Stabilizability of uncertain switched systems to characterize antibiotic resistance evolution

A. Anderson[1], M. O. Ohemeng[1], A. H. Gonzalez[2], E. A. Hernandez-Vargas[1]

***Abstract*— The evolution of antibiotic resistance in bacteria is a significant public health risk influenced by several factors. Switched systems can abstract the evolutionary aspects driven by antibiotic use in a given population. However, mathematical models are not perfect, and uncertain dynamics remain. Based on a set theory approach, our main result is the development of an algorithm to demonstrate the stabilizability of a robust invariant set for the uncertain switched system. The algorithm also provides a characterization of invariant regions for switched systems under perturbations. Our findings provide insights into how to incorporate uncertainties in switched systems. This paves the way for selecting antibiotics to tackle drug-resistant infections.**

I. Introduction

The increase in drug-resistant bacteria poses a serious threat to public health, killing millions worldwide every year [1]. Bacteria become resistant through genetic mutations or by acquiring resistance genes from other bacteria through horizontal gene transfer [2]. The overuse of antibiotics has increased the prevalence of drug-resistant infections [3].

Recent biological studies have uncovered that while antibiotics can promote resistance to one drug, they can also induce sensitivity to another drug. This is known as collateral sensitivity, and the converse is known as cross-resistance [4]–[6]. Based on these biological observations, a foundational interrogative would be developing strategies for better treatment by alternating ("switching") our current arsenal of antibiotics. Addressing this question would require the effective forecasting of bacterial evolution to personalized therapies known as "Evolutionary Therapies" [7].

Mathematical modeling provides a platform for studying the dynamics of drug resistance evolution in bacterial populations [8]. In particular, switched systems have been used to abstract drug resistance to sequential antibiotic exposure [9], [10], where the states represent different bacterial population dynamics, and the inputs of control given by the set of antibiotics is the switching between systems. However, previous models did not consider any model uncertainty. Biomedical problems are complex, with a myriad of factors that strongly complicate the model-building and affect its respective predictions [11]. There is a significant amount of theory developed in the last three decades in the stability analysis and switching control design for switched linear systems [12]. Several studies were conducted on the robust stability of general switched systems, in which the switching signal is not necessarily the manipulated input but an autonomous signal [13], [14]. These studies consider the uncertainty in the family of possible models, *e.g.*, uncertainty parameter [15]. However, only a few studies consider additive uncertainty, *e.g.*, when stochastic signals are added/subtracted directly from state dynamics. This is important as additive noise refers to missing mechanisms that were not included in the model.

There arises a natural interrogative about whether one can define measures of stabilizability robustness for switched linear systems that can help design evolutionary therapies. This can be formulated as a problem of robust stabilizability of linear uncertain systems, which involves determining stabilizing switching sequences that result in asymptotically stable behavior in the presence of uncertainties [16]. Previous studies in [17] presented necessary and sufficient conditions for the existence of asymptotically stabilizing switching laws for a class of switched linear systems with time-variant parametric uncertainties. More recently, robust stabilizability has been introduced for periodically switched systems [18].

Eradicating a pathogenic population would require driving it to equilibrium at the origin. Stabilizing the origin is a very restrictive condition and not always feasible, especially in the presence of uncertainties and in the context of evolutionary dynamics that lead to resistance. Invariant sets, unlike fixed equilibrium, offer a more realistic control goal to enhance controllability by offering alternative stable regions and providing safety zones to maintain infection suppression. In [19], the stabilizability was provided based on the characterization of contractive invariant sets for a nominal switched linear system. The approach was based on set-control theory [20], which has been previously used for switched systems [21], [22]. These previous studies demonstrated the complexity of characterizing invariant sets for switched systems and their implications in biomedical problems.

This paper proposes an extension of the strategy presented in [19] to account for uncertainties explicitly. The resulting robust formulation, based on the results in [23]–[25], considers restricted constraints for the uncertainty and account for the robust stability of the system. The strategy is illustrated through numerical simulations. Furthermore, we exemplify the potential of the results in the problem of bacterial resistance, in which we investigate how selecting one drug among two affects the evolution of the drug's resistance.

*This material is based upon work supported by the National Science Foundation under Grant No. 2315862.

[1]Department of Mathematics and Statistical Science, University of Idaho, Moscow, Idaho, USA esteban@systemsmedicine.de

[2]University of Littoral (UNL), Institute of Technological Development for the Chemical Industry (INTEC) and National Scientific and Technical Research Council (CONICET), Santa Fe, Argentina

A. Notation

- We denote the set of integers $\mathbb{N}_q := \{1, \cdots, q\}$.
- Given a constant $a \in \mathbb{R}$, a constant function $w(t) = a$, for all $t \geq 0$ is denoted by $w(t) \equiv a$.
- Minkowski addition: $\mathcal{A} \oplus \mathcal{B} = \{a + b \mid a \in \mathcal{A}, b \in \mathcal{B}\}$.
- Minkowski subtraction: $\mathcal{A} \ominus \mathcal{B} = \{a \mid a + b \in \mathcal{A}, \text{ for all } b \in \mathcal{B}\}$.
- Euclidean distance: $d(x, y) := [(x - y)^t (x - y)]^{1/2}$.
- Closed ball: $\mathcal{B}(x, \varepsilon) := \{y \in \mathbb{R}^n \mid d(x, y) \leq \varepsilon\}$.
- Set interior: x is an interior point of Ω if the there exist $\varepsilon > 0$ such that $\mathcal{B}(x, \varepsilon) \subseteq \Omega$. The interior of Ω is given by all interior points of Ω and denoted by $\text{int}(\Omega)$.
- Star-convex set: A set Ω is star-convex if there exists $x_0 \in \Omega$ such that every convex combination of $x \in \Omega$ and x_0 belongs to Ω, i.e. $\alpha x_0 + (1 - \alpha)x \in \Omega$ for all $\alpha \in [0, 1]$.
- C^*-set: A set Ω with the origin in its interior is a C^*-set if it is compact and star-convex with respect to the origin.
- Set subtraction: $\mathcal{A} \setminus \mathcal{B} = \{a \mid a \in \mathcal{A} \text{ and } a \notin \mathcal{B}\}$.
- Cartesian product: Given a set $\mathbb{W} \subseteq \mathbb{R}^n$, we denote the set $\mathbb{W}^N = \underbrace{\mathbb{W} \times \cdots \times \mathbb{W}}_{N \text{ times}}$.

II. Preliminaries

The dynamics of the (additive) uncertain switched system can be described by the following equation:

$$x(k + 1) = A_{\sigma(k)} x(k) + w(k), \tag{1}$$

where $x(k) \in \mathbb{X} \subset \mathbb{R}^n$ is the state of the system, $w(k) \in \mathbb{W} \subset \mathbb{R}^n$ is the current disturbance, $A_{\sigma(\cdot)}$ is the transition matrix, and $\sigma(k) \in \mathbb{N}_q$ is the switching law that selects the mode $\sigma(k)$, at time $k \in \mathbb{N}$, among $q > 1$ possible values. The set $\mathbb{X}$ is closed and $\mathbb{W}$ is a compact convex set that contains the origin in their interior.

Given an initial state $x_0 \in \mathbb{X}$ and a switching law $\sigma_N := \{\sigma(1), \cdots, \sigma(N)\}$, for $N \in \{1, \cdots, \infty\}$, we denote with $\phi(x_0; \sigma_N, w_N)$, all the states at time $k = N$, by applying the switching law σ_N to the initial state x_0, corresponding to all admissible disturbances realization $w_N \in \mathbb{W}^N$. Also, the state of the nominal system (i.e., $w(k) \equiv 0$) is denoted by $\phi(x_0; \sigma_N)$, which is the state at time $k = N$, by applying the switching law σ_N to initial state x_0, without uncertainties.

Let us recall some properties of the Minkowski addition and subtraction that we will utilize in the next section.

Property 1: Given a C^*-set Ω and a convex set $\mathcal{W}$, it follows that $(\Omega \ominus \mathcal{W}) \oplus \mathcal{W} \subseteq \Omega$. Moreover, if $0 \in \mathcal{W}$, then $\Omega \ominus \mathcal{W} \subseteq \Omega$.

Set-control theory studies regions in the state space where the system can feasibly remain over time, known as control invariant sets, which play a pivotal role in the stability properties of the dynamical system. Thus, a robust control invariant set, for system (1), can be defined as follows.

Definition 1 (Robust Control Invariant Set): A set $\Omega \subset \mathbb{X}$ is said to be a robust control invariant set of switched system (1), if for every state $x(k) \in \Omega$ there is a mode $\sigma(k) \in \mathbb{N}_q$ such that the next state follows the condition $x(k + 1) \in \Omega$, for all $w(k) \in \mathbb{W}$.

A. Global Lyapunov function: Nominal approach

Necessary and sufficient conditions for the stabilizability of a nominal switched system (i.e., $w \equiv 0$), and the concept of a global control Lyapunov function within a set-control framework were introduced by [19]:

Definition 2: A positive definite continuous function $V : \mathbb{R}^n \to \mathbb{R}$ is a global *Lyapunov* function for the nominal system if there exist a positive $N \in \mathbb{N}$ and a switching law σ_∞, such that V is non-increasing in one step and decreasing after N steps, for all $x \in \mathbb{X}$, i.e. $V(\phi(x; \sigma(1)) \leq V(x)$ and $V(\phi(x; \sigma(k)) < V(x)$, for all $k \geq N$, and for all $x \in \mathbb{X}$.

Based on the former concept, [19] proved that the nominal system is stabilizable by showing that the *Minkowsky* function

$$\Psi_\Omega(x) = \min_{\alpha \geq 0} \{\alpha \in \mathbb{R} : x \in \alpha\Omega\}, \tag{2}$$

where Ω is a C^*-set, is a *Lyapunov* function. We will demonstrate next that the *Minkowsky* function can be utilized to establish the decreasing property of a global Lyapunov function for the uncertain system as well.

B. Global Lyapunov function: Robust approach

Based on concepts presented in [26] to tackle uncertain systems, we propose the following robust extension for the *Lyapunov* function. A function $V(\cdot)$ is a robust control *Lyapunov* function for the uncertain system (1), and for a given set $\Omega \subset \mathbb{X}$, if there is a switching law $\sigma_N = \{\sigma(1), \cdots, \sigma(N)\}$ such that

$$\sup_{z \in \phi(x; \sigma(1), w)} V(z) \leq V(x) \tag{3}$$

for all $w \in \mathbb{W}$ and $x \in \mathbb{X}$ and

$$\sup_{z \in \phi(x; \sigma_N, w_N)} V(z) < V(x). \tag{4}$$

for all $w_N \in \mathbb{W}^N$ and for all $x \notin \Omega$.

III. Stabilizability of Uncertain Switched Systems

We propose the following algorithm to compute the robust stabilizability of the uncertain switched system (1):

Algorithm 1: Stabilizability of the uncertain switched system (1).

- **Initialization:** Given the disturbance set $\mathbb{W} \subset \mathbb{R}^n$ and a C^*- set $\Omega \subseteq \mathbb{X}$ such that $\Omega \ominus \mathbb{W} \neq \emptyset$. Define $\Omega_0 = \Omega$ and $k = 0$;
- **Iteration** for $k \geq 0$:

$$\Omega_{k+1}^i = A_i^{-1} (\Omega_k \ominus \mathbb{W}), \forall i \in \mathbb{N}_q,$$

$$\Omega_{k+1} = \bigcup_{i \in \mathbb{N}_q} \Omega_{k+1}^i;$$

- **Stop** if $\Omega \subseteq \text{int}\left(\bigcup_{j\in\mathbb{N}_{k+1}} \Omega_j\right)$; denote $\hat{N} = k+1$ and $\hat{\Omega} = \bigcup_{j=1}^{\hat{N}} \Omega_j$.

Algorithm 1 can be used to construct a switching law $\sigma(\cdot)$ for the uncertain system (1), such that it drives every $x_0 \in \hat{\Omega}$ to the set Ω in a finite number of time steps, as formalized in the following property.

Property 2: If Algorithm 1 ends in finite steps $\hat{N}$, then for every $x_0 \in \hat{\Omega}$ there is a switching law $\sigma_{\hat{N}+1}$ such that $\phi(x_0; \sigma_{\hat{N}+1}, w_{\hat{N}+1}) \in \Omega$ for all $w_{\hat{N}+1} \in \mathbb{W}^{\hat{N}+1}$.

Proof: Consider $x(0) := x_0 \in \hat{\Omega} := \bigcup_{j=1}^{\hat{N}} \Omega_j$. Then there is $j_{\hat{N}} \in \{1, \cdots, \hat{N}\}$ such that

$$x(0) \in \Omega_{j_{\hat{N}}} := \bigcup_{i\in\mathbb{N}_q} \Omega^i_{j_{\hat{N}}}$$

w.l.o.g. we assume that $x(0) \in \Omega^{i_0}_{j_{\hat{N}}}$ for some $i_0 \in \mathbb{N}_q$. Then,

$$x(0) \in \Omega^{i_0}_{j_{\hat{N}}} := A_{i_0}^{-1}\left(\Omega_{j_{\hat{N}}-1} \ominus \mathbb{W}\right),$$

or, $A_{i_0}x(0) \in \Omega_{j_{\hat{N}}-1} \ominus \mathbb{W}$, then:

$$A_{i_0}x(0) + w \in \Omega_{j_{\hat{N}}-1}, \text{ for all } w \in \mathbb{W},$$

or the same, $\phi(x_0; i_0, w) \in \Omega_{j_{\hat{N}}-1}$. Let assume the stochastic event at time $k = 0$ is $w(0) \in \mathbb{W}$, and define $x(1) = A_{i_0}x(0) + w(0) \in \Omega_{j_{\hat{N}}-1}$. Now, we repeat the procedure:

$$x(1) \in \Omega_{j_{\hat{N}}-1} = \bigcup_{i\in\mathbb{N}_q} \Omega^i_{j_{\hat{N}}-1}$$

w.l.o.g. we assume that $x(1) \in \Omega^{i_1}_{j_{\hat{N}}-1}$ for some $i_1 \in \mathbb{N}_q$. Then,

$$x(1) \in \Omega^{i_1}_{j_{\hat{N}}-1} := A_{i_1}^{-1}\left(\Omega_{j_{\hat{N}}-2} \ominus \mathbb{W}\right),$$

or, $A_{i_1}x(1) \in \Omega_{j_{\hat{N}}-2} \ominus \mathbb{W}$, then:

$$A_{i_1}x(1) + w \in \Omega_{j_{\hat{N}}-2}, \text{ for all } w \in \mathbb{W}.$$

or the same, $\phi(x_0; \{i_0, i_1\}, w_2) \in \Omega_{j_{\hat{N}}-2}$, for all $w_2 \in \mathbb{W}^2$.

By the same procedure, we can find a switching signal $\sigma_{\hat{N}+1} := \{i_0, i_1, \cdots, i_{j_{\hat{N}}}\}$ such that

$$\phi(x_0; \sigma_{\hat{N}+1}, w_{\hat{N}+1}) \in \Omega_0 = \Omega,$$

for all $w_{\hat{N}+1} \in \mathbb{W}^{\hat{N}+1}$.

The last proves that the sequence $\sigma_{\hat{N}+1} := \{i_0, i_1, \cdots, i_{j_{\hat{N}}}\}$ drives the initial state $x_0 \in \hat{\Omega}$ to the set Ω in $\hat{N}+1$ steps. ■

Next, we will demonstrate that the set to which the algorithm converges is a robust invariant control set for the uncertain switched system.

Lemma 3: If Algorithm 1 ends in finite steps $\hat{N}$, then the set $\hat{\Omega}$ is a robust control invariant for the switched system (1).

Proof: The conclusion of Property 2 and the fact that $\Omega \subseteq \text{int}(\hat{\Omega})$ lead to the result. ■

Now, we will show that the *Minkowski* function (2) is a proper candidate for the robust Lyapunov function introduced in Equations (3) and (4).

Theorem 4: If Algorithm 1 ends with finite $\hat{N}$, then equation (4) holds, i.e.

$$\sup_{z\in\phi(x;\sigma_{\hat{N}}, w_{\hat{N}})} V(z) < V(x).$$

for $w_{\hat{N}} \in \mathbb{W}^{\hat{N}}$ and for all $x \notin \Omega$.

Proof: Let $x \in \hat{\Omega}\backslash\Omega$, by Property 2 there exists a signal $\sigma_{\hat{N}}$ such that $\phi(x; \sigma_{\hat{N}}, w^{\hat{N}}) \in \Omega$. Also, note that $\Omega \subset \lambda\hat{\Omega}$ for some $\lambda < 1$, since $\Omega \subset \text{int}(\hat{\Omega})$. This means that there is $\sigma_{\hat{N}}$ such that,

$$\Psi_{\hat{\Omega}}(\phi(x; \sigma_{\hat{N}}, w_{\hat{N}})) \leq \lambda\Psi_{\hat{\Omega}}(x)$$

for all $w_{\hat{N}} \in \mathbb{W}^{\hat{N}}$, then

$$\sup_{z\in\phi(x;\sigma_{\hat{N}}, w_{\hat{N}})} \Psi_{\hat{\Omega}}(z) < \Psi_{\hat{\Omega}}(x),$$

for all $w_{\hat{N}} \in \mathbb{W}^{\hat{N}}$, which proves Equation (4) for all $x \in \hat{\Omega}\backslash\Omega$. Finally, by the homogeneity of the *Minkowski* function and the linearity of the switched system, the inequality holds for all $x \in \mathbb{X}$. ■

Conjecture 5: If Algorithm 1 ends with finite $\hat{N}$. Then equation (3) holds, i.e.

$$\sup_{z\in\phi(x;\sigma(1),w)} V(z) \leq V(x)$$

for all $w \in \mathbb{W}$ and for all $x \in \mathbb{X}$.
The proof of this last result is left for future work.

A. Numerical example

The next numerical example is taken from [19], where the stability of the origin for the nominal switched system was studied. We will conduct the same analysis as performed by [19] and compare the results with those obtained from our algorithm.

Given the following subsystems

$$A_1 = \begin{pmatrix} 0 & -1.01 \\ 1 & -1 \end{pmatrix}, \quad A_2 = \begin{pmatrix} 0 & -1.01 \\ 1 & -0.5 \end{pmatrix}$$

We applied the proposed algorithm for the nominal case, that is, for a $\mathbb{W} = \emptyset$, and the initial set

$$\Omega = \{(x_1, x_2) : \ x_1^2 + x_2^2 \leq 1\}.$$

The algorithm converges after 3 iterations. The result is shown in Figure 1**A**. Given that the initial conditions considered are the same, we obtained the same results as [19] experiments. For the case of the uncertain switched system (1), we consider an uncertainty bounded by the set

$$\mathbb{W} = \{(w_1, w_2) \in \mathbb{R}^2 : -0.04 \leq w_i \leq 0.04, i = 1, 2\}.$$

In Figure 1B, we observe the initial set Ω, represented by the unit circle centered at zero, followed by the set $\Omega \ominus \mathbb{W}$, obtained by the Minkowski subtraction. The algorithm ends for this $\mathbb{W}$ after 5 iterations, demonstrating that the uncertain switched system (1) can be robustly stabilized.

It is noteworthy that Property 2 establishes that for any initial state within $\hat{\Omega}$, there exists a robust switching law that drives the states of the nominal system to the set

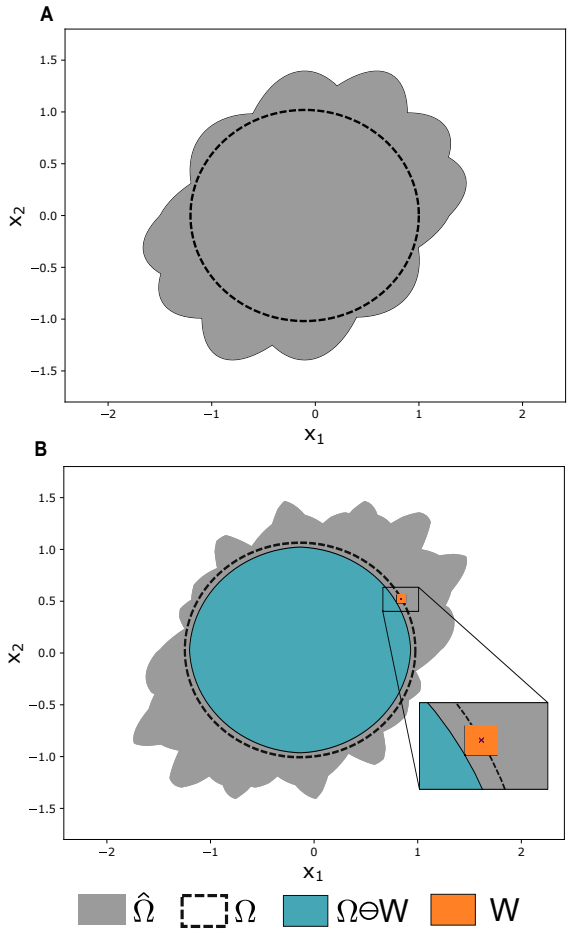

Fig. 1: Stabilizability of the nominal switched system is shown in Panel (A). Panel (B) shows the stabilizability of nominal systems *vs* the uncertain switched system. The initial set is given by Ω, the disturbance set is $\mathbb{W}$, and the solution is the robust control invariant denoted by the set $\hat{\Omega}$.

$\Omega \ominus \mathbb{W}$. Consequently, leveraging Property 1, the uncertain model cannot escape from Ω. This illustrates the algorithm design, which establishes a robust strategy by constraining the uncertain system evolution around the nominal state.

IV. Control Invariant Set to Characterize Bacterial Populations

The proposed theory to characterize robust control invariant sets in the previous section can provide a framework for defining the limitations of antibiotics given a bacterial population. To this end, we considered previous work by [10], [27] that presents a mathematical model to represent the bacterial population in two states: sensitive and resistant. The dynamics of the population are governed by the following uncertain switched linear system,

$$\dot{x}_i = \rho_{i,\sigma(t)} x_i(t) - \delta x_i(t) + \mu \sum_{j \neq i}^{n} m_{ij,\sigma} x_j(t) + w_c(t), \quad (5)$$

where the state of the bacteria population is represented by x_i for the different genotypes i at every given time t, with the control $\sigma(t)$ (antibiotic regimen), and w_c an uncertainty of the switched system. The uncertainty accounts for unmodeled components in the biological system. The parameter $\rho_{i,\sigma}$ is the proliferation rate, which depends on the antibiotic used ($\sigma(t)$). The death rate is represented by δ. We assume that the antibiotic used only affects the proliferation rate.

A mutation term to account for the evolution towards resistance or sensitivity is represented with the mutation network $m_{ij,\sigma(t)} \in \{0, 1\}$. This term also depends on the antibiotic used to represent the genetic connections between genotypes, that is, $m_{i,j} = 1$ if and only if genotype x_j can mutate into genotype x_i. The mutation rate is represented by μ. Equation (5) can be written in the vector form as

$$\dot{x}(t) = \Delta G_{\sigma(t)} x(t) + \mu M_{\sigma(t)} x(t) + w_c(t), \quad (6)$$

where $M_\sigma(t) := [m_{ij,\sigma(t)}] \in \mathbb{R}^{n \times n}$, which defines the observed mutations based on the therapy ($\sigma(t)$) in use at time t. The matrix $\Delta G = diag\{\rho_{i,\sigma(t)}\} - \delta I$, where $diag\{\rho_{i,\sigma(t)}\}$ is the diagonal matrix with the proliferation rate for the different genotypes i, and I is the identity matrix.

A. Two bacterial population case study

Focusing on two populations can provide us with valuable insights from the control invariant sets. Assuming two antibiotics X and Y, the population $x_1 = X_R Y_S$ is resistant to drug X and sensitive to drug Y, and the population $x_2 = X_S Y_R$ that is resistant to drug Y and sensitive to drug X. The switching represents the administration of different antibiotics (X and Y). Figure 2 presents a scheme of the proposed example.

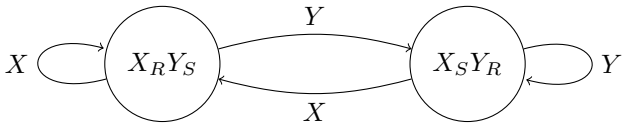

Fig. 2: An evolutionary network system showing the interaction between antibiotics X and Y, and strains $X_R Y_S$ and $X_S Y_R$.

For the applicability of the algorithms proposed in the previous section, we consider the following qualitative cases for the example presented in Figure 2:

Case 1: Each population is sensitive to one drug

$$\Delta G_{\sigma=1} = \begin{pmatrix} + & 0 \\ 0 & - \end{pmatrix}, \Delta G_{\sigma=2} = \begin{pmatrix} - & 0 \\ 0 & + \end{pmatrix}$$

Case 2: One population is resistant to both drugs

$$\Delta G_{\sigma=1} = \begin{pmatrix} + & 0 \\ 0 & + \end{pmatrix}, \Delta G_{\sigma=2} = \begin{pmatrix} - & 0 \\ 0 & + \end{pmatrix}$$

Remark 1 (Sign in $\Delta G_{\sigma(t)}$): The positive sign in matrices $\Delta G_{\sigma=1}$ and $\Delta G_{\sigma=2}$ can be understood that the bacterial population growth is larger than the respective death. Therefore, it would be an expansion of that population given an antibiotic $\sigma(t)$. Vice versa, the negative sign would imply

the proliferation is less than the death, thus would be a contraction of that population given an antibiotic $\sigma(t)$. We adopt this nomenclature to generalize examples independent on the values of the parameters.

Remark 2 (On the nominal system framework): Mutation rates (μ) in microbes range from 10^{-6} to 10^{-11} [28]. Considering the system (6), the matrix $\|\Delta G\| >> \mu\|M\|$, therefore, the stability of the system (6) will be governed by the eigenvalues in the diagonal matrix of ΔG. Case 1 can be stabilizable under switching as the diagonal matrix ΔG changes the directions of the eigenvalues from positive to negative. Case 2 is not stabilizable as the second eigenvalue is positive independently of the switching law.

B. Numerical results

We must first show that the continuous model (6) is equivalent to a discrete model, as in Equation (1). To do this, we need to demonstrate that bounded disturbances of the continuous system will also be bounded in the discrete system; this way, we can characterize the sets in Algorithm 1. Note that in practice, measurements are considered for a fixed interval Δt, where it can be assumed the treatment $\sigma(t)$ is fixed. If we use $k \in \mathbb{N}$ to denote the discrete intervals, then,

$$\begin{aligned} x(k+1) &= \mathrm{e}^{(\Delta G_{\sigma(k)}+\mu M_{\sigma(k)})\Delta t}x(k) \\ &\quad + \int_0^{\Delta t} \mathrm{e}^{(\Delta G_{\sigma(k)}+\mu M_{\sigma(k)})(\Delta t-\tau)}w_c(k)d\tau \\ &= A_{\sigma(k)}x(k) + w(k) \end{aligned} \tag{7}$$

where $x(k)$ is sampled state, $A_{\sigma(k)} := \mathrm{e}^{(\Delta G_{\sigma(k)}+\mu M_{\sigma(k)})\Delta t}$, and $w(k)$ is given by the integration term. In order to bound $w(k)$, for all $k \geq 0$, note that for a given norm $\|\cdot\|$ we have:

$$\left\| \int_0^{\Delta t} \mathrm{e}^{\bar{A}_{\sigma(k)}(\Delta t-\tau)}w_c(k)d\tau \right\| \leq \left\| \mathrm{e}^{\bar{A}_{\sigma(k)}\Delta t} \right\| \cdot \|w_c(k)\| \cdot \Delta t$$

where $\bar{A}_{\sigma(k)} := (\Delta G_{\sigma(k)} + \mu M_{\sigma(k)})$. So, $\|w(k)\|$ can be bounded if we take the upper bound of $\left\| \mathrm{e}^{\bar{A}_{\sigma(k)}\Delta t} \right\|$ for all $\sigma \in \mathbb{N}_q$, and we assume that the disturbance of the continuous system, $w_c(t)$, is bounded for all $t \geq 0$.

1) Invariance analysis on bacterial escape: For the qualitative analysis, let us first consider *Case 1*. In this scenario, both matrices are non-Hurwitz, implying that the system cannot be stabilized by a constant $\sigma(t)$ for all $t > 0$. In biological terms, it is necessary to apply both antibiotics to prevent population escape due to resistance. This is known as *evolutionary rescue* [29], a phenomenon in which the use of a single antibiotic leads to population escape due to the emergence of resistance. In other words, if the population is exposed to single-antibiotic over time, the sensitive strain is eradicated. However, the emergent resistant strain escapes the monotherapy, and this occurs for any positive initial condition (i.e., $x_i > 0$, for some $i = 1, 2$). Consequently, at least two antibiotics must be considered in this framework.

As we mentioned in Remark 2, *Case 1* can be stabilized for a nominal switched system (i.e., without uncertainty).

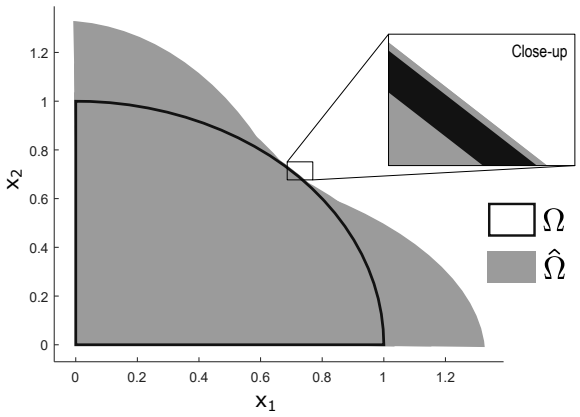

Fig. 3: Limiting Bacterial resistance evolution. The initial condition for Algorithm 1 is given by set Ω, the solution of the algorithm is a robust control invariant set, $\hat{\Omega}$, for the uncertain switched system. The close-up indicates the stop condition of Algorithm 1 is fulfilled, i.e., $\Omega \subset \text{int}(\hat{\Omega})$.

Here, we show in this case that we can still be stabilized for the uncertain system. Algorithm 1 was implemented using MATLAB, leveraging the MPT3 toolbox [30]. In this instance, Algorithm 1 converges within two iterations for an uncertainty set $\mathbb{W} \neq \emptyset$, and for an initial set Ω, given by the unit circle in the positive octant, see Figure 3. We observe in the close-up window of Figure (3) that $\Omega \subset \text{int}(\hat{\Omega})$, showing that the algorithm stops and suggesting that using sequential therapies with synergistic drugs could prevent infection escape in *evolutionary rescue* context.

Note that we construct a bounded robust control invariant set, $\hat{\Omega}$, of system (1). Therefore, we can ensure that the population $(x_1(k), x_2(k)) \in \hat{\Omega}$ for all $k \geq 0$, given any initial condition $(x_1(0), x_2(0)) \in \hat{\Omega}$.

Remark 3: Let us assume two bacterial populations, x_1 and x_2, satisfying the condition $(x_1, x_2) \in \hat{\Omega}$. Thus, the synergy between the two drugs is sufficient to prevent this population from escaping due to the evolutionary rescue curve.

Finally, *Case 2* cannot be stabilized for the nominal system, as described in Remark 2. Since we assume $0 \in \mathbb{W}$, it is also not possible to stabilize it for the uncertain system. Algorithm 1 does not converge in this case. This shows that bacterial population in *Case 2* cannot be contained with these antibiotics.

V. Conclusion

In this study, we achieved stabilizability for the uncertain switched linear system through a robust control invariant set characterization. This approach guarantees that once the states of the nominal system reach certain regions, the uncertain states will remain bounded. These findings were then leveraged to investigate the dynamics of antibiotic resistance in bacterial populations. Our approach has the potential to assess the selection of antibiotics and evaluate their potential to eradicate a bacterial population.

REFERENCES

[1] M. A. Salam, M. Y. Al-Amin, M. T. Salam, J. S. Pawar, N. Akhter, A. A. Rabaan, M. A. Alqumber, Antimicrobial resistance: a growing serious threat for global public health, in: Healthcare, Vol. 11, MDPI, 2023, p. 1946.

[2] S. Tao, H. Chen, N. Li, T. Wang, W. Liang, The spread of antibiotic resistance genes in vivo model, Canadian Journal of Infectious Diseases and Medical Microbiology 2022 (2022).

[3] S. Höjgård, Antibiotic resistance–why is the problem so difficult to solve?, Infection ecology & epidemiology 2 (1) (2012) 18165.

[4] L. Imamovic, M. O. Sommer, Use of collateral sensitivity networks to design drug cycling protocols that avoid resistance development, Science translational medicine 5 (204) (2013) 204ra132–204ra132.

[5] A. Huynh, K. B. Wood, Finding the right sequence of drugs, Elife 10 (2021) e72562.

[6] M. Rodriguez de Evgrafov, H. Gumpert, C. Munck, T. T. Thomsen, M. O. Sommer, Collateral resistance and sensitivity modulate evolution of high-level resistance to drug combination treatment in staphylococcus aureus, Molecular biology and evolution 32 (5) (2015) 1175–1185.

[7] M. Baym, L. K. Stone, R. Kishony, Multidrug evolutionary strategies to reverse antibiotic resistance, Science 351 (6268) (2016) aad3292.

[8] J. N. Tetteh, F. Matthäus, E. A. Hernandez-Vargas, A survey of within-host and between-hosts modelling for antibiotic resistance, Biosystems 196 (2020) 104182.

[9] E. A. Hernandez-Vargas, C. Parra-Rojas, S. Olaru, Switching logistic maps to design cycling approaches against antimicrobial resistance, in: 2021 60th IEEE Conference on Decision and Control (CDC), IEEE, 2021, pp. 4248–4253.

[10] J. N. A. Tetteh, S. Olaru, H. Crauel, E. A. Hernandez-Vargas, Scheduling collateral sensitivity-based cycling therapies toward eradication of drug-resistant infections, International Journal of Robust and Nonlinear Control 33 (9) (2023) 4824–4842.

[11] L. Geris, D. Gomez-Cabrero, Uncertainty in biology, Studies in Mechanobiology, Tissue Engineering and Biomaterials (2016).

[12] H. Lin, P. J. Antsaklis, Stability and stabilizability of switched linear systems: A short survey of recent results, Proceedings of the 20th IEEE International Symposium on Intelligent Control, ISIC '05 and the 13th Mediterranean Conference on Control and Automation, MED '05 2005 (2005) 24–29.

[13] L. Hetel, Robust stability and control of switched linear systems, Ph. D. dissertation (2007).

[14] N. K. Son, L. Van Ngoc, On robust stability of switched linear systems, IET Control Theory & Applications 14 (1) (2020) 19–29.

[15] F. Blanchini, P. Colaneri, G. Giordano, I. Zorzan, Vertex results for the robust analysis of uncertain biochemical systems, Journal of Mathematical Biology 85 (2022) 1–43.

[16] C. A. Yfoulis, Robust stabilizability of linear uncertain switched systems: A computational algorithm, 22nd IEEE International Symposium on Intelligent Control, ISIC 2007. Part of IEEE Multi-conference on Systems and Control (2007) 106–111.

[17] H. Lin, P. J. Antsaklis, A necessary and sufficient condition for robust asymptotic stabilizability of continuous-time uncertain switched linear systems, Proceedings of the IEEE Conference on Decision and Control 4 (2004) 3690–3695.

[18] D. D. Thuan, L. V. Ngoc, Robust stability and robust stabilizability for periodically switched linear systems, Applied Mathematics and Computation 361 (2019) 112–130.

[19] M. Fiacchini, M. Jungers, Necessary and sufficient condition for stabilizability of discrete-time linear switched systems: A set-theory approach, Automatica 50 (1) (2014) 75–83.

[20] S. Miani, Set-Theoretic Methods in Control. Systems & Control: Foundations & Applications, Springer, 2008.

[21] A. L. Anderson, P. Abuin, A. Ferramosca, E. A. Hernandez-Vargas, A. H. Gonzalez, Cyclic control equilibria for switched systems with applications to ecological systems, International Journal of Robust and Nonlinear Control 33 (9) (2023) 5159–5175.

[22] M. Perez, A. Anderson, P. Abuin, E. A. Hernandez-Vargas, A. H. Gonzalez, M. Actis, Computing control invariant sets for waiting-time switched systems: A study case of glucose regulation, IEEE Control Systems Letters (2023).

[23] A. Anderson, A. H. González, A. Ferramosca, A. D'Jorge, E. Kofman, Robust mpc suitable for closed-loop re-identification, based on probabilistic invariant sets, Systems & Control Letters 118 (2018) 84–93.

[24] D. Q. Mayne, E. C. Kerrigan, E. Van Wyk, P. Falugi, Tube-based robust nonlinear model predictive control, International journal of robust and nonlinear control 21 (11) (2011) 1341–1353.

[25] A. D'Jorge, A. Ferramosca, A. H. González, A robust gradient-based mpc for integrating real time optimizer (rto) with control, Journal of Process Control 54 (2017) 65–80.

[26] J. B. Rawlings, D. Q. Mayne, M. Diehl, Model predictive control: theory, computation, and design, Vol. 2, Nob Hill Publishing Madison, WI, 2017.

[27] E. Hernandez-Vargas, P. Colaneri, R. Middleton, F. Blanchini, Discrete-time control for switched positive systems with application to mitigating viral escape, International journal of robust and nonlinear control 21 (10) (2011) 1093–1111.

[28] J. W. Drake, B. Charlesworth, D. Charlesworth, J. F. Crow, Rates of spontaneous mutation (1998).

[29] G. Bell, Evolutionary rescue, Annual Review of Ecology, Evolution, and Systematics 48 (2017) 605–627.

[30] M. Herceg, M. Kvasnica, C. N. Jones, M. Morari, Multi-parametric toolbox 3.0, in: 2013 European control conference (ECC), IEEE, 2013, pp. 502–510.