0$ and M satisfying (73). As in Proposition 11, this can be understood via the corresponding Lie derivatives of γ. Note that near $R = 0$, X and Y point to opposite sides of $\mathcal{L}$, while at $(S, R) = \left(0, \frac{c}{b}\right)$, both X and Y point away from $\gamma > 0$. The line $\bar{\mathcal{L}}$ is the unique singular arc in Ω_c.

Theorem 12. *If $\alpha > 0$, and M satisfies (73), a singular arc exists in the (S, R) plane as a segment of the line $\mathcal{L}$. Along this singular arc, the control is given by equation (74), where $aS + bR = c$. Therefore, in this case the necessary minimum conditions on u_* from (47) can be updated as follows:*

$$u_*(t) = \begin{cases} 0 & \Phi(t) > 0, \\ M & \Phi(t) < 0, \\ u_s(t), & \Phi(t) \equiv 0 \text{ for } t \in I, \end{cases} \tag{75}$$

where I is an open interval. Recall again that this is the optimal control at points interior to Ω_c.

Proof. See the discussion immediately preceding Theorem 12. □

In the case $\alpha = 0$, the line $\mathcal{L}$ is horizontal, and as R is increasing, no segment $\bar{\mathcal{L}} \subseteq \mathcal{L}$ is admissible in phase space. Thus, the interior controls in this case are bang-bang.

Theorem 13. *If $\alpha = 0$, there are no singular arcs for the optimal time problem presented in Section 3. Thus, the interior control structure is bang-bang.*

Outside of the singular arc $\bar{\mathcal{L}}$, the control structure is completely determined by (47) and (65). The precise result, utilized later for optimal synthesis presented in Section 6, is stated in the following theorem. We first introduce a convenient (and standard) notation. Let finite words on X and Y denote the concatenation of controls corresponding to vector fields X ($u \equiv 0$) and Y ($u \equiv M$), respectively. The order of application is read left-to-right, and an arc appearing in a word may not actually be applied (e.g. XY denotes an X arc followed by a Y arc or a Y arc alone).

Theorem 14. *Consider an extremal lift $\Gamma = ((x,u),\lambda)$. Trajectories x remaining entirely in Ω_c^+ or Ω_c^- can have at most one switch point. Furthermore, if $x \in \Omega_c^+$, then the corresponding control is of the form YX. Similarly, $x \in \Omega_c^-$ implies that $u = YX$. Hence multiple switch points must occur across the singular arc $\bar{\mathcal{L}}$.*

Proof. If τ is a switching time, so that $\Phi(\tau) = 0$, equation (65) allows us to calculate $\dot{\Phi}(\tau)$ as

$$\dot{\Phi}(\tau) = \gamma(x(\tau)). \tag{76}$$

Thus, in Ω_c^+ where $\gamma > 0$, $\dot{\Phi}(\tau) > 0$, and hence Φ must increase through τ. The expression for the control (47) then implies that a transition from a Y-arc to an X-arc occurs at τ (i.e. a YX arc). Furthermore, another switching time cannot occur unless x leaves Ω_0^+, since otherwise there would exist a $\bar{\tau} > \tau$ such that $\Phi(\bar{\tau}) = 0, \dot{\Phi}(\bar{\tau}) < 0$ which is impossible in Ω_c^+. Similarly, only XY-arcs are possible in Ω_c^-. ∎

The structure implies by Theorem 14 is illustrated in Figure 2. Note that outside inside the sets Ω_c^+, Ω_c^-, and $\bar{\mathcal{L}}$, extremal lifts are precisely characterized. Furthermore, the results of Section 5.1 (and particularly equation (43)) yield the characterization only the boundary N. What remains is then to determine the synthesis of these controls to the entire domain Ω_c, as well as to determine the order local optimality of the singular arc $\bar{\mathcal{L}}$. The latter is addressed in the following section.

5.4 Optimality of Singular Arcs

We begin by proving that the singular arc is extremal, i.e. that it satisfies the necessary conditions presented in Section 5.2 (note that it is interior by assumption). This is intuitively clear from Figure 2, since X and Y point to opposite sides along $\bar{\mathcal{L}}$ by the construction of $\bar{\mathcal{L}}$.

Theorem 15. *The line segment $\bar{\mathcal{L}} \subset \mathcal{L}$ is a singular arc.*

Proof. We find an expression for $u = u(x)$ such that the vector $f(x) + u(x)g(x)$ is tangent to $\bar{\mathcal{L}}$ at x, i.e. we find the unique solution to

$$L_{f+ug}(\gamma) = 0 \tag{77}$$

Note that we can invert (72):

$$\begin{aligned} f(x) &= X(x) \\ g(x) &= \frac{1}{M}\left(Y(x) - X(x)\right) \end{aligned} \tag{78}$$

so that $f + ug = \left(1 - \frac{u}{M}\right) X + \frac{u}{M} Y$. Thus,

$$L_{f+ug}(\gamma) = \left(1 - \frac{u}{M}\right) L_X\gamma + \frac{u}{M} L_Y\gamma$$

Setting the above equal to zero, and solving for $u = u(x)$ yields

$$u(x) = M \frac{L_X\gamma(x)}{L_X\gamma(x) - L_Y\gamma(x)} \tag{79}$$

As $L_X\gamma < 0$ and $L_Y\gamma > 0$ on $\bar{\mathcal{L}}$ by Proposition 11, we see that $0 < u(x) < M$. We must also verify that the associated controlled trajectory (79) is extremal by constructing a corresponding lift. Suppose that $x(t)$ solves

$$\begin{aligned} \dot{x} &= f(x) + u(x)g(x), \\ x(0) &= q, \end{aligned}$$

for $q \in \bar{\mathcal{L}}$. Let $\phi \in (\mathbb{R}^2)^*$ such that

$$\langle \phi, g(q) \rangle = 0, \qquad \langle \phi, f(q) \rangle = 1.$$

Let $\lambda(t)$ solve the corresponding adjoint equation (46) with initial condition $\lambda(0) = \phi$. Then the extremal lift $\Gamma = ((x, u), \lambda)$ is singular if $\Phi(t) = \langle \lambda(t), g(x(t)) \rangle \equiv 0$. By construction of $u(x)$, the trajectory remains on $\bar{\mathcal{L}}$ on some interval containing zero, and we can compute $\dot{\Phi}$ as (using (56))

$$\begin{aligned} \dot{\Phi}(t) &= \langle \lambda(t), [f, g](x(t)) \rangle \\ &= \gamma(x(t)) \langle \lambda(t), f(x(t)) \rangle + \beta(x(t)) \langle \lambda(t), g(x(t)) \rangle \\ &= \beta(x(t)) \Phi(t), \end{aligned}$$

Note that we have used (65) and the fact that $\gamma = 0$ by our choice of u. Since $\Phi(0) = 0$ by hypothesis, this implies that $\Phi(t) \equiv 0$, as desired. □

The above then verifies that $\bar{\mathcal{L}}$ is a singular arc. Note that an explicit expression for $u = u(x)$ was given in (74), which can be shown to be equivalent to (79).

Having shown that the singular arc $\bar{\mathcal{L}}$ is extremal, we now investigate whether it is locally optimal for our time-optimization problem. The singular arc is of intrinsic order k if the first $2k - 1$ derivatives of the switching function are independent of u and vanish identically on an interval I, while the $2k^{\text{th}}$ derivative has a linear factor of u. We can compute (this is standard for control-affine systems (5)) that

$$\Phi^{2k}(t) = \langle \lambda(t), \mathrm{ad}_f^{2k}(g)(x(t)) \rangle + u(t) \langle \lambda(t), [g, \mathrm{ad}_f^{2k-1}(g)](x(t)) \rangle, \tag{80}$$

where ad_Z is the adjoint endomorphism for a fixed vector field Z:

$$\mathrm{ad}_Z(V) = [Z, V], \tag{81}$$

and powers of this operator are defined as composition. Fix an extremal lift $\Gamma = ((x, u), \lambda)$ of a singular arc of order k. The Generalized Legendre-Clebsch condition (also known as the Kelley condition) [10] states that a necessary condition for Γ to satisfy a minimization problem with corresponding Hamiltonian H is that

$$(-1)^k \frac{\partial}{\partial u}\frac{d^{2k}}{dt^{2k}}\frac{\partial H}{\partial u}(\lambda_0, \lambda(t), x(t), u(t)) \geq 0 \tag{82}$$

along the arc. Note that $\frac{\partial H}{\partial u} = \Phi$, so that the above is simply the u coefficient of the $2k$th time derivative of the switching function (multiplied by $(-1)^k$). The order of the arc, as well as the Legendre-Clebsch condition, are addressed in Theorem 16.

Theorem 16. *The singular control is of order one. Furthermore, for all times t such that $x(t) \in \bar{\mathcal{L}}$, $\langle \lambda(t), [g, [f, g]](x(t))\rangle > 0$. Thus, the Legendre-Clebsch condition is violated, and the singular arc $\bar{\mathcal{L}}$ is not optimal.*

Proof. Along singular arcs we must have $\Phi(t), \dot{\Phi}(t), \ddot{\Phi}(t) \equiv 0$, and we can compute these derivatives using iterated Lie brackets as follows:

$$\begin{aligned} \Phi(t) &= \langle \lambda(t), g(x(t))\rangle, \\ \dot{\Phi}(t) &= \langle \lambda(t), [f, g](x(t))\rangle, \\ \ddot{\Phi}(t) &= \langle \lambda(t), [f + ug, [f, g]](x(t))\rangle. \end{aligned} \tag{83}$$

The final of the above in (83) can be simplified as

$$\ddot{\Phi}(t) = \langle \lambda(t), [f, [f, g]](x(t))\rangle + u(t)\langle \lambda(t), [g, [f, g]](x(t))\rangle \equiv 0, \tag{84}$$

which is precisely (80) for $k = 1$. Order one is then equivalent to being able to solve this equation for $u(t)$. Thus, $\langle \lambda(t), [g, [f, g]](x(t))\rangle > 0$ will imply that the arc is singular of order one. We directly compute $\langle \lambda(t), [g, [f, g]](x(t))\rangle = \langle \lambda(t), [g, \mathrm{ad}_f(g)](x(t))\rangle$. Using equation (56) and recalling properties of the singular arc ($\gamma = 0$ and the remaining relations in (83), as well as basic "product rule" properties of the Lie bracket), we can show that

$$[g, [f, g]] = (L_g\gamma)f - \gamma[f, g] + (L_g\beta)g. \tag{85}$$

Recall that for extremal lift along the arc $\bar{\mathcal{L}}$,

$$\begin{aligned} \langle \lambda(t), g(x(t))\rangle &\equiv 0, \\ \langle \lambda(t), [f, g](x(t))\rangle &\equiv 0 \\ \langle \lambda(t), f(x(t))\rangle &\equiv 1. \end{aligned} \tag{86}$$

The first two of the above follow from $\Phi, \dot{\Phi} \equiv 0$, and the third is a consequence of $H \equiv 0$ (see (44)). Equations (85) and (86) together imply that

$$\begin{aligned} \langle \lambda(t), [g, [f, g]](x(t))\rangle &= L_g\gamma\langle \lambda(t), f(x(t))\rangle - \gamma\langle \lambda(t), [f, g](x(t))\rangle + L_g\beta\langle \lambda(t), g(x(t))\rangle \\ &= L_g\gamma(x(t)) \\ &= \frac{1}{M}\left(L_Y\gamma(x(t)) - L_X\gamma(x(t))\right). \end{aligned} \tag{87}$$

The last equality is due to (78). As $L_Y\gamma > 0$ and $L_X\gamma < 0$ along $\bar{\mathcal{L}}$ (Proposition 11), $\langle\lambda(t), [g,[f,g]](x(t))\rangle > 0$, as desired. Furthermore,

$$-\langle\lambda(t), [g,[f,g]](x(t))\rangle < 0, \quad \text{or equivalently} \tag{88}$$

$$(-1)^1 \frac{\partial}{\partial u}\frac{d^2}{dt^2}\frac{\partial H}{\partial u} < 0, \tag{89}$$

showing that (82) is violated (substituting $k = 1$). Thus, $\bar{\mathcal{L}}$ is not optimal. □

Theorem 16 then implies that the singular arc is suboptimal, i.e. that $\bar{\mathcal{L}}$ is "fast" with respect to the dynamics. In fact, comparing time along the trajectories can be computed explicitly using the "clock form," a one-form on Ω. As one-forms correspond to linear functional on the tangent space, and f and g are linearly independent, there exists a unique $\omega \in (T\Omega)^{vee}$ such that

$$\omega_x(f(x)) \equiv 1, \qquad \omega_x(g(x)) \equiv 0. \tag{90}$$

In fact, we compute it explicitly:

$$\omega_x = \frac{g_2(x)dx^1 - g_1(x)dx^2}{\det(f(x), g(x))}. \tag{91}$$

Then, along any controlled trajectory (x, u) defined on $[t_0, t_1]$, the integral of ω computes the time $t_1 - t_0$:

$$\begin{aligned}
\int_x \omega &= \int_{t_0}^{t_1} \omega_{x(t)}(\dot{x}(t))\,\mathrm{d}t \\
&= \int_{t_0}^{t_1} \omega_{x(t)}(f(x(t)) + u(t)g(x(t))))\,\mathrm{d}t \\
&= \int_{t_0}^{t_1} \omega_{x(t)}(f(x(t))\,\mathrm{d}t + \int_{t_0}^{t_1} u(t)\omega_{x(t)}(g(x(t))))\,\mathrm{d}t \\
&= \int_{t_0}^{t_1} \mathrm{d}t \\
&= t_1 - t_0.
\end{aligned} \tag{92}$$

We can then use ω and Stokes' Theorem to compare bang-bang trajectories with those on the singular arc. See Figure 3 below for a visualization of a singular trajectory connecting $q_1, q_2 \in \bar{\mathcal{L}}$ and the corresponding unique XY trajectory connecting these points in Ω_c^- (note that uniqueness is guaranteed as long as q_1 and q_2 are sufficiently close).

Let τ denote the time spent along the singular arc, s the time spent along the X arc, and t the time spent along the Y arc. Denote by Δ the curve traversing the X and Y arcs positively, and the singular arc negatively, and R its interior. As X and Y are positively oriented (they have the same orientation as f and g), Stokes' Theorem yields

$$s + t - \tau = \int_\Delta \omega = \int_R d\omega \tag{93}$$

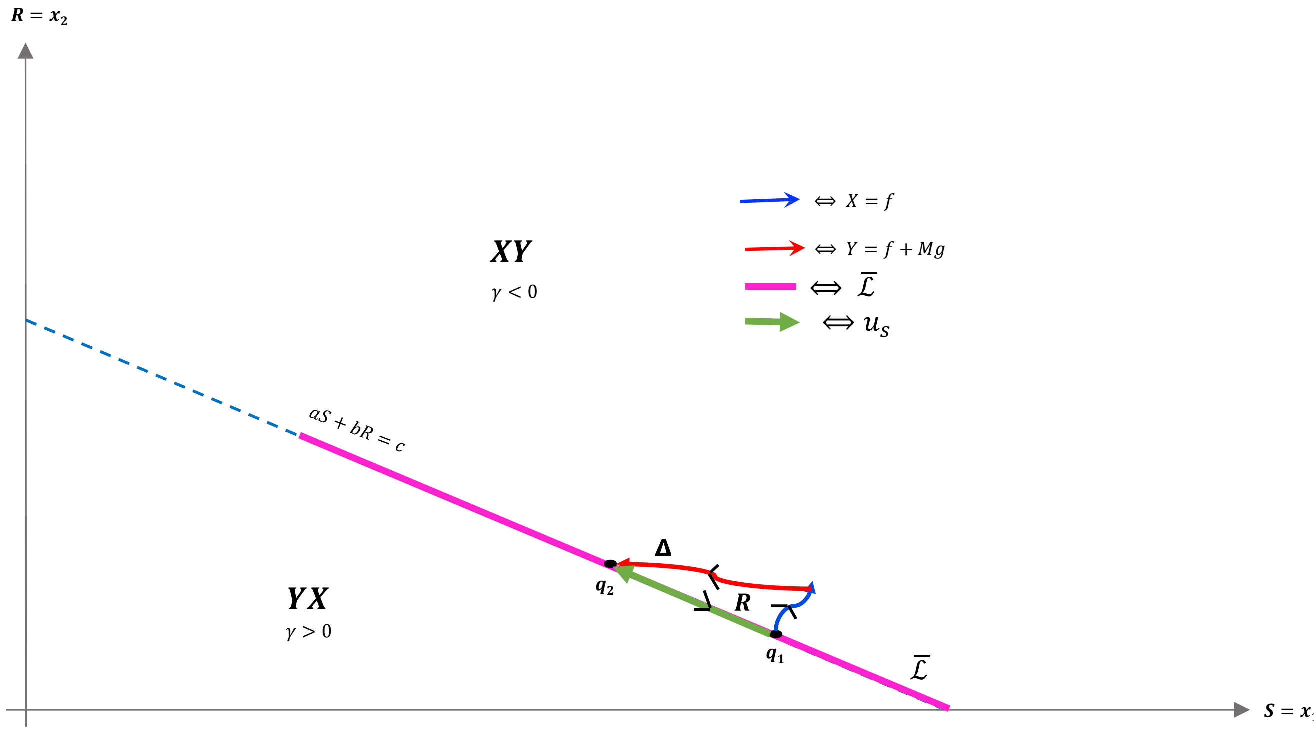


Figure 3: Both XY and singular trajectories taking q_1 to q_2.

A straightforward calculation yields the two-form $d\omega$:

$$d\omega = -\frac{\gamma}{\det(f,g)}. \tag{94}$$

As the determinant is everywhere positive (see the proof of Proposition 8), and R lies entirely in $\gamma < 0$, the integral on the right-hand side of (93) is positive, so that we have

$$\tau < s + t \tag{95}$$

Thus, time taken along the singular arc is shorter than that along the XY trajectory, implying that the singular arc is locally suboptimal for our problem (recall that we want to maximize time). Since local optimality is necessary for global optimality, trajectories should never remain on the singular arc for a measurable set of time points. This reaffirms the results of Theorem 16. A completely analogous statement holds for YX trajectories in the region $\gamma > 0$. We can also demonstrate, utilizing the same techniques, that increasing the number of switchings at the singular arc speeds up the trajectory; see Figure 4. This again reinforces Theorem 16, and implies that trajectories should avoid the singular arc to maximize the time spent in Ω_c.

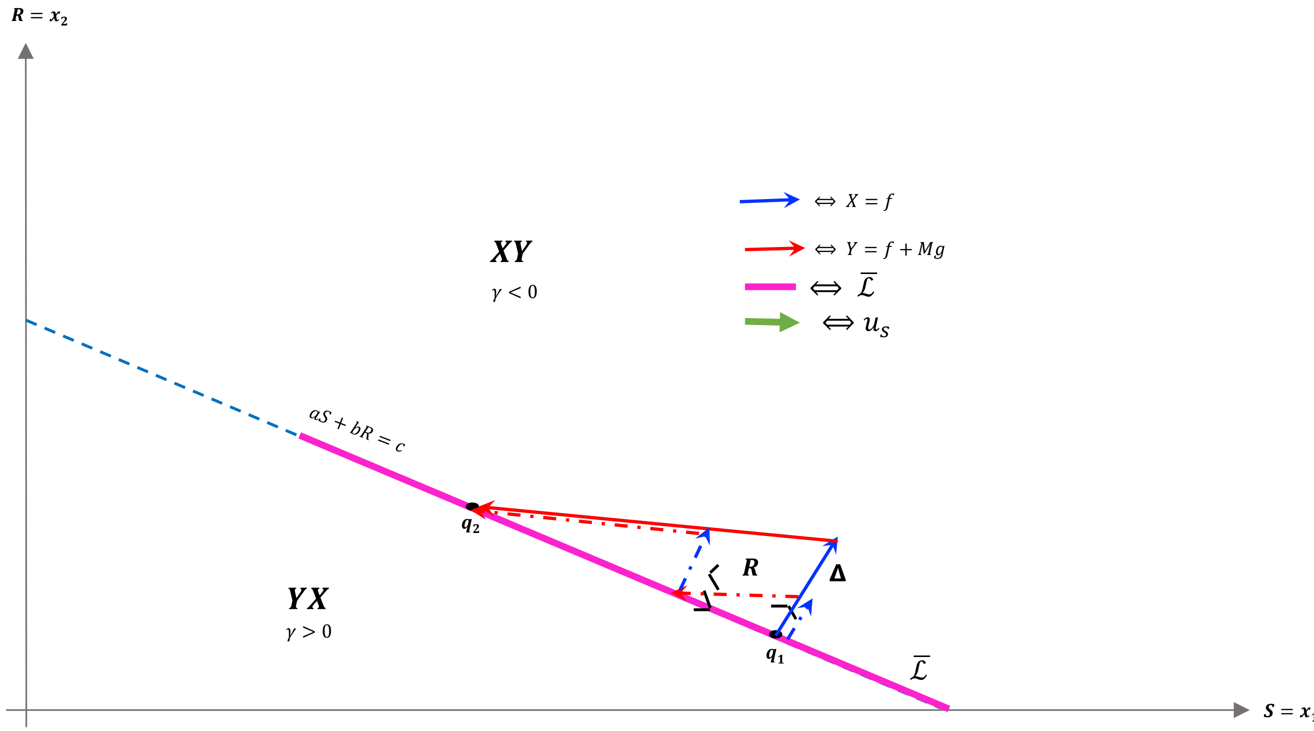


Figure 4: XY (solid) and $XYXY$ (dashed) trajectories taking q_1 to q_2 in the region $\gamma > 0$. The time difference between the two trajectories can again be related to the surface integral in the region R, where $\gamma < 0$. The XY trajectory can then be seen to be slower in comparison.

6 Characterization of Optimal Control

The results of Section 5.1, 5.2, 5.3, and 5.4 may now be combined to synthesize the optimal control introduced in Section 3.

Theorem 17. *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*

$$(YX)^n(u_pY)^m, \tag{96}$$

where $(YX)^n := (YX)^{n-1}YX$ and similarly for $(u_pY)^m$, for $n, m \in \mathbb{N}$, and the order should be interpreted left to right. Here u_p is defined in (43).

Proof. Formula (96) is simply a combination of the results presented previously. Note that singular arcs are never (locally) optimal, and hence do not appear in the equation. We also observe that X arcs are not admissible once the boundary N has been obtained, as an X arc always decreases γ (see Figure 2). A Y arc may bring the trajectory back into $\text{int}(\Omega_c)$, but an XY trajectory is no longer admissible, as the switching structure in Ω_- is XY. □

Note that in Theorem 17, the switchings must occur across the singular arc $\bar{\mathcal{L}}$, if it exists (recall that it is not admissible if $\alpha = 0$). The control u_p is determined along the boundary of Ω_c, and provides the synthesis between exterior and boundary controls.

7 Conclusions and Future Work

We have provided the mathematical details presented in [7]. Specifically, proofs relating to identifiability and the optimal synthesis are detailed.

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Author Contributions

All authors contributed equally to this work.

Conflict of Interest

None declared.

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