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Invariant set theory for predicting potential failure of antibiotic cycling

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ABSTRACT

Collateral sensitivity, where resistance to one drug confers heightened sensitivity to another, offers a promising strategy for combating antimicrobial resistance, yet predicting resultant evolutionary dynamics remains a significant challenge. We propose here a mathematical model that integrates fitness trade-offs and adaptive landscapes to predict the evolution of collateral sensitivity pathways, providing insights into optimizing sequential drug therapies.

Our approach embeds collateral information into a network of switched systems, allowing us to abstract the effects of sequential antibiotic exposure on antimicrobial resistance. We analyze the system stability at disease-free equilibrium and employ set-control theory to tailor therapeutic windows. Consequently, we propose a computational algorithm to identify effective sequential therapies to counter antibiotic resistance. By leveraging our theory with data on collateral sensivity interactions, we predict scenarios that may prevent bacterial escape for chronic *Pseudomonas aeruginosa* infections.

1. Introduction

Antimicrobial resistance (AMR) causes 4.95 million deaths yearly globally (Murray et al., 2022), and the estimated cost of AMR is projected to reach $1 trillion annually by 2050 worldwide (Dadgostar, 2019). Two strategies to slow the spread of AMR involve deploying combinatorial and cycling protocols in clinical settings (van Duijn et al., 2018). However, there is currently no approved framework for effectively implementing antibiotic cycling due to an incomplete understanding of interactions involving antibiotic combinations (Birkegård et al., 2018; Cheng et al., 2019). One approach suggests that antibiotic cycling can overwhelm bacterial selection by exploiting collateral sensitivity between antimicrobials (Beardmore et al., 2017; Hall et al., 2009; Pluchino et al., 2012). Collateral sensitivity occurs when genetic changes confer resistance to one agent and

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simultaneously decrease bacterial fitness against a second agent (Lázár et al., 2018; Pál et al., 2015). Conversely, cross-resistance is the opposite phenomenon, and insensitivity occurs when there are no discernible changes in bacterial fitness. Currently, researchers employ laboratory evolution (Imamovic et al., 2018; Lázár et al., 2013, 2014; Oz et al., 2014), genome sequencing (Barbosa et al., 2019; Gonzales et al., 2015; Liakopoulos et al., 2022; Podnecky et al., 2018), and mathematical modeling (Aulin et al., 2021; Maltas & Wood, 2019; Nichol et al., 2019; Udekwu & Weiss, 2018; Van Hasselt & Iyengar, 2019; Yoon et al., 2018) to study collateral sensitivity.

Mathematical modeling plays a critical role in optimization-based methods across various systems (Grüne et al., 2017). Advanced control techniques leverage these models (Rawlings et al., 2017) to establish a framework for designing effective therapies (Cai et al., 2020). However, controlling a system requires understanding its regions of stability to design a well-defined control objective. These regions include steady states, equilibrium sets, and control invariant sets. Lyapunov theory provides a formal framework for stabilizing them (Blanchini & Miani, 2015). Equilibrium states - representing positions with zero population change rates - cannot always be characterized, especially for hybrid systems (Sanchez et al., 2023). In contrast, control invariant sets offer a broader framework for assessing the stability and controllability of more general dynamics (Chen et al., 2021; Perez et al., 2023). A control invariant set denotes a region of stationary states where trajectories can remain within a set over time under admissible laws (Rakovic et al., 2005). These sets are typically identified using level surfaces of a Lyapunov-like function (Blanchini, 1999; Kiendl et al., 1992), and they have proven robust for addressing biological and ecological challenges (Abate et al., 2009; Anderson, Abuin, et al., 2021; Esterhuizen et al., 2021).

The adaptation of *Pseudomonas aeruginosa* to the antibiotics in Table 1 was studied by (Imamovic et al., 2018). The data provided by (Imamovic et al., 2018) is adapted here to represent a qualitative profile of the antibiotic interactions (see Fig. 1a). Fig. 1a illustrates drug-induced physiological states on the wild-type strain and how the concomitant susceptibility changes concerning other drugs. The color coding represents collateral sensitivity (red), cross-resistance (green), or insensitivity (yellow).

On the other hand, the susceptible or resistance categories of a microorganism to a given antimicrobial are formally defined by clinical breakpoints (Andrews, 2001; Kahlmeter et al., 2006). For convenience, the minimum inhibitory concentration (MIC), defined as the lowest concentration of a drug that inhibits the visible growth of a microorganism, can be used as a parameter of antibiotic action (Regoes et al., 2004). The MIC breakpoints categorize microorganisms as susceptible or resistant, dependent on the quantitative antimicrobial susceptibility indicated by the MIC values (Kahlmeter et al., 2003; Mouton et al., 2012). To illustrate the MIC breakpoints, Fig. 1b examines the scenario for two antibiotics, Levofloxacin (LEV) and Aztreonam (AZE). The MIC of the wild-type (Variant *WT*) indicates a profile of susceptibility to both drugs. Exposed to the antibiotic AZE, the *WT* evolves resistance to the drug (population AZE_R), and the MIC of AZE_R increases for AZE and LEV; thus, the drug AZE shows cross-resistance to LEV. On the other hand, when exposed to antibiotic LEV, the *WT* evolves towards a resistant variant (LEV_R), and the MIC increases concerning LEV but decreases for AZE. In this case, drug LEV shows collateral sensitivity to AZE.

The antibiotics interactions from Fig. 1a are leveraged to ascertain the susceptibility profile of emerging variants through a combinatorial mutation network (Komarova & Wodarz, 2005). We integrate the network using a switched system for modeling cycling drug therapies (Anderson, Gonzalez, et al., 2021; Hernandez-Vargas et al., 2011; Liberzon, 2003; Settati & Lahrouz, 2014). Switched systems have previously been employed to model bacterial populations under sequential therapies (Tetteh et al., 2023). However, computing invariant sets for predicting potential failure of antibiotics is novel. We prove that the existence of a bounded control invariant region implies there is a sequence of antibiotics capable of preventing the population from escaping. We introduce an algorithm to compute these invariant sets and a predetermined control law to contain the infection within given therapeutic windows. Our simulations suggest several combinations of antibiotics from Table 1 for designing effective sequential therapies to counter resistance in chronic *P. aeruginosa* infections.

2. Problem statement

In our previous research, we have proposed switching logistic maps to design drug cycling protocols to counter antimicrobial resistance development (Hernández-Vargas et al., 2021; Tetteh et al., 2023). In this study, we have expanded our model to include collateral sensitivity, cross-resistance, and insensitivity between antibiotic pairs in Table 1. This extension is

Table 1
Antibiotics used in (Imamovic et al., 2018) for the evolution of the wild-type (WT) *P. aeruginosa*, and antibiotic targets.

ANTIBIOTIC	ABBREVIATION	CLASS	TARGET
Aztreonam	AZE	β-lactam (monobactam)	cell wall
Carbenicillin	CAR	β-lactam (penicillin)	cell wall
Ampicillin	AMP	β-lactam (penicillin)	cell wall
Imipenem	IMI	β-lactam (carbapenem)	cell wall
Ciprofloxacin	CIP	quinolone	DNA gyrase
Levofloxacin	LEV	quinolone	DNA gyrase
Colistin	COL	polymyxin	lipopolysaccharide
Amikacin	AMI	aminoglycoside	protein synthesis
Tobramycin	TOB	aminoglycoside	protein synthesis

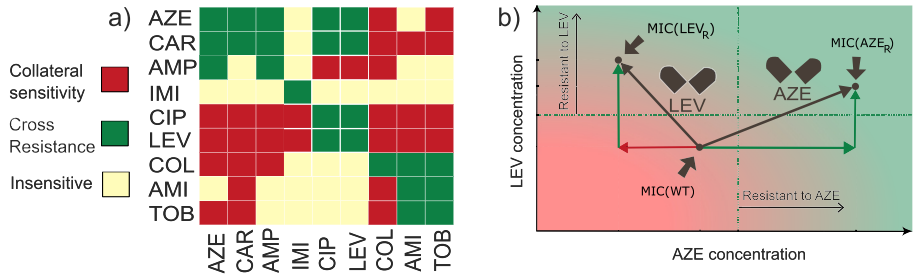

Fig. 1. a) **Antibiotic interactions for *P. aeruginosa*,** (Imamovic et al., 2018)**:** A row delineates the profiles of a drug-evolved resistant strain. Cross-resistance is shown in green, collateral sensitivity in red, and insensitivity in yellow. b) **Quantifying collateral sensitivity:** The two-dimensional space shows AZE and LEV antibiotic concentrations, with red and green surfaces indicating susceptibility and resistance regions, respectively. The red arrow represents collateral sensitivity, while the green arrows show cross-resistance. Reflecting on the MIC position, when exposed to the antibiotic AZE, the wild-type (WT) strain evolves to variant AZE_R, becoming resistant to both drugs. However, under LEV antibiotic stress, WT evolves to LEV_R, which remains sensitive to AZE but resistant to LEV. This figure illustrates how different phenotypic states connect when a drug is active.

achieved by formulating a mutational network that incorporates the antibiotic interactions within the structure of the switched system. The mutational network is used to avoid antibiotic combinations that trigger the emergence of multi-resistant strains. The switched system approach helps us identify effective control measures to minimize population growth.

We examine the stability of the origin for various drug schedules and antibiotic interactions. In addition, we study the feasibility of controlling the emergence of resistance by a control invariant set characterization. We propose an algorithm to compute control invariant sets within a therapeutic window and a switching control law to prevent infection from spreading.

3. Network-based switched system for cycling drugs

3.1. Drug resistance formulation

Let us consider N antibiotics $\sigma \in \{1, \ldots, N\} := \Sigma$, and define a drug concentration space for these N drugs: $\mathcal{C} \subseteq \mathbb{R}^N_{\geq 0}$, where $c = (c_1, \ldots, c_N) \in \mathcal{C}$ is such that c_σ represents concentration of drug σ, for all $\sigma = 1, \ldots, N$ (see Fig. 1b for antibiotics $\Sigma = \{AZE, LEV\}$). For a given microorganism, x, we define the Minimum Inhibitory Concentration as an N-dimensional vector as follows:

$$MIC(x) = (MIC_1(x), \ldots, MIC_N(x)) \in \mathcal{C},$$

where $MIC_\sigma(x)$ is the Minimum Inhibitory Concentration of drug $\sigma \in \Sigma$ for microorganism x. Utilizing the N-dimensional MIC enables the determination of susceptibility changes across all drugs, even when the microorganism x is exposed to a singular agent. In addition, the breakpoint vector of every antibiotic in Σ is given by:

$$Br_\Sigma = (Br_1, \ldots, Br_N) \in \mathcal{C},$$

where Br_σ represents a maximum concentration of drug σ allowed for use, for all $\sigma = 1, \ldots, N$. MIC values and breakpoints for specific antibiotics and bacteria can be accessed on the European Committee on Antimicrobial Susceptibility Testing (EUCAST) website.

In this manner, we can define the subsequent states for a microorganism x.

Definition 1. (Sensitive/Resistant state). Consider a microorganism x and N antibiotics, $\sigma \in \Sigma$. It is said that x is sensitive *(*resistant*)* to drug σ, with $\sigma = 1, \ldots, N$, if the σ^{th} element of the vector $MIC(x) - Br_\Sigma$, is negative *(*non-negative*)*.

The phenomenon where any population of a microorganism x_i, changes to a new phenotypic state, x_j, after being exposed to a drug $\sigma \in \Sigma$ (represented by a row of Fig. 1a), can be represented by the following mutation graph:

$$x_i \xrightarrow{\sigma} x_j,$$

where the arrow represents a mutation (or evolution) direction, measured by the following vector.

Definition 2. (Collateral effects). Consider the following mutation graph $x_i \xrightarrow{\sigma} x_j$. The drug-driven vector for drug σ is defined by:

$$\vec{v}_\sigma := MIC(x_j) - MIC(x_i).$$

Negative elements of $\vec{v}_\sigma$ represent collateral sensitivity; positive elements represent cross-resistance; and null elements represent insensitive interactions of drug σ.

3.2. Combinatorial evolutionary network

The mutation path of pathogens exposed to a sequence of N drugs can be determined by an evolutionary network (Komarova & Wodarz, 2005). Every node of the network represents a variant of the bacteria characterized by a unique profile of susceptibility - resistant (R) or sensitive (S) - with respect to all other antibiotics; this way, 2^N is the potential number of nodes. Formally, a state x_i, $i \in \{1, \ldots, 2^N\}$, is given by a unique binary strain $x_i := 1_S, 2_R, \ldots, N_S$, representing a variant susceptible to drug 1, resistant to drug 2 and so on. According to Definition 1, the state x_i can be defined by the following conditions:

$$MIC_1(x_i) < Br_1, \quad MIC_2(x_i) \geq Br_2, \quad \cdots, \quad MIC_N(x_i) < Br_N.$$

The following is the premise of evolutionary rescue (Bell, 2017), which states that exposure to a drug selects for resistance to that drug.

Assumption 1. (Resistance development). For every state sensitive to $\sigma \notin \Sigma$, x_i, the antibiotic σ triggers a connection $x_i \xrightarrow{\sigma} x_j$ in the mutational network, such that x_j becomes resistant to σ.

To construct the mutational network for N antibiotics we assume preexisting strains present in the population and the emerging strains that will arise from the drug-driven vector on Definition 2. For the sake of simplicity, here we assume that the only preexisting strain is the wild-type (sensitive to all antibiotics), and the connections between nodes can be determined by Fig. 1a as follows: we assume that interactions are sufficient to ensure that cross-resistance always leads to a resistant strain (R), collateral sensitivity always results in a sensitive strain (S), and insensitive interactions do not alter susceptibility. Consider next two examples.

Example 1. Consider the antibiotics with mutual collateral sensitivity, Levofloxacin ($A = LEV$) and Ampicillin ($B = AMP$) in Fig. 2a, along with an initial population comprising only the wild-type A_SB_S. According to the interactions between LEV and AMP, following exposure to antibiotic LEV, the wild-type A_SB_S transitions to a variant A_RB_S resistant to LEV but sensitive to AMP. Conversely, after exposure to the drug AMP, the wild-type A_SB_S transitions to a variant A_SB_R resistant to AMP but sensitive to LEV. Furthermore, the mutual collateral sensitivity between LEV and AMP dictates an evolutionary trajectory between A_SB_R and A_RB_S, and vice versa, when these drugs are used, as indicated in the mutational network in Fig. 2a.

Example 2. Consider antibiotics Tobramycin ($A = TOB$), Carbenicillin ($B = CAR$), and Colistin ($C = COL$) in Fig. 2b. These drugs exhibit both collateral sensitivity and cross-resistance interactions. The mutation network for these antibiotics is given by 4 states: the wild type $A_SB_SC_S$, $A_RB_SC_S$, $A_SB_RC_S$ and $A_RB_SC_R$. These can mutate among themselves in accordance with the collateral effects of antibiotics TOB, CAR, and COL.

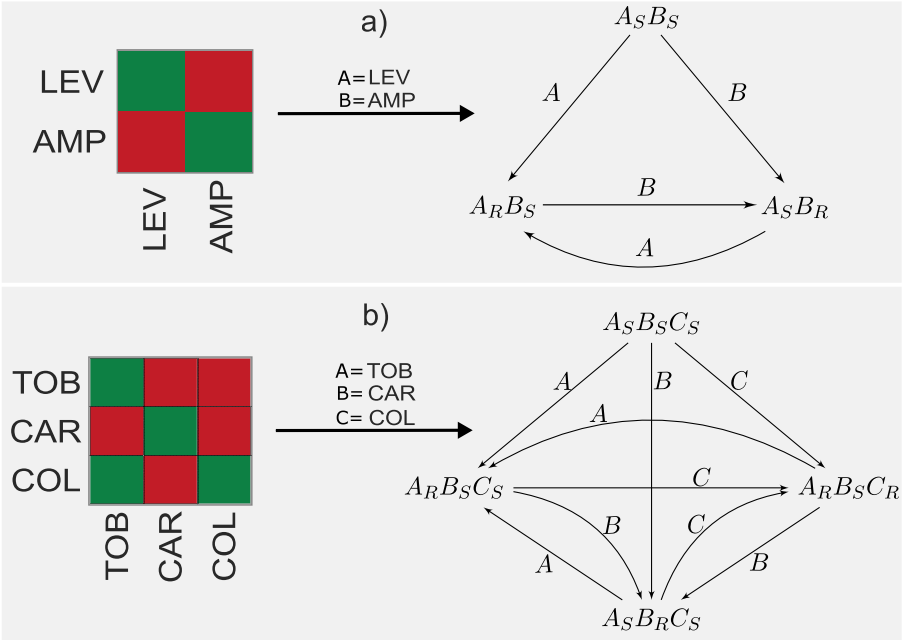

Fig. 2. a) The interactions between antibiotic Levofloxacin ($A = LEV$) and Ampicillin ($B = AMP$) from Table 1, give rise to the evolutionary network between 3 variants A_SB_S, A_RB_S and A_SB_R. b) The interactions between antibiotic Tobramycin ($A = TOB$), Carbenicillin ($B = CAR$) and Colistin ($C = COL$) from Table 1, give rise to the evolutionary network between 4 variants $A_SB_SC_S$, $A_SB_RC_S$, $A_RB_SC_S$ and $A_RB_SC_R$.

Property 1. (Dead-end selection towards multi-resistant states). If Assumption 1 holds then:

i. Given two antibiotics without mutual collateral sensitivity, the mutational network for these antibiotics will present a node resistant to both antibiotics.
ii. Given a set of N antibiotics, where at least one antibiotic presents cross-resistance against the other $N-1$ antibiotics, the mutational network for these antibiotics will present a node resistant to all antibiotics.
iii. Given N antibiotics, where at most one antibiotic exhibits collateral sensitivity with one or more drugs, the mutational network for these antibiotics will present a node resistant to all antibiotics.

These conditions, together with Assumption 1, lead to a multi-resistant node in the mutational network. For Property 1 *i.*, the case of two antibiotics $\{A, B\}$ without mutual collateral sensitivity. For simplicity, we can assume that B does not show collateral sensitivity with respect to A. We can take the wild type (sensitive to both drugs) as the starting point to construct the mutational network, then expose first to drug A, which means the state $A_RB_?$ emerges, as per Assumption 1. Subsequently, when the state $A_RB_?$ is exposed to drug B, the multi-drug resistant variant A_RB_R emerges. This occurs because B does not show collateral sensitivity and cannot reverse the resistance to A. Items *ii.* and *iii.* follow similar reasoning.

3.3. Switched system modeling

A switched system can be linked with the evolutionary network for N drugs, where the nodes of the network represent the states of the system: $(x_1, x_2, \ldots, x_n)$, where $x_i \in \mathbb{R}_{\geq 0}$ is a particular sub-population, and the N modes represent the inputs of control, given by the set of antibiotics (Hernández-Vargas et al., 2021; Tetteh et al., 2023). We model the effect of cycling drugs using a drug-induced death rate framework: where $\alpha_i^\sigma > 0$ is the growth rate for variant x_i under exposure of drug σ and $\delta_i^\sigma > 0$ is the death rate. Drug σ determines mutation from one state x_i to another state x_j, with a given mutation rate μ, according the mutation network given by the matrix $m_{i,j}^\sigma \in \{0, 1\}$, where $m_{i,j}^\sigma = 1$ implies $x_i \xrightarrow{\sigma} x_j$, and $m_{i,j}^\sigma = 0$ that there is no connection. With a total carrying capacity given by $K > 0$, the following switched system describe population growth under therapy $\sigma(\cdot)$:

$$\dot{x}_i(t) = \alpha_i^{\sigma(t)} x_i(t)\left(1 - \frac{\sum_{j=1}^n x_j(t)}{K}\right) - \delta_i^{\sigma(t)} x_i(t) + \mu \sum_{j \neq i}^n m_{i,j}^{\sigma(t)} x_j(t). \tag{1}$$

The states of the system are given by $x = (x_1, x_2, \ldots, x_n)$, and the control input by a function $\sigma(\cdot)$: $[0, \infty) \to \Sigma$. The switch of drugs, described by the switching function $\sigma(t)$, shifts the balance of birth and death such that the population declines or escapes.

Remark 1. Equation (1) introduces an extension to the logistic term compared to our previous proposals. Here, we consider that the total population load, i.e., $\sum_{i=1}^n x_i(t)$, affects the growth of each strain x_i, as all strains compete for the same resource. The introduced logistic term $1 - \frac{\sum_{i=1}^n x_i(t)}{K}$ accounts for this phenomenon.

Remark 2. The main objective of model (1) is to highlight potential failures in antibiotic recycling strategies and provide insights into the dynamics of resistance emergence under cycling therapies. Our approach here can be extended to include probabilistic distributions of the main parameters, to obtain a probabilistic model and, eventually, a robust control strategy. Also, the mathematical model can be extended into a more general fitness landscape, to explicitly account for competition between phenotypic states. In the current model, competition is masked by the driving force of artificial selection - exerted by antibiotics - that determines the mutation pattern masking any kind of competition between phenotypic states. For the sake of brevity and clarity, both extensions are left for future work.

Assumption 2. In Equation (1), we classify sensitive and resistant states to a given antibiotic σ, so that sensitive (S) is associated with values $\alpha^\sigma - \delta^\sigma < 0$ and resistant (R) with $\alpha^\sigma - \delta^\sigma > 0$.

Note that the origin is an equilibrium state of the switched system (1) for all modes $\sigma \in \Sigma$, since $\dot{x}_i = 0$ if $x_i = 0$, for all $i = 1, \ldots, n$. The following proposition determines therapy scenarios where the origin is an unstable equilibrium state.

Proposition 2. The origin is unstable for the switched system (1) in the following scenarios:

i. In a single-drug regimen, where the drug input remains fixed ($\sigma(t) = \sigma$) over time.
ii. For multiple antibiotics regimen $\sigma(t)$ that satisfy one of the items (i, ii, or iii) of Property 1.

Proof. Consider any positive initial condition $x_l(0) > 0$ for some $l = 1, \ldots, n$, at time $t = 0$.

i. Given Assumption 1, there exists a state x_j resistant to drug σ, such that $x_l \xrightarrow{\sigma} x_j$, i.e. the element of the mutation matrix is $m_{lj}^\sigma = 1$. Hence, it can be proved that if mode σ is active for all $t \geq 0$, then $x_j(t) > 0$ for all $t > 0$.

Let us assume by contradiction that the origin is a stable equilibrium. This implies that for any $\bar{\epsilon} > 0$, there is a small enough positive initial condition $x_l(0) > 0$, such that $\frac{\sum_{i=1}^{n} x_i(t)}{K} < \bar{\epsilon}$ for all $t \geq 0$. Since the state x_j is resistant to σ, then according to Assumption 2, $\alpha_j^\sigma - \delta_j^\sigma > 0$. Therefore, we can find a constant $\bar{\epsilon} > 0$ such that $\alpha_j^\sigma - \delta_j^\sigma - \epsilon\alpha_j^\sigma > 0$ for all $\epsilon \leq \bar{\epsilon}$. This is equivalent to:

$$\alpha_j^\sigma(1-\epsilon) - \delta_j^\sigma > 0,$$

for all $\epsilon \leq \bar{\epsilon}$. As shown before, we can consider a small enough initial condition $x_l(0) > 0$ for which $\frac{\sum_{i=1}^{n} x_i(t)}{K} < \bar{\epsilon}$ for all $t \geq 0$. So, it holds that:

$$\alpha_j^\sigma\left(1 - \frac{\sum_{i=1}^{n} x_i(t)}{K}\right) - \delta_j^\sigma > 0,$$

for all $t \geq 0$. Since $x_j > 0$ then,

$$\alpha_j^\sigma x_j(t)\left(1 - \frac{\sum_{i=1}^{n} x_i(t)}{K}\right) - \delta_j^\sigma x_j(t) > 0,$$

for $t \geq 0$. Therefore,

$$\alpha_j^\sigma x_j(t)\left(1 - \frac{\sum_{i=1}^{n} x_i(t)}{K}\right) - \delta_j^\sigma x_j(t) + \mu\sum_{j=1}^{n} m_{i,j}^{\sigma(t)} x_j(t) > 0,$$

for all $t \geq 0$. In other words, $\dot{x}_j(t) > 0$, for all $t \geq 0$. This implies that $x_j(t)$ is increasing for all $t \geq 0$. Therefore, we can find a constant $M > 0$ such that $x_j(t) > M$ for all $t \geq T$ for some positive time T. If we consider $\bar{\epsilon} = M$, then the condition $\frac{\sum_{i=1}^{n} x_i(t)}{K} < \bar{\epsilon}$ for all $t \geq 0$ is not satisfied, contradicting the initial assumption of stability (for any $\bar{\epsilon} > 0$).

Similarly, items ii) can be demonstrated since Property 1 ensures in all cases the presence of a strain $x_j > 0$ resistant to all drugs used in a switching law $\sigma(t)$. Then we follow the same reasoning as in the proof of the above item. ∎

4. Control invariant sets for analyzing cycling drugs

Let us introduce the definition of the control invariant set (Yu et al., 2013).

Definition 3. (Control Invariant Set - CIS). A set $\Omega \subseteq \mathbb{R}^n$ is said to be a control invariant set of switched system (1), with $x = (x_1, \ldots, x_n)$, if there exits a switching law $\sigma(\cdot)$: $[t_0, \infty) \to \Sigma$ such that for all $x(t_0) \notin \Omega$, $x(t) \notin \Omega$ for all $t \geq t_0$.

The existence of a control invariant set implies the existence of a control law that traps the system's trajectories inside the set. Notably, in cases where the origin is not stabilizable (see Proposition 2), the characterization of the invariant set relaxes the control objectives. If the invariant set is sufficiently small, the bacterial population can be trapped within low population levels. This can help to avoid the risk of healthcare-associated infections (Tong et al., 2012). To achieve this, we define a therapeutic window for the bacterial population outside the origin:

Definition 4. (Therapeutic window). A bounded and closed set $\mathbb{T} \subset \mathbb{R}^n$, containing the origin, is defined as a therapeutic window for a bacterial population $(x_1, \ldots, x_n)$ if any point $x \in \mathbb{T}$ represents a bacterial lead maintained within safe levels.

The set $\mathbb{T} \subset \mathbb{R}^n$ can be related to a control problem, given by the minimization of the following cost function:

$$V_{\mathbb{T}}(x(t_0), \sigma(\cdot)) = \int_{t_0}^{t_f} \min_{y \in \mathbb{T}} \|x(t) - y\|^2 dt, \tag{2}$$

where t_0 and t_f are the initial and final treatment times, respectively.

Fig. 3 illustrates three potential behaviors when cycling between mutually collateral sensitive antibiotics A and B and their effects on two bacterial states. The horizontal axis represents the first state ($A_R B_S$), which is resistant to antibiotic A but sensitive to B. The vertical axis represents the second state ($A_S B_R$), which is sensitive to antibiotic A but resistant to B. The three observed behaviors are: (a) perfect balance, where the population stays within the therapeutic window without complete eradication; (b) population decline, and (c) population escape, despite mutual collateral sensitivity, where no control invariant can be established within $\mathbb{T}$.

4.1. Numerical characterization of control invariant sets

The carrying capacity is the maximum load of the bacterial population that the environment can support, depending on species, environmental conditions, and available resources (Smaal et al., 1997). Nutrients are in excess for several infectious

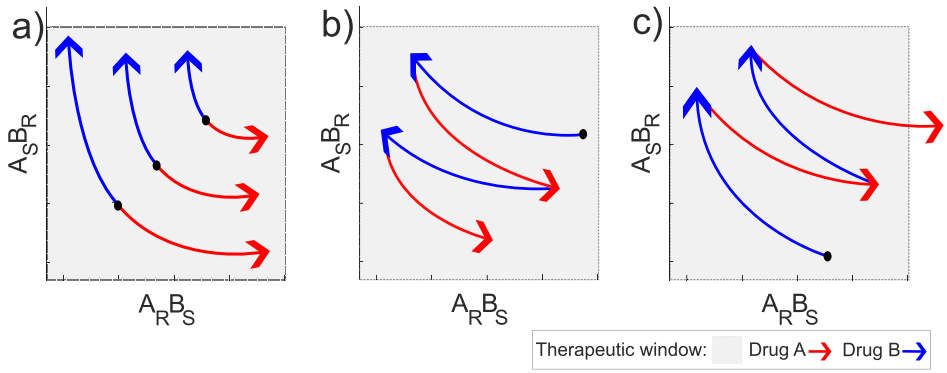

Fig. 3. Illustrative dynamic evolution of mutual collateral sensitivity cycling. Exposure to drug A reduces the concentration of A_SB_R but allows the escape of A_RB_S. Oppositely, exposure to drug B reduces the concentration of A_RB_S but induces the escape of A_SB_R. a) A proper balance between the dynamic of drugs A and B implies that the total population can be feasibly bounded. b) The best scenario of mutual collateral sensitivity implies the asymptotic stability of the origin. c) Despite a mutual collateral sensitivity, it may not be feasible to prevent the escape of the infection.

diseases (Duvigneau et al., 2016; Sharma-Chawla et al., 2019; Tetteh et al., 2023), that is $K \approx \infty$ within the therapeutic window. Thus, the nonlinear model described by model (1) can be simplified to a linear model, since $(1 - \frac{\sum_{i=1}^{n} x_i}{K}) \approx 1$ inside $\mathbb{T}$:

$$\dot{x}(t) = A_{\sigma(t)}x(t) + \mu M_{\sigma(t)}x(t), \tag{3}$$

with

$$A_\sigma = \begin{pmatrix} \alpha_1^\sigma - \delta_1^\sigma & 0 & \cdots & 0 \\ 0 & \alpha_2^\sigma - \delta_2^\sigma & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \alpha_n^\sigma - \delta_n^\sigma \end{pmatrix}, \; M_\sigma = \begin{pmatrix} 0 & m_{1,2}^\sigma & \cdots & m_{1,n}^\sigma \\ m_{2,1}^\sigma & 0 & \cdots & m_{2,n}^\sigma \\ \vdots & \vdots & \ddots & \vdots \\ m_{n,1}^\sigma & m_{n,2}^\sigma & \cdots & 0 \end{pmatrix},$$

where A_σ represents the susceptibility profiles of the n strains to antibiotic σ, and M_σ represents the adjacency matrix of the mutation network when drug σ is active.

Model (3) is described in continuous-time. In practice, we consider a regular treatment interval $\tau > 0$, during which treatment is fixed. If we use $k \in \mathbb{N}$ to denote the number of discrete intervals, then the discretization of model (3) is given by:

$$x(k+1) = \Lambda_{\sigma(k)}x(k), \tag{4}$$

where $x(k) = x(k\tau)$ is the sampled state and $\Lambda_\sigma = exp(A_\sigma + \mu M_\sigma)\tau$. We assume the following.

Assumption 3. Matrix Λ_σ is nonsingular for all $\sigma \in \Sigma$.

The control invariant set for the discrete switched system (4) within the therapeutic window $\mathbb{T}$ can be defined as follows:

Definition 5. (CIS within $\mathbb{T}$). Given the therapeutic window $\mathbb{T} \subset \mathbb{R}^n$, a set $\Omega \subseteq \mathbb{T}$ is said to be a control invariant set of the discrete switched system (4) if for every state $x(k) \in \Omega$ there is $\sigma \in \Sigma$ such that $x(k+1) \in \Omega$.

To characterize a CIS, we use the concept of controllable sets (Anderson, Gonzalez, et al., 2021). The controllable set to Ω is given by all states that can be driven in one step to Ω. It can be formally defined as follows:

$$\mathcal{S}(\Omega) := \{x(k) \in \mathbb{R}^n_{\geq 0} : \exists \; \sigma \in \Sigma \text{ s.t. } x(k+1) \in \Omega\}.$$

For the discrete system (4) the controllable set can be characterized by the following property (Anderson, Gonzalez, et al., 2021):

Property 3. Given a set Ω, the controllable set to Ω for the switched system (4) is given by:

$$\mathcal{S}(\Omega) = \bigcup_{\sigma \in \Sigma} \Lambda_\sigma^{-1}\Omega \tag{5}$$

The following result is well established on set-control theory (Blanchini & Miani, 2015):

Property 4. Ω is a control invariant set (CIS) if and only if $\Omega \subseteq \mathcal{S}(\Omega)$.

We propose the following algorithm to compute a control invariant set within $\mathbb{T}$:

Algorithm 1. CIS within $\mathbb{T}$ for the system (4)

Data: $\Lambda_\sigma, \mathbb{T}, \quad \sigma = 1, 2, \ldots, N$
Result: CIS Ω
$\Omega_0 = \mathbb{T}$;
for $i \geq 0$ **do**
  $\Omega_{i+1} = \Omega_i \cap \mathcal{S}(\Omega_i)$;
  if $\Omega_i \subseteq \mathcal{S}(\Omega_i)$ **then**
    return $\Omega = \Omega_i$;
    stop;
  end
end

Remark 3. Algorithm 1 follows the approach outlined in (Fiacchini & Jungers, 2014). The key difference is that we consider the intersection with the therapeutic window in each iteration. This way, we find the control invariant set within window $\mathbb{T}$.

The characterization of Ω allows to minimize the following cost function, usually utilized in set-control theory (Anderson et al., 2018):

$$V_\Omega(x(0); \sigma(\cdot)) = \sum_{k=0}^{\infty} \min_{y \in \Omega} \|x(k) - y\|^2, \tag{6}$$

for $x(0) \in \Omega$ and the decision function $\sigma(\cdot)$. Function $\min_{y \in \Omega} \|x(k) - y\|^2$ represents the distance from state $x(k)$ to the set Ω, for a closed set Ω. If $\Omega \subseteq \mathbb{T}$, the minimization of function (6) is equivalent to the minimization of function (2). The following proposition describes the optimal switching law $\sigma_{CIS}(\cdot)$ that minimizes the cost function (6).

Proposition 5. (Switching law σ_{CIS}). If Algorithm 1 converges to the set Ω, then for every $x(0) \not\equiv \Omega$ there is a feasible discrete control law $\sigma_{CIS}(\cdot) : \mathbb{N} \to \{1, \ldots, N\}$ such that $x(k) \not\equiv \Omega$ for all $k \geq 0$, where $x(k)$ is given by Equation (4).

Proof. Consider $x(0) \in \Omega$, then there is $i \geq 0$ such that $x(0) \in \Omega_i$, where Ω_i is determined by the last iteration of the Algorithm 1. By the stop condition, Ω_i is such that $\Omega_i \subseteq \mathcal{S}(\Omega_i)$. This implies there is $\sigma_{CIS}(0) \in \Sigma$ such that $x(1) \in \Omega_i$, with $x(1) = \Lambda_{\sigma_{CIS}(0)} x(0)$. Note that $x(1) \in \Omega_i$, then by induction we can determine a switching law $\sigma_{CIS}(k)$ for all $k \geq 0$ such that $x(k) \in \Omega_i$, which concludes the proof. ∎

The results on Proposition 5 remain valid for the case of nonlinear modes. However, the numerical solution of Equation (5) requires appropriate numerical methods for nonlinear modes (Li & Liu, 2016).

5. Numerical results

5.1. Antibiotic interactions shape the dynamics of cycling drugs

In what follows, we present some numerical simulations demonstrating the impact of collateral sensitivity, cross-resistance, and insensitive interactions on the population evolution described by the system (1).

Fig. 4 shows two mutation networks for three antibiotics. For the first case in Fig. 4a, we consider antibiotics Aztreonam ($A = AZE$), Amikacin ($B = AMI$), and Imipenem ($C = IMI$). These antibiotics show only insensitive collateral effects; see Fig. 1a, giving rise to a combinatorial network with 2^3 different phenotypic states. These interactions lead to mutations that follow a dead-end path to the multidrug resistance strain $A_R B_R C_R$, as predicted by Property 1.iii. Proposition 2.ii suggests the origin is an unstable equilibrium for this combination of antibiotics.

For the second case in Fig. 4b, we consider antibiotics Aztreonam ($A = AZE$), Ciprofloxacin ($B = CIP$), and Tobramycin ($C = TOB$). These antibiotics show collateral sensitivity and cross-resistance profiles, see Fig. 1a. Fig. 4b gives the combinatorial network in this case. Significantly, drug interactions, in this case, alter potential mutation pathways, so not all theoretically possible phenotype strains manifest in the network. The bacteria cannot mutate to become fully resistant to all drugs.

In both scenarios, we consider a preexistent wild-type strain (10^{10} number of bacteria) for bacterial evolution. We simulate bacterial growth under 50-h cyclic dosing of antibiotics A, B, and C over 600 h (Fig. 4c). Fig. 4a (right) shows that this sequential therapy fails with antibiotics $A = AZE$, $B = AMI$, and $C = IMI$. Fig. 4b (right) shows this therapy generates a cyclical pattern of population fluctuations with antibiotics $A = AZE$, $B = CIP$, and $C = TOB$.

5.2. Control law by characterizing a control invariant set

To design a control strategy aimed at combating the evolution of resistance, we consider the antibiotics Tobramycin ($A = TOB$), Carbenicillin ($B = CAR$), and Colistin ($C = COL$) with a high degree of collateral sensitivity (see Fig. 2b left). The

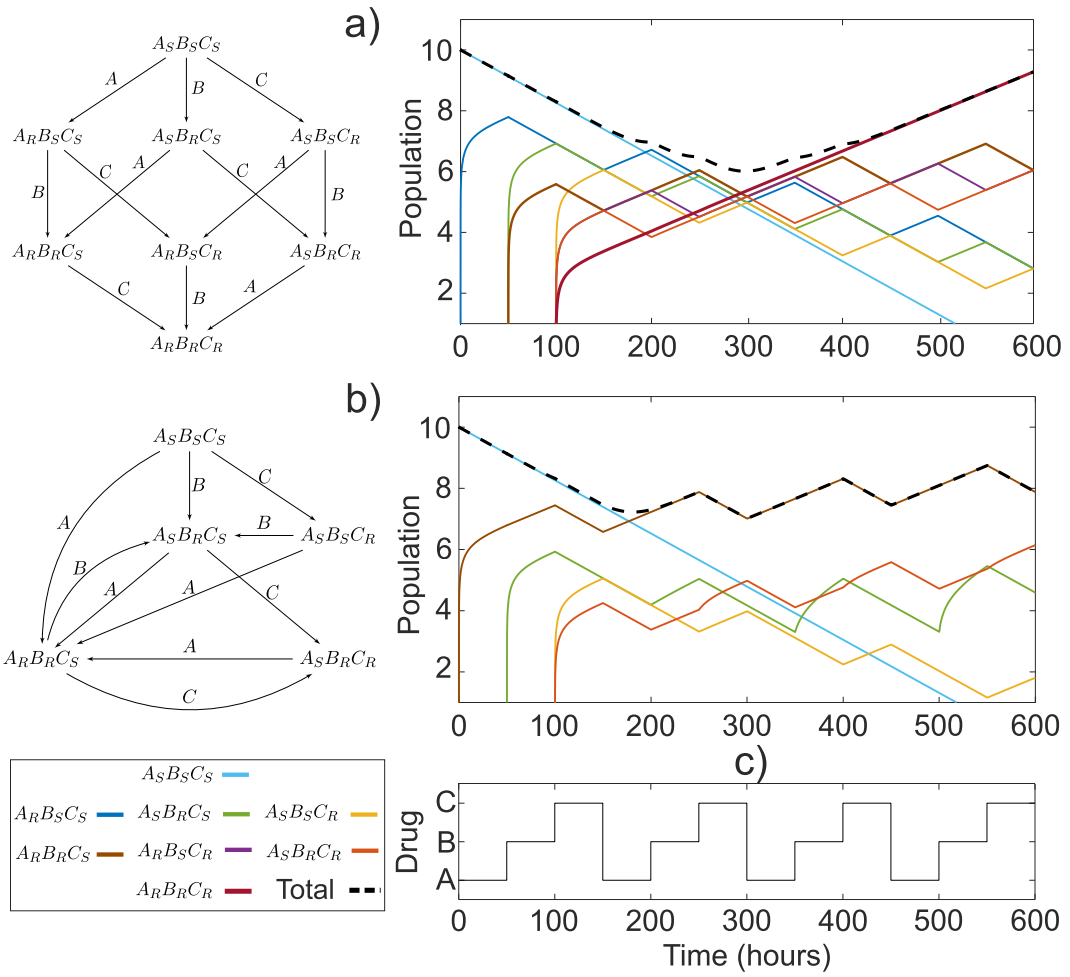

Fig. 4. Combinatorial mutation network and dynamic evolution of cycling antibiotics. a) Aztreonam ($A = AZE$), Amikacin ($B = AMI$), and Imipenem ($C = IMI$). The interactions between these antibiotics give rise the multi-resistant state $A_RB_RC_R$, which leads to the escape of the total population. b) Aztreonam ($A = AZE$), Ciprofloxacin ($B = CIP$), and Tobramycin ($C = TOB$). The interactions between these antibiotics prevent the emergence of the multi-resistant state. c) Cycling antibiotics A, B, and C, 50hr cyclic dosing of drugs over 600hr, affecting a population given initially by the wild-type (10^{10} number of bacteria).

combinatorial mutation network is given in Fig. 2b right. The states present in the network are the wild-type $A_SB_SC_S$ and the emerging variants $A_RB_SC_R$, $A_RB_SC_S$, and $A_SB_RC_S$. The wild-type strain's sensitivity to all antibiotics means we can examine only the balance between the three emerging states to determine whether the colony shrinks or escapes. We propose the therapeutic window given by the polytope:

$$\mathbb{T} = \{z \in \mathbb{R}^3 : \mathbb{T}_A z \leq \mathbb{T}_b\},$$

where $\mathbb{T}_A$ and $\mathbb{T}_b$ are given by:

$$\mathbb{T}_A = \begin{bmatrix} 0 & 0 & -1 \\ -1 & 0 & 0 \\ 0 & 0.7071 & 0.0031 \\ 0 & -1 & 0 \\ 0.7071 & 0 & 0 \\ 0 & 0.2369 & 0.6226 \\ 0 & 0 & 0.7071 \end{bmatrix}, \quad \mathbb{T}_b = \begin{bmatrix} 0 \\ 0 \\ 0.7071 \\ 0 \\ 0.7071 \\ 0.7458 \\ 0.7071 \end{bmatrix}.$$

The matrix $\mathbb{T}_A$ and the vector $\mathbb{T}_b$ define the therapeutic window $\mathbb{T}$ as a polytope in the non-negative octant of $\mathbb{R}^3$. For more details on its characterization, see the software availability section.

Algorithm 1 converges to a non-empty control invariant set Ω within $\mathbb{T}$, given in Fig. 5a, where a vector field of the switched system is shown for the boundary of the set. On the other hand, Fig. 5b shows that the controllable set to Ω, $\mathcal{S}(\Omega)$, fulfills Property 4, i.e., $\Omega \subseteq \mathcal{S}(\Omega)$, showing that Ω is a control invariant set.

By applying Property 3 we derive the following implication:

$$\Omega \lhd \bigcup_{\sigma \in \{TOB, CAR, COL\}} \Lambda_\sigma^{-1}\Omega.$$

Note that, if state $x(k) \in \Omega$, then $x(k) \in \Lambda_\sigma^{-1}\Omega$ for some $\sigma \in \{TOB, CAR, COL\}$, then is feasible that $x(k+1) = \Lambda_\sigma x(k) \in \Omega$ for some $\sigma \in \{TOB, CAR, COL\}$. In Fig. 5c, we consider the following initial state:

$$(A_R B_S C_S, A_S B_R C_S, A_R B_S C_R) = (1, 1, 0) \in \Omega.$$

We can easily verify that $x(0) \in \Lambda_\sigma^{-1}\Omega$ with $\sigma = COL$. Hence, we apply antibiotic COL as long as the trajectory remains within $\Lambda_{COL}^{-1}\Omega$. In this way, we ensure that the trajectory stays within the set Ω. However, after 80 h, the trajectory escapes $\Lambda_{COL}^{-1}\Omega$ and enters $\Lambda_{CAR}^{-1}\Omega$. At this point, we must switch to CAR to prevent the trajectory from escaping Ω. The trajectory remains within $\Lambda_{CAR}^{-1}\Omega$ until 169 h; at this point, it escapes $\Lambda_{CAR}^{-1}\Omega$ but enters $\Lambda_{TOB}^{-1}\Omega$. Here, we switch to TOB to keep the population within Ω. We apply TOB to maintain the trajectory within Ω until 260 h. Following this reasoning, we can control the population indefinitely inside the therapeutic window $\mathbb{T}$. In Fig. 5h, the cycling strategy between drugs TOB, CAR, and COL can be observed. Fig. 5d shows the evolution of the total population given by $Total = A_R B_S C_S + A_S B_R C_S + A_R B_S C_R$, and Fig. 5e-g illustrate the states' evolution separately under this switching law σ_{CIS}.

Remark 4. For parameter simulations, we use mutation rate $\mu = 10^{-4}h^{-1}$ and carrying capacity $K = 10^{10}$. Also, we adopt qualitative values for growth and clearance rates, such that $\alpha^\sigma - \delta^\sigma < 0$ for states sensitive to drug σ, and $\alpha^\sigma - \delta^\sigma > 0$ for states resistant to drug σ.

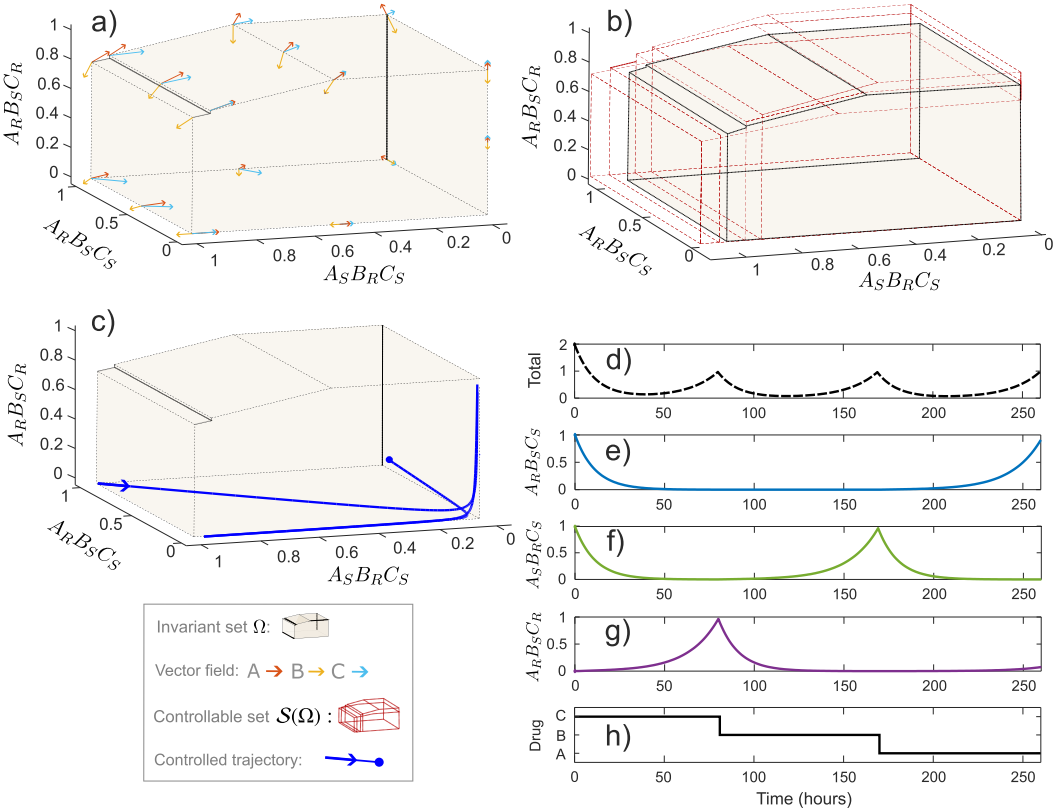

Fig. 5. Control law within therapeutic window $\mathbb{T}$. Set-control analysis for antibiotics $A = TOB$, $B = CAR$, and $C = COL$ with a high degree of collateral sensitivity. a) Control invariant set Ω within the therapeutic window $\mathbb{T}$ for states $A_R B_S C_S$, $A_S B_R C_S$, and $A_R B_S C_R$. b) Invariant set fulfilling condition $\Omega \subseteq \mathcal{S}(\Omega)$ c) A controlled trajectory inside set Ω. From d) to g) Total population, and $A_R B_S C_S$, $A_S B_R C_S$, and $A_R B_S C_R$ state dynamics over time, respectively. h) Switching control law σ_{CIS}.

6. Conclusion

In this study, we integrated a dataset from (Imamovic et al., 2018) on the evolution of *P. aeruginosa* under sequential antibiotic exposure into a dynamic flow. We used a birth/death switching model to capture population dynamics to sequential therapies. Our results indicate that multidrug-resistant bacteria can emerge when the wild-type strain is exposed to inadequate cycles of antibiotics with high cross-resistance or insufficient collateral sensitivity. We analyzed the stability of the healthy equilibrium under specific therapies and leveraged set-control theory to develop a cycling law that maintains the population within a therapeutic window. Multiple *in silico* simulations demonstrated the dynamics of cycling antibiotics with different collateral interactions.

CRediT authorship contribution statement

Alejandro Anderson: Writing – original draft, Methodology, Formal analysis, Conceptualization. **Matthew W. Kinahan:** Writing – original draft, Visualization. **Alejandro H. Gonzalez:** Writing – original draft, Formal analysis. **Klas Udekwu:** Writing – original draft, Conceptualization. **Esteban A. Hernandez-Vargas:** Writing – original draft, Supervision, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Software availability

https://github.com/systemsmedicine/invariant_sets_drug_resistance.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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