On the Analysis of Cyclic Drug Schedules for Cancer Treatment using Switched Dynamical Systems

Margaret P. Chapman¹, Eric V. Mazumdar¹, Ellen Langer², Rosalie Sears², and Claire J. Tomlin¹

Abstract—Motivated by our prior work on a Triple Negative breast cancer cell line, the focus of this paper is controller synthesis for cancer treatment, through the use of drug scheduling and a switched dynamical system model. Here we study a cyclic schedule of \( d \) drugs with maximal waiting times between drug inputs, where each drug is applied once per cycle in any order. We suppose that some of the \( d \) drugs are highly toxic to normal cells and that these drugs can shrink the live cancer cell population. The remaining drugs are less toxic to normal cells and can only reduce the growth rate of the live cancer cell population. Also, we assume that waiting time bounds related to toxicity, or to the onset of resistance, are available for each drug. A cancer cell population is said to be stable if the number of live cells tends to zero, as time becomes sufficiently large. In the absence of modeling error, we derive conditions for exponential stability. In the presence of modeling error, we prove exponential stability and derive a settling time, under certain mathematical conditions on the error. We conclude the paper with a numerical example that uses models which were identified on Triple Negative breast cancer cell line data.

I. INTRODUCTION

Building mathematical models of the response of cancer cell populations to a particular drug is an active area of research [1], [2], [3], [4], [5]. However, analyzing the effects of drugs individually yields insights that are not always clinically useful. For example, in a prior study on the response of the Triple Negative breast cancer cell line, HCC1143, to various targeted therapeutics, only one of the drugs, the equal-ratio Trametinib+BEZ235 combination, demonstrated the potential to kill cancer cells effectively [4], [5]. This drug is not expected to work in practice due to toxicity concerns [6], [7], [8], transient rather than long-term efficacy [9], low rate of response [10], and negative secondary reactions [8], [11]. Fortunately, recent evidence suggests that, if carefully designed, drug schedules have the potential to be effective methods for cancer treatment; e.g., see [1] and [3].

In this paper, we assume that linear time-invariant (LTI) models of the response of cancer cell populations to different drugs are given, as such models have been identified in prior work; e.g., see [4] and [5]. We suppose that there are some drugs that can shrink the live cancer cell population, but are very toxic to healthy cells. In addition, there are other drugs that only slow the growth of the live cancer cell population, but are less toxic to healthy cells. While applying any drug in the first group repeatedly should eradicate the cancer, we suppose that this is impractical due to toxicity concerns, negative secondary reactions, or the development of drug resistance. The less toxic drugs, on the other hand, cannot kill the cancer alone, but they do reduce the cancer growth rate and are better tolerated by the patient. We further assume that longer waiting times between treatments are preferable: they correspond to fewer in-patient hospital visits, which may suggest higher patient convenience and lower healthcare costs.

Given LTI models of the response of cancer cell populations to various drugs, we seek to address a controller synthesis problem for cancer treatment. The system that we analyze is a population of cancer cells subject to therapeutic intervention, and the control input is how the available drugs are administered (e.g., drug type, order of application, and time between treatments). Our goal is to stabilize the live cancer cell population, meaning to drive the number of live cancer cells to zero, as time becomes sufficiently large. The focus of this paper is the analysis of schedules composed of drugs with varying toxicities and long waiting times between treatments, using a switched dynamical system model of drug-treated cancer cells.

Stability and controller synthesis of switched systems has been well-studied in the literature (e.g., see [12], [13], [14], [15], [16]). Further, the synthesis of drug schedules for HIV treatment has been posed as the optimization of control laws for switched systems [17], [18], [19]. Inspired by these works, we consider the following problem at the intersection of switched systems and cancer treatment.

Contributions. We propose the use of a cyclic schedule of \( d \in \mathbb{N} \) drugs, where each drug is applied once per cycle in any order. Some of the \( d \) drugs, \( \mathcal{I} \), can shrink the live cancer cell population but are extremely toxic to healthy cells. Other less toxic drugs, \( \mathcal{J} \), can only slow the growth of the live cancer cell population. We provide an upper bound on the cancer growth rate in response to a single drug, using the matrix norm induced by the vector \( L^1 \)-norm and a particular matrix structure from our previous work (Lemma 1). We derive a set of maximal waiting times between drug inputs, under the assumption that waiting time bounds representing a measure of toxicity to normal cells, or the onset of resistance, are given for each drug (Lemma 2). This assumption is justified in part by the limited efficacy of using one therapy to treat certain cancers. In the absence of modeling error, we show that a cyclic schedule with a set of maximal waiting times stabilizes the live cancer cell population exponentially (Theorem 1). Further, we prove that if the modeling error is bounded and if the product of the errors in each cycle

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is sufficiently small, then a cyclic schedule with a set of maximal waiting times also induces exponential stability (Theorem 2). Using this last result, we derive a loose upper bound on the amount of time required for the population to settle to a small size (Corollary 1).

This paper offers substantive novel contributions beyond those of our previous papers, [4] and [5]. The focus of the current paper is the analysis of drug schedules in terms of switched systems, using the models that we developed in [4] and [5]. In particular, Chapman et al. proposes a drug schedule based on the eigenvectors and eigenvalues of the models [4]. Risom et al. studies the biology of breast cancer and uses the models to convey biological insights [5].

The paper is structured as follows. Sec. II summarizes the switched dynamical system model of a drug-treated cancer cell population. Sec. III presents the preliminary results: Lemma 1 and Lemma 2. Sec. IV provides the main results: Theorem 1, Theorem 2, and Corollary 1. Sec. V presents a numerical example that uses models that were trained on HCC1143 cell line data. Brief conclusions are in Sec. VI.

Notation is provided below.

- $\mathbb{R}^{p \times q}$ is the set of $p \times q$ matrices with real non-negative entries.
- $\mathbb{N} = \{1, 2, \ldots \}$ is the set of natural numbers.
- $\mathbb{N}_0 = \{0, 1, 2, \ldots \}$ is the set of natural numbers including zero.
- $\Pi_{p=1}^D A(i) = A(p)A(p-1) \cdots A(1)$ is a product of $p$ matrices.
- $\lceil y \rceil$ is the cell function, and $\lfloor y \rfloor$ is the floor function.

II. MATHEMATICAL MODEL

A cancer cell population can be partitioned into a finite number of classes, called phenotypic states. A phenotypic state is a set of observable traits that arises from the synthesis of proteins and that has important implications for drug response; e.g., see [1] and [2]. In this paper, we model a drug-treated cancer cell population as a switched linear time-invariant dynamical system,

$$\dot{x}(t + 1) = \tilde{A}_\delta \tilde{x}(t); \quad t \in \mathbb{N}_0, \quad \delta \in D, \quad \tilde{x}(0) = \tilde{x}_0. \quad (1)$$

$\tilde{x} \in \mathbb{R}_+^{n}$ is the non-negative cell type vector; $\tilde{x} = [\tilde{x}_1, \ldots, \tilde{x}_n]^T$ with $\tilde{x}_i \geq 0$ for each $i$. If $i < n$, then $\tilde{x}_i$ is the number of live cells in phenotypic state $i$. $\tilde{x}_n$ is the number of dead or dying cells in total. $D$ is the set of drugs, and $|D| = d$. $\tilde{A}_\delta \in \mathbb{R}^{n \times n}$ is the dynamics matrix for drug $\delta \in D$. If $\delta_t = j$, then we say that drug $j$ is active at time $t$. The duration of the discrete-time interval, $[t, t + 1)$, is the period between two consecutive measurements.

The dynamics matrix of (1), $\tilde{A}_\delta \in \mathbb{R}^{n \times n}$, takes the form [4][5],

$$\tilde{A}_\delta = \begin{bmatrix} \alpha_1 & \rho_{21} & \cdots & \rho_{p1} & 0 \\ \rho_{12} & \alpha_2 & \cdots & \rho_{p2} & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ \rho_{1p} & \rho_{2p} & \cdots & \alpha_p & 0 \\ \rho_{1D} & \rho_{2D} & \cdots & \rho_{pD} & 1 \end{bmatrix}, \quad (2a)$$

$$\alpha_i := \rho_i - \rho_iD - \sum_{s=1, s \neq i}^{p} \rho_{is}; \quad i = 1, \ldots, p, \quad (2b)$$

$$p := n - 1. \quad (2c)$$

The parameters, $\rho_i = \rho_i(\delta)$, $\rho_iD = \rho_iD(\delta)$, and $\rho_{ij} = \rho_{ij}(\delta)$ are defined in Table I. $A_\delta$ is subject to a set of linear constraints, which are provided in Table II. Eq. (2) is derived by assuming that a live cell can divide, transition, or die on the discrete-time interval, $[t, t + 1)$; please see our prior work [4], [5].

Because the division parameters are equal and the death gains are equal (Table II), the $i$th diagonal entry of $A_\delta$ for $i = 1, \ldots, p$ takes the form,

$$\alpha_i(\delta) = \mu_\delta - \sum_{s=1, s \neq i}^{p} \rho_{is}(\delta), \quad (3a)$$

such that

$$\mu_\delta = \rho_1(\delta) - \rho_1D(\delta) = \ldots = \rho_p(\delta) - \rho_pD(\delta). \quad (3b)$$

The focus of this paper is the problem of stabilizing the live subsystem of (1),

$$x(t + 1) = A_\delta x(t); \quad t \in \mathbb{N}_0, \quad \delta \in D, \quad x(0) = x_0, \quad (4)$$

such that $x = [\tilde{x}_1, \ldots, \tilde{x}_n]^T$, and $A_\delta$ is the first $p$ rows and $p$ columns of $A_\delta$; see (1)-(3). We assume without loss of generality that $x_0$ is non-zero.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Name</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\rho_i = \rho_i(\delta)$</td>
<td>Division parameter</td>
<td>Average ratio of the number of live cells in phenotypic state $i$ at time $k+1$, derived from their own kind, to the number of live cells in phenotypic state $i$ at time $k$</td>
</tr>
<tr>
<td>$\rho_iD = \rho_iD(\delta)$</td>
<td>Death gain</td>
<td>Average proportion of live cells in phenotypic state $i$ at time $k$ that begin to die, or are dead, by time $k + 1$</td>
</tr>
<tr>
<td>$\rho_{ij} = \rho_{ij}(\delta)$</td>
<td>Transition gain</td>
<td>Average proportion of live cells in phenotypic state $i$ at time $k$ that transition to phenotypic state $j$ by time $k + 1$; $i \neq j$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Constraint</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each entry is non-negative.</td>
<td>Eq. (1) is a positive system (see [20], Th. 2).</td>
</tr>
<tr>
<td>The last column is $[0, \ldots, 0, 1]^T \in \mathbb{R}^p$.</td>
<td>Dead/dying cells accumulate over time and cannot come back to life.</td>
</tr>
<tr>
<td>$\rho_i(\delta) = \rho_1(\delta); \quad i = 2, \ldots, p$</td>
<td>The fractions of dividing cells were found to be consistent across the phenotypic states in HCC1143 populations.</td>
</tr>
<tr>
<td>Each off-diagonal entry is less than or equal to 1.</td>
<td>Death gains and transition gains are proportions; see Table I.</td>
</tr>
<tr>
<td>$\rho_i(\delta) \geq 1; \quad i = 1, \ldots, p$</td>
<td>Cell division can only increase the live cancer cell population; see Table I.</td>
</tr>
<tr>
<td>$\rho_iD(\delta) = \rho_1D(\delta); \quad i = 2, \ldots, p$</td>
<td>Motivated by preliminary data analysis.</td>
</tr>
</tbody>
</table>

Refer to (2). Many of the above constraints are equivalent to those used in our prior work [4], [5], and are included here for the reader’s convenience.
The dynamics matrices, \( \{\tilde{A}_\delta\}_{d \in D} \), need to be estimated from time series data. Collecting such data can be a laborious process, yielding a small number of samples for the purpose of estimation. Until more data is readily available, we assume linear time-invariance to promote parsimonious modeling.

The switched system assumes, in particular, that the response to a drug applied at time \( t \) does not depend on the drugs applied previously. This assumption is not valid usually. Our results on modeling error (Theorem 2, Corollary 1) start to address the possibility of drug-drug interactions.

Eq. (1) is called a positive system because each element of \( \bar{x} \) is non-negative [20]. Positive systems may make computational tasks, such as estimation, more challenging due to the presence of additional constraints. On the other hand, positive switched systems may be useful for the optimization of drug schedules; see [17], [18], [19], and the next section.

III. PRELIMINARY RESULTS

This section presents the preliminary results. In Lemma 1, we derive an upper bound on the cancer growth rate, using the matrix structure provided in (2) and (3).

**Lemma 1:** Let \( \tilde{A}_\delta \in \mathbb{R}^{p \times p} \) be the first \( p \) rows and \( p \) columns of \( \tilde{A}_\delta \) (2), whose diagonal entries are given by (3). Then, the matrix norm of \( \tilde{A}_\delta \) induced by the vector \( L^1 \)-norm is \( \mu_{\delta} \).

**Proof:**

\[
||\tilde{A}_\delta||_1 = \max_{i \in \{1,...,p\}} \left\{ \left| \mu_{\delta} - \sum_{s=1, s \neq i}^{p} \rho_{is}(\delta) \right| + \sum_{s=1, s \neq i}^{p} \left| \rho_{is}(\delta) \right| \right\} \\
= \max_{i \in \{1,...,p\}} \left\{ \mu_{\delta} - \sum_{s=1, s \neq i}^{p} \rho_{is}(\delta) + \sum_{s=1, s \neq i}^{p} \rho_{is}(\delta) \right\} \\
= \mu_{\delta},
\]

where the second line holds because each entry of \( \tilde{A}_\delta \) is non-negative. \( \blacksquare \)

**Remark 1:** If (3) is not assumed, then \( ||\tilde{A}_\delta||_1 = \max_{i \in \{1,...,p\}} \rho_{i}(\delta) - \rho_{i}(\delta) \).

**Definition 1:** \( k_j \in \mathbb{N} \) is the waiting time between the application of drug \( j \in D \) and the application of the next drug.

Lemma 2 provides a set of maximal waiting times between treatments, under the assumption that waiting time bounds related to toxicity, or to the onset of resistance, are available for each drug. The waiting times, together with a drug sequence, determine which drug is applied and when the drug is applied. The waiting times are designed so that the treatment regimen shrinks the live cancer cell population over time, while limiting the toxicity to normal cells or avoiding the onset of drug resistance.

**Lemma 2:** Suppose \( (L_j, U_j) \in \mathbb{N}^2 \) with \( L_j \leq U_j \) for \( j \in D \). Let \( \mathcal{I} = \{ i \in D : \mu_i \in (0,1) \} \) and \( \mathcal{J} = \{ j \in D : \mu_j \geq 1 \} \) be non-empty. Assume \( \beta = \prod_{i \in \mathcal{I}} \mu_{i}^{L_i} \prod_{j \in \mathcal{J}} \mu_{j}^{L_j} \in (0,1) \). Choose any \( \epsilon \in (\beta, 1) \). Consider the optimization program,

\[
\begin{align*}
\text{maximize} & \quad \sum_{(k_j) \in \mathcal{D}} k_j \\
\text{subject to} & \quad \prod_{j \in \mathcal{D}} (\mu_j)^{k_j} \leq \epsilon \\
& \quad k_j \in [L_j, U_j] \cap \mathbb{N}; \quad j \in D.
\end{align*}
\]

Then, \( k_2^* = U_i \) for all \( i \in \mathcal{I} \), and \( (k_j^*)_{j \in \mathcal{J}} \) can be found via Algorithm 1. Further, if \( \mathcal{I} = \{1\} \) and \( \mathcal{J} = \{2\} \), then \( k_2^* = \min \left( U_2, \left[ \frac{\log \epsilon - U_1 \log \mu_1}{\log \mu_2} \right] \right) \).

**Data:** \( n_i \in \mathcal{J} \) s.t. \( \mu_{n_1} \leq \mu_{n_2} \leq \cdots \leq \mu_{n_j}, J = |\mathcal{J}|; \)

**Result:** \( (k_j^*)_{j \in \mathcal{J}} \);

**initialize** \( q = J, k_{n_q} = U_{n_1} \) for \( l = 1, \ldots, J; \)

**while** true do

\[
\begin{align*}
\text{if} & \quad \prod_{i \in \mathcal{I}} (\mu_i)^{U_i} \prod_{j \in \mathcal{J}} (\mu_j)^{k_j^*} \leq \epsilon \text{ then} \\
& \quad k_{n_q} = k_{n_q} \text{ for } l = 1, \ldots, J; \\
& \quad \text{break}; \\
\text{else} & \quad \text{if } k_{n_q} = U_{n_q} \text{ then} \\
& \quad q = q - 1; \\
& \quad \text{end} \\
& \quad k_{n_q} = k_{n_q} - 1; \\
\text{end}
\end{align*}
\]

**Algorithm 1:** Solves program (6) of Lemma 2.

**Proof:** Choose any \( (k_j)_{j \in \mathcal{D}} \) satisfying the constraints of (6). Because \( \mu_i \in (0,1) \) and \( k_i \leq U_i \) for all \( i \in \mathcal{I} \),

\[
\epsilon \geq \prod_{i \in \mathcal{I}} \mu_{i}^{k_i} \prod_{j \in \mathcal{J}} \mu_{j}^{k_j^*} \geq \prod_{i \in \mathcal{I}} \mu_{i}^{U_i} \prod_{j \in \mathcal{J}} \mu_{j}^{k_j^*}. \tag{7}
\]

Thus, \( k_2^* = U_i \) \( \forall i \in \mathcal{I} \). Algorithm 1 initializes each \( k_j \) \( (j \in \mathcal{J}) \) to be as large as possible. If this choice satisfies the inequality constraint of (6), then the algorithm terminates. If not, the algorithm decreases the waiting time associated with the largest \( \mu_j, k_j \), by 1. The algorithm starts with the largest \( \mu_j \) to obtain the largest reduction, \( \mu_j^{k_j} \geq \mu_j^{k_j-1} \). If the \( k_j \) reaches its minimum, the algorithm moves onto the waiting time associated with the second largest \( \mu_j \). The algorithm is guaranteed to terminate because \( \beta \leq \epsilon \).

Finally, if \( \mathcal{I} = \{1\} \) and \( \mathcal{J} = \{2\} \), then the inequalities \( \mu_1^{U_1} \mu_2^{U_2} \leq \mu_1^{k_2^*} \leq \epsilon \) are equivalent to

\[
L_2 \leq k_2 \leq \frac{\log \epsilon - U_1 \log \mu_1}{\log \mu_2}. \tag{8}
\]

Choose \( k_2^* \) as the largest value satisfying (8) and \( k_2 \in [L_2, U_2] \cap \mathbb{N}. \)

**Remark 2:** In Lemma 2, \( \beta \) is the fastest possible decay rate of the live cancer cell population per treatment cycle, if each of the \( d \) drugs is applied once per cycle and the waiting times are provided by (6).

IV. MAIN RESULTS

This section presents the main results. First, we define a cyclic schedule of \( D \) as a sequence of drugs,

\[
(l_{1m}, l_{2m}, \ldots, l_{dm})_{m=1}^\infty. \tag{9}
\]
such that \( l_i m \in \mathcal{D} \) is the \( i \)th drug applied in cycle \( m \), and \( \bigcup_{i=1}^{d} \{ l_i m \} = \mathcal{D} \) for each \( m \). This means that each drug in \( \mathcal{D} \) is applied once per cycle, and the order of the drugs in each cycle may vary. Fig. 1 illustrates a cyclic schedule of \( \mathcal{D} := \{ \emptyset, \square, \triangle \} \) with the waiting times, \( (k_{i1m})_{i=1}^{3} \), for two cycles; note that \( l_{i2m} \in \mathcal{D} \) and \( \bigcup_{i=1}^{d} \{ l_{i2m} \} = \mathcal{D} \) for \( m = 1, 2 \).

![Cyclic Schedule](image)

**Fig. 1.** A cyclic schedule of three drugs, \( \mathcal{D} := \{ \emptyset, \square, \triangle \} \), with the waiting times, \((k_0, k_\square, k_\triangle)\), is shown for two cycles; see (9). For example, \( l_{i2} = \square \) means that drug \( \square \) is the third drug applied in cycle 2, and the next drug will be applied \( k_\square \) time points later. Notice that each drug in \( \mathcal{D} \) is applied once per cycle and the order of the drugs in each cycle may vary.

### A. Analysis in the Absence of Modeling Error

Theorem 1 says that, with no modeling error, a cyclic schedule that uses the maximal waiting times derived in Lemma 2 and an arbitrary ordering of the drugs in each cycle will exponentially stabilize the live cancer cell population.

**Theorem 1:** Assume the conditions of Lemma 2, choose any \( \epsilon \in [\beta, 1) \), and let \( \mathcal{K} := \{ k_j \}_{j \in \mathcal{D}} \) be a solution to (6). Then, a cyclic schedule (9) with the waiting times, \( \mathcal{K} \), stabilizes the system (4) exponentially at the decay rate per cycle, \( \epsilon \).

**Proof:** Define \( T_p := p \sum_{j \in \mathcal{D}} k_j \) for \( p \in \mathbb{N}_0 \). Let \( m \in \mathbb{N} \). By induction on (4) and (9),

\[
x(T_m) = \frac{m}{\Pi_{i \in \mathcal{D}} k_i^{|l_{i\mathcal{D}}}} x_0,
\]

such that \( l_{i\mathcal{D}} \in \mathcal{D} \) is the \( i \)th drug applied in cycle \( \mathcal{D} \). Take the \( L^1 \)-norm of (10) and use \( \| A_\delta \|_1 = \mu_\delta \) from Lemma 1 to find,

\[
\| x(T_m) \|_1 \leq \sum_{i=1}^{m} \left( (\mu_{i\mathcal{D}})^{k_{i\mathcal{D}}} \cdots (\mu_{1\mathcal{D}})^{k_{1\mathcal{D}}} (\mu_{i\mathcal{D}})^{k_{i\mathcal{D}}} \right) \| x_0 \|_1.
\]

(11)

because each drug is applied once per cycle. Since \( \Pi_{i \in \mathcal{D}} k_i^{|l_{i\mathcal{D}}} \leq \epsilon \) by Lemma 2, we have

\[
\| x(T_m) \|_1 \leq \epsilon^m \| x_0 \|_1.
\]

(12)

Define \( K_m = \arg \max_{(\epsilon(t))} \{ \| x(t) \|_1 : t \in [T_{m-1}, T_m] \cap \mathbb{N} \} \). Because local maxima (or minima) only occur at times of drug application, we have

\[
x(K_m) = (A_{l_{i1m}})^{k_{i1m}} \cdots (A_{l_{i2m}})^{k_{i2m}} (A_{l_{i1m}})^{k_{i1m}} x(T_{m-1}),
\]

(13)

such that \( l_{i1m} \in \mathcal{D} \) is the \( i \)th drug applied in cycle \( m \) and \( i \in \{1, \ldots, d\} \), by (4) and (9). Define \( U < \infty \) such that

\[
U \geq \prod_{j \in \mathcal{D}} \mu_j^{k_j} \forall \mathcal{D}' \subset \mathcal{D}.
\]

(14)

Take the \( L^1 \)-norm of (13) and use \( \| A_\delta \|_1 = \mu_\delta \) from Lemma 1 to obtain,

\[
\| x(K_m) \|_1 \leq (\mu_{i1m})^{k_{i1m}} \cdots (\mu_{i2m})^{k_{i2m}} (\mu_{i1m})^{k_{i1m}} \| x(T_{m-1}) \|_1
\]

\[
= \Pi_{j \in \mathcal{D}} (\mu_j)^{k_j} \| x(T_{m-1}) \|_1
\]

\[
\leq U \| x(T_{m-1}) \|_1,
\]

(15)

where \( \mathcal{D}' \) is the second line. Finally, use (12) with (15) to see that

\[
\| x(K_m) \|_1 \leq U \| x(T_{m-1}) \|_1 \leq U \epsilon^{m-1} \| x_0 \|_1.
\]

(16)

Because \( 0 < \epsilon < 1 \), \( \| x(K_m) \|_1 \rightarrow 0 \) exponentially with decay rate \( \epsilon \), as \( m \rightarrow \infty \). Since \( \| x(K_m) \|_1 \) is a maximum on cycle \( m \), the proof is complete.

### B. Analysis in the Presence of Modeling Error

The remaining results allow for modeling error. An important source of modeling error arises because how the cancer responds at the current time to the most recent drug input likely depends on the prior treatment regimen, but the models, \( \{ A_\delta \}_{\delta \in \mathcal{D}} \), are typically identified separately. Drug \( \delta \) is applied to a cancer cell population that has not been treated before, and the model, \( A_\delta \), is identified from the time series data in response to that drug. Because the experiments are laborious, one would like to conduct the least number of experiments, specifically one experiment per drug, and then use the models identified from the experiments to predict drug schedules that could be more effective than standard regimens. Using the machinery of switched systems, we sequence the models together, knowing that when the models are used in this way error arises, and we ask, what are mild conditions on the error under which stability is attained.

More formally, suppose that the dynamics of the drug-treated live cancer cell population are time-varying,

\[
x(t + 1) = A_{\delta_t}(t)x(t); \quad t \in \mathbb{N}_0, \delta_t \in \mathcal{D},
\]

(17a)

where \( x_0 \) is non-zero without loss of generality. The dynamics matrix, \( A_{\delta_t}(t) \), quantifies the effect of applying drug \( \delta_t \) at, or before, time \( t \) in addition to the effect of the prior treatment regimen: the ordering and the timing of the drugs applied before drug \( \delta_t \). Suppose that the dynamics matrix of Eq. (17a), \( A_{\delta_t}(t) \), is related to the dynamics matrix of Eq. (4), \( A_{\delta_i} \), through the bounded multiplicative error, \( \xi_{\delta_i}(t) \in (0, E] \), as follows,

\[
\| A_{\delta_t}(t) \|_1 \leq \| A_{\delta_i} \|_1 \xi_{\delta_i}(t) = \mu_{\delta_i} \xi_{\delta_i}(t),
\]

(17b)

where the second line holds by Lemma 1. Multiplicative error is mathematically convenient for quantifying the distance from the origin because the state, \( x \), is determined by matrix multiplication; see (17a). While the dynamics matrix, \( A_{\delta_i}(t) \), and the multiplicative error, \( \xi_{\delta_i}(t) \), are functions of the prior treatment regimen, we do not write these dependencies explicitly to simplify notation.
Remark 3: System (17) reduces to the error-free system (4) if \( \xi_\delta(t) = 1 \) \( \forall t \in \mathbb{N}_0 \).

Remark 4: If \( \xi_\delta(t) > 1 \), then the error has a destabilizing effect. If \( \xi_\delta(t) < 1 \), then the error has a stabilizing effect. If \( \xi_\delta(t) = 1 \), then the error has no effect.

We would like to find mild conditions on the modeling error, under which a cyclic schedule (with waiting times given by Lemma 2) stabilizes the live cancer cell population. Next, we show that exponential stability is attained, if the errors are bounded and if the error product in each cycle is sufficiently small.

**Theorem 2:** Assume the conditions of Lemma 2, choose any \( \epsilon \in (\beta, 1) \), and let \( \mathcal{K} := (k_j)_{j \in \mathcal{D}} \) be a solution to (6). Define \( T_p := p \sum_{j \in \mathcal{D}} k_j \) for \( p \in \mathbb{N}_0 \). If \( \xi_\delta(t) \in (0, E) \) \( \forall t \in \mathbb{N}_0 \) for some \( E < \infty \), and if \( \exists \eta \in (\epsilon, \infty) \) such that
\[
\frac{1}{\eta} \geq \prod_{t=T_p-1}^{T_p-1} \xi_\delta(t) \quad \forall m \in \mathbb{N},
\]
then a cyclic schedule (9) with the waiting times, \( \mathcal{K} \), stabilizes the system (17) exponentially at the decay rate per cycle, \( \frac{\epsilon}{\eta} \).

**Proof:** Let \( m \in \mathbb{N} \). Use (17a) to find,
\[
x(T_m) = \left( \prod_{t=0}^{T_m-1} A_{\delta}(t) \right) x_0.
\] Take the \( L^1 \)-norm of (19) to obtain,
\[
\|x(T_m)\|_1 \leq \left( \prod_{t=0}^{T_m-1} \|A_{\delta}(t)\|_1 \right) \|x_0\|_1
\]
\[
= \left( \prod_{t=0}^{T_m-1} \mu_\delta \xi_\delta(t) \right) \|x_0\|_1
\]
\[
\leq \prod_{c=1}^{m} \left( \prod_{t=T_p-1}^{T_p-1} \mu_\delta \xi_\delta(t) \right) \|x_0\|_1.
\]

Because each drug \( j \in \mathcal{D} \) is active for \( k_j \) time points in every cycle, we have
\[
\prod_{t=T_p-1}^{T_p-1} \mu_\delta = \prod_{j \in \mathcal{D}} (\mu_j)^{k_j} \quad \forall c \in \{1, \ldots, m\}.
\]
\[
(21)
\]
Thus, (20) and (21) imply
\[
\|x(T_m)\|_1 \leq \left( \prod_{j \in \mathcal{D}} (\mu_j)^{k_j} \right)^{\frac{1}{\eta}} \|x_0\|_1
\]
\[
(22)
\]
Since \( \prod_{j \in \mathcal{D}} (\mu_j)^{k_j} \leq \epsilon \) by Lemma 2, we have
\[
\|x(T_m)\|_1 \leq \epsilon^m \frac{1}{\eta} \|x_0\|_1.
\]
\[
(23)
\]
where the second line holds by (18).

Let \( K_m \in \text{argmax} \{\|x(t)\|_1 : t \in (T_m-1, T_m] \cap \mathbb{N}\} \). Because \( \|x(K_m)\|_1 \) is a maximum on cycle \( m \), it suffices to show that \( \|x(K_m)\|_1 \to 0 \) exponentially with decay rate \( \epsilon/\eta \), as \( m \to \infty \).

Because the errors are bounded, \( \exists B < \infty \) such that
\[
B \geq \prod_{t=T_m-1}^{T_m-1} \mu_\delta \xi_\delta(t) \quad \forall \tau \in (T_m-1, T_m-1] \cap \mathbb{N}, \quad \forall m \in \mathbb{N},
\]
\[
(24)
\]
For example, if \( E \geq 1 \), then \( B = E^L \prod_{j \in \mathcal{J}} (\mu_j)^{k_j} \) satisfies (24), where \( L = \sum_{j \in \mathcal{D}} k_j \) and \( \mathcal{J} = \{ j \in \mathcal{D} : \mu_j \geq 1 \} \).

Eq. (17a) implies that
\[
x(K_m) = \left( \prod_{t=T_m-1}^{T_m-1} A_{\delta}(t) \right) x(T_m-1).
\]
\[
(25)
\]
Take the \( L^1 \)-norm of (25) to find,
\[
\|x(K_m)\|_1 \leq \left( \prod_{t=T_m-1}^{T_m-1} \mu_\delta \xi_\delta(t) \right) \|x(T_m-1)\|_1
\]
\[
\leq B \|x(T_m-1)\|_1
\]
\[
\leq B \left( \frac{\epsilon}{\eta} \right)^{m-1} \|x_0\|_1,
\]
where the last line holds by (23).

Lastly, we provide a settling time result for the system (17) subject to a cyclic schedule with waiting times given by Lemma 2.

**Definition 2:** For any \( \gamma \in (0, 1) \), \( T \) is a \( \gamma \)-settling time for system (17), if \( \|x(t)\|_1 \leq \gamma \|x_0\|_1 \) for all \( t \geq T \).

**Corollary 1:** Assume the conditions of Lemma 2, choose any \( \epsilon \in (\beta, 1) \), and let \( \mathcal{K} := (k_j)_{j \in \mathcal{D}} \) be a solution to (6). Let the system (17) evolve under a cyclic schedule (9) with the waiting times, \( \mathcal{K} \). Let \( B < \infty \) satisfy (24). Suppose \( \exists \eta \in (\epsilon, \infty) \) that satisfies (18). Then, for any \( \gamma \in (0, 1) \), a \( \gamma \)-settling time is \( K_{m_\gamma} \), where
\[
K_{m_\gamma} \in \text{argmax} \{\|x(t)\|_1 : t \in (T_m-1, T_m) \cap \mathbb{N}\}
\]
\[
T_m = m_\gamma \sum_{j \in \mathcal{D}} k_j
\]
\[
(27)
\]
\[
m_\gamma = \frac{\log \gamma - \log B}{\log \epsilon - \log \eta + 1}, \quad B > \gamma.
\]

**Proof:** Take \( m \in \mathbb{N} \). By (26), we have
\[
\|x(K_{m_\gamma})\|_1 \leq B \left( \frac{\epsilon}{\eta} \right)^{m_\gamma-1} \|x_0\|_1.
\]
\[
(28)
\]
Let \( S_m := B \left( \frac{\epsilon}{\eta} \right)^{m-1} \|x_0\|_1 \), and notice that \( (S_m)_{m \in \mathbb{N}} \) is a decreasing sequence. Let \( \gamma \in (0, 1) \). It suffices to find \( m_\gamma \in \mathbb{N} \) such that
\[
\|x(K_{m_\gamma})\|_1 \leq B \left( \frac{\epsilon}{\eta} \right)^{m_\gamma-1} \|x_0\|_1 \leq \gamma \|x_0\|_1, \quad (29)
\]
because \( K_{m_\gamma} \) is a \( \gamma \)-settling time; see that \( \|x(t)\|_1 \leq \|x(K_{m_\gamma})\|_1 \leq \gamma \|x_0\|_1 \) for all \( t \geq K_{m_\gamma} \). Choose \( B > \gamma \); we can do this because \( B \) is an upper bound. Use (29) and recall \( \|x_0\|_1 > 0 \), \( 0 < \frac{\epsilon}{\eta} < 1 \), and \( 0 < \frac{\epsilon}{\eta} < 1 \) to find,
\[
B \left( \frac{\epsilon}{\eta} \right)^{m_\gamma-1} \leq \gamma \quad \iff \quad (m_\gamma - 1) \log \left( \frac{\epsilon}{\eta} \right) \leq \log \left( \frac{\gamma}{B} \right)
\]
\[
(30)
\]
\[
m_\gamma \geq \frac{\log \gamma - \log B}{\log \epsilon - \log \eta} + 1.
\]

We choose \( m_\gamma \) to equal the smallest natural number that satisfies the last line above.
V. Numerical Example

In our previous work, cancer cell populations derived from the Triple Negative breast cancer cell line, HCC1143, were treated with a particular drug $\delta \in \mathcal{D} = \{\text{Trametinib+BEZ235, BEZ235, Trametinib}\}$ [5].¹ Cell phenotype and cell death measurements were recorded every 12 hours over a 72-hour horizon following drug treatment [5]. So, the duration of the discrete-time interval, $[t, t+1)$, is 12 hours; see (1). A drug-specific dynamics matrix of the form of (2) and (3), $A_j$, was estimated from the data for $p = 2$ phenotypic states [5]. For each drug $\delta \in \mathcal{D}$, the dynamics matrix for the live cancer subsystem (4), $A_j$, was extracted from $A_j$ and is provided below,

$$A_p = \begin{bmatrix} 0.755 & 0.081 \\ 0.169 & 0.843 \end{bmatrix}, \quad (31)$$

$$A_B = \begin{bmatrix} 0.896 & 0 \\ 0.186 & 1.083 \end{bmatrix}, \quad (32)$$

$$A_T = \begin{bmatrix} 1.030 & 0.231 \\ 0.022 & 0.821 \end{bmatrix}, \quad (33)$$

where drug P is Trametinib+BEZ235, drug B is BEZ235, and drug T is Trametinib. Using (31)-(33), we find that $||A_p||_1 = \mu_p = 0.924$, $||A_B||_1 = \mu_B = 1.083$, and $||A_T||_1 = \mu_T = 1.052$. Thus, $\mathcal{I} = \{i \in \mathcal{D} : \mu_i \in (0, 1)\} = \{\text{P}\}$ and $\mathcal{J} = \{j \in \mathcal{D} : \mu_j \geq 1\} = \{\text{B, T}\}$.

In our example, we set $L_i := 2$ (1 day) $\forall i \in \mathcal{D}$, since receiving treatment several times per day seems inconvenient. We chose $U_p := 4$ (2 days), $U_B := 8$ (4 days), and $U_T := 6$ (3 days) to illustrate a conservative scenario, since $\mu_p < 1$ and $1 \leq \mu_T < \mu_B$. Thus, $\beta = \mu_p^{U_p} \mu_B^{U_B} \mu_T^{U_T} = 0.947$. We set $\epsilon := 0.95$, because $\epsilon \in [\beta, 1)$. We computed waiting times using Lemma 2: $k_p = 4$, $k_B = 2$, and $k_T = 2$. We set $\eta := 0.96$, because $\eta \in (\epsilon, \infty)$. We chose the errors, $\xi_{\delta_i}(t) \in (0, E]$, to be pseudorandom values drawn from the uniform distribution on the interval, $[0.9, 1.5]$; $E = 1.5$. The upper bound, $B = E(L(\mu_p)^{k_p}(\mu_T)^{k_T}) = 33.3$, where $L = k_p + k_B + k_T = 8$ (4 days).

Fig. 2 shows an example simulation of the cancer system (17) in response to a cyclic schedule of the drugs, {P, B, T}, with the waiting times, $(k_p, k_B, k_T)$, for 40 cycles (160 days).² For example, if drug P is applied at time zero, then $x(k_p)$ is given by,

$$x(k_p) = \left( k_p \prod_{t=0}^{k_p-1} \xi_P(t) \right) x_0 = \left( k_p \prod_{t=0}^{k_p-1} \xi_P(t) \right) \left( \prod_{t=0}^{k_p-1} A_p \right) x_0$$

$$= \left( k_p \prod_{t=0}^{k_p-1} \xi_P(t) \right) \left( \prod_{t=0}^{k_p-1} A_p \right) x_0$$

$$= \left( k_p \prod_{t=0}^{k_p-1} \xi_P(t) \right) \left( A_P \right)^{k_p} x_0. \quad (34)$$

Further, if drug T is applied next, then $x(k_p + k_T)$ is given by,

$$x(k_p + k_T) = \left( \prod_{t=k_p}^{k_p+k_T-1} \xi_T(t) \right) \left( A_T \right)^{k_T} x(k_p). \quad (35)$$

We randomly chose an ordering of the three drugs for each cycle. If (18) was not satisfied for any cycle, then the errors for that cycle were regenerated. The initial condition, $x_0 := [220, 612]^T$, is the estimated number of live cells in each phenotypic state at time zero averaged over fifteen samples, where the data comes from [5].

In Fig. 2, the saw-tooth behavior arises mainly because the cancer cell population shrinks following treatment with Trametinib+BEZ235 (drug P) but grows following treatment with the other two drugs. The simulation indicates that the settling time derived in Corollary 1 is quite conservative.³ For example, if $\gamma := \frac{1}{10}$, then $m_\gamma = 556$ cycles, according to Corollary 1. However, after about 19.5 cycles, the population stays below one-tenth its original size in Fig. 2. Further, the simulation shows that although the errors are similar in magnitude throughout the time horizon, the size of the live cancer cell population decays exponentially.

VI. Conclusions

In this paper, we studied a cyclic schedule composed of drugs with varying toxicities, using a switched system model of a cancer cell population. It is relatively easy to identify a model of how a single drug affects a treatment-naive population (a population that is receiving treatment for the first time). But, it is not easy to predict how a sequence of drugs affects the population, and it is not possible to evaluate all schedules experimentally. A key contribution of this paper is studying the modeling error that arises from treating a cancer cell population again (possibly with a new drug). We show that if the modeling errors are bounded, and if the product of the errors over each cycle is below a particular threshold, then exponential stability is guaranteed. Thus, we tolerate some large errors, but the cumulative error over each cycle must remain sufficiently small.

To use the current framework, an experimentalist would first evaluate the modeling errors over each cycle for several cycles to estimate $\eta$, and then use $\eta$ to choose $\epsilon$. The choice of $\epsilon$ largely determines the waiting times between treatments. Smaller $\epsilon$ implies longer exposure to the drugs that are more toxic to healthy cells, $\mathcal{I} = \{i \in \mathcal{D} : \mu_i \in (0, 1)\}$, and faster decay of the cancer cell population. This points to an important trade-off between toxicity and eliminating cancer.

Laboratory experiments are needed to better quantify toxicity, validate our models, estimate the waiting time bounds, and test our cyclic schedules. Pilot experiments are in progress to examine the efficacy of drugs on previously treated populations (with the same, or a new, drug), which will inform our future models.

¹Trametinib+BEZ235 is an equal-ratio combination of Trametinib and BEZ235 [5].
²MATLAB R2016b, The MathWorks, Inc., Natick, MA
³The conservativeness arises because $B$ is a worst-case upper bound.
Fig. 2. An example simulation of the cancer system (17) in response to a cyclic schedule of the drugs, \( \{P, B, T\} \), with the waiting times, \((k_P, k_B, k_T)\), for 40 cycles (160 days). Each vertical grid line denotes the start of a cycle. Top: Normalized population size, \( \frac{\|x(t)\|_1}{\|x_0\|_1} \), was plotted at each time \( t \) of drug application. E.g., in the first cycle, if the drug order was \( T \) first, \( B \) second, and \( P \) third, then \( \frac{\|x(t)\|_1}{\|x_0\|_1} \) was plotted at \( t \in \{k_T, k_B + k_T, k_P + k_B + k_T\} \). Middle: Error, \( \xi(t) \), was plotted at each time point \( t \in \{0, 1, \ldots, 319\} \). There are 320 time points in total, since 40 cycles \( \times \frac{\text{time point}}{\text{cycle}} = 320 \). The duration of each discrete interval, \( [t, t + 1) \), is \( 0.5 \) days. Bottom: Error product, \( \Pi_{m=0}^{m-1} \xi(t) \), per cycle \( m \in \{1, 2, \ldots, 40\} \). Note that each error product is less than or equal to a vulnerable chemotherapy-induced phenotypic transition,” Nature Communications, vol. 6, no. 6139, 2015.

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