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Switching Logistic Maps to Design Cycling Approaches Against Antimicrobial Resistance

E.A. Hernandez-Vargas^{1,2}, C. Parra-Rojas² and S. Olaru³

Abstract—Antimicrobial resistance is a major threat to global health, in particular, new SARS-CoV-2 variants during the COVID-19 pandemic. Scheduling cycling therapies by targeting phenotypic states associated with specific mutations can help us to eradicate pathogenic variants. In this paper, we introduce a logistic switching model to abstract mutation networks of collateral resistance. We found conditions for which the unstable zero-equilibrium of the logistic maps can be stabilized through a switching signal. That is, persistent populations can be eradicated through tailored switching regimes.

Starting from an optimal-control formulation, the switching policies show their potential in the stabilization of the zero-equilibrium for dynamics governed by logistic maps. Simulation results show the applicability of Parrondo’s Paradox to design cycling therapies against drug resistance.

I. INTRODUCTION

Antimicrobials such as antibiotics and antivirals are powerful antidotes to fight against infections. However, the misuse and overuse of drugs have led to *drug resistance*, which can be roughly defined as the ability of a microorganism to replicate in the presence of a drug. For instance, during the COVID-19 pandemic, there have been new variants such as the B.1.1.7 in the UK and B.1.351 in South Africa which are more resistant to neutralization by convalescent plasma and vaccine sera [1].

Modeling of infectious diseases has been developed at different scales and pursuing different goals [2]. Between-hosts models have helped to propose new vaccination strategies or support public health strategies [3], [4]. On the other hand, for within-host infection, mathematical modeling has been used to capture the dynamics of different infectious diseases inside the host and understand the interaction of the pathogen and the immune system, as well as the scheduling of therapies [5], [6]. Most mathematical models to represent microbial dynamics are shown to be based on variations of the classical Verhulst logistic growth equation. For instance, the logistic model has served as a key mathematical tool in representing the growth of tumors [7] and microbes [8].

The logistic model indicates that a stable population has a saturation level, known as the *carrying capacity* which forms a numerical upper bound on the growth size [9]. While theoretical approaches to mitigate drug resistance have been

mainly developed at between-host level [10], too little has been directed at investigating within-host strategies against antimicrobial resistance [6].

Here, for a given mutation network, we introduce a logistic switching map to capture the drug resistance dynamics of bacteria. This model is instrumental to design control strategies to minimize the ability of a bacterial sub-population to survive a drug concentration, known as *persistence*. However, designing switching strategies in dynamical systems is not trivial and leads to a context similar to the so-called Parrondo’s Paradox [11], in which two losing games are combined in a determined order as to obtain a winning game [12]. Previous numerical simulations of switching logistic maps [11] have shown that switching decisions may follow either the “undesirable + undesirable = desirable” or the “chaotic+chaotic = order” dynamics.

In the next sections, the mathematical abstraction of antimicrobial resistance dynamics is formulated in the form of switched systems. Subsequently, evolutionary and control algorithms are used to find sub-optimal switching policies. Simulation results show the applicability of Parrondo’s Paradox to design cycling therapies against drug resistance.

II. LOGISTIC SWITCHING MAPS

Throughout, \mathbb{R} denotes the field of reals, \mathbb{R}^n stands for the vector space of all n -tuples of real numbers. $\mathbb{R}^{n \times n}$ is the space of $n \times n$ matrices with real entries. \mathbb{N} denotes the set of natural numbers, while the restriction to positive natural numbers bounded by q will be used under the compact notation $\mathbb{N}_q = \{n \in \mathbb{N} : 1 \leq n \leq q\}$. For x in \mathbb{R}^n , x_i denotes the i^{th} component of x , and the notation $x \succeq 0$ means that $x_i \geq 0$ for $1 \leq i \leq n$. $\mathbb{R}_+^n = \{x \in \mathbb{R}^n : x \succeq 0\}$ denotes the non-negative orthant in \mathbb{R}^n . The transpose is represented as A' .

Using a switching signal $\sigma(t)$, one can formally deal with a selection mechanism among $q \in \mathbb{N}$ possible subsystems. These subsystems are represented mathematically by a family of functions $f_i(\cdot) : \mathbb{R}^n \rightarrow \mathbb{R}^n$, $i \in \mathbb{N}_q$ which characterize the right hand side of ordinary differential equation. Based on these elements, one can define a switched non-linear autonomous system as follows:

$$\dot{x}(t) = f_{\sigma(t)}(x(t)), \quad (1)$$

where $x(t) \in \mathbb{X}$ is the system state at time t , and the state space \mathbb{X} is a closed subset of \mathbb{R}^n . Given the initial condition $x(0) = x_0$ at time $t_0 = 0$, the solution of (1) is denoted $x(t, x_0, \sigma(t))$.

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Problem 1: In this work, $\sigma(\cdot)$ is considered as the only manipulable control signal for the system (1). The primary goal would be to design, whenever this is possible, a switching path to make the origin of the system (1) stable. However, for practical application of the policy described in the next sections and biological reasons, we relax the problem to the design of a sub-optimal switching path $\sigma(\cdot)$ that yields a minimal cost functional \mathbb{J} in a fix horizon of time (t_f).

A. Modeling Antimicrobial Resistance as Logistic Maps

To abstract the dynamics of the different genotypes during drug therapy, the following switched logistic model is described:

$$\dot{x}_i(t) = \rho_{i,\sigma(t)} x_i(t) \left(1 - \frac{x_i(t)}{K}\right) - \delta x_i(t) + \mu \sum_{j \neq i}^{\eta} m_{i,j} x_j(t). \quad (2)$$

The population of different η pathogenic variants are represented by the state variable x_i . $\rho_{i,\sigma(t)}$ is the proliferation rate of the variant i under the treatment $\sigma(t) \in \{1, 2, 3, \dots, N\}$ which can be changed at any time t . N is the total number of possible drug therapies that can be administered. The maximum carrying capacity is K . δ is the clearance of the variant x_i .

The mutation rate is represented by μ . The genetic connections between genotypes are represented by $m_{i,j} \in \{0, 1\}$, that is, $m_{i,j} = 1$ if and only if it is possible for genotype j to mutate into genotype i . An illustrative example to represent the mutation network for n variant and m therapies is presented in Figure 1. However, more complex mutation trees can be considered.

III. STABILITY ANALYSIS WITHOUT SWITCHING OF THERAPIES

Let us consider the system (2) and focus on the case of a single therapy. Without loss of generality, we simplify the notation by taking $\rho_{i,\sigma(t)} \rightarrow \rho_i$, and normalize the bacterial populations by the carrying capacity of the system, $x_i/K \rightarrow x_i$, so that

$$\dot{x}_i(t) = \rho_i x_i(t) (1 - x_i(t)) - \delta x_i(t) + \mu \sum_{j \neq i}^{\eta} m_{i,j} x_j(t). \quad (3)$$

The strains that mutate act as a *source* to one or more strains, whereas each strain can have at most one source, with the case of zero sources corresponding to the wildtype. In other words, we do not take into account the case when two or more different strains can yield exactly the same genotype upon mutation, since this is unlikely in a real-life scenario. At the same time, and for the same reason, all *backwards* mutations are forbidden, so that if $m_{j,i} \neq 0$ then necessarily $m_{i,j} = 0$. More generally, there is no way of coming back to strain i starting from strain j ; that is, once a mutation from strain i to strain j occurs, there exists no possible sequence of L mutations $x_{j1} \rightarrow x_{j2} \rightarrow \dots \rightarrow x_{jL} \rightarrow x_i$ for any length L .

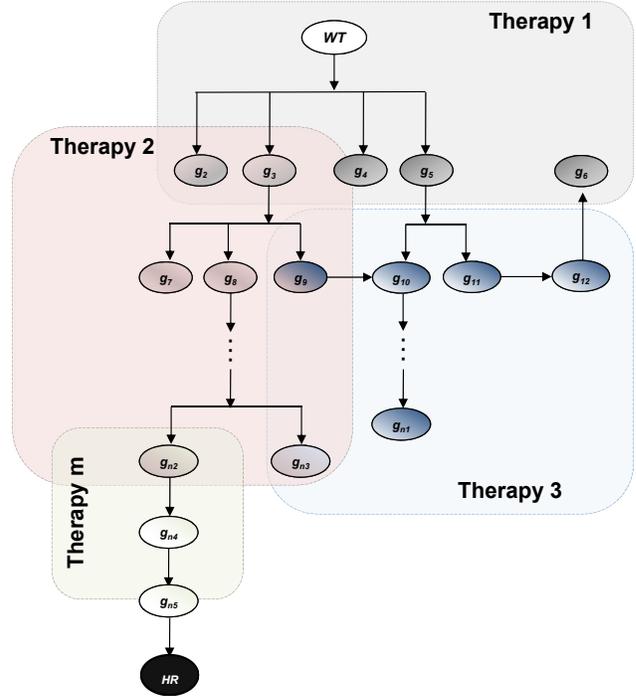


Fig. 1. Illustrative mutation tree for n variants and m therapies. WT represents the wild type. Different variants would mutate as effect of a given therapy which is indicated with color squares. The appearance of a highly resistant variant (black circle HR) is hypothesized as a consequence of a sequence of mutations, meaning that it is resistant to all available therapies.

The equilibrium points of the system with n strains, which we denote by $(\bar{x}_1, \dots, \bar{x}_n)$, can be found recursively by solving for $\dot{x}_i = 0$ in Eq. (3), and have the form

$$\bar{x}_i = \begin{cases} \left\{ 0, \max\left(\frac{\lambda_i}{\rho_i}, 0\right) \right\}, & \bar{s}_i = 0 \\ \frac{\lambda_i + \sqrt{\lambda_i^2 + 4\mu\rho_i\bar{s}_i}}{2\rho_i}, & \bar{s}_i > 0 \end{cases} \quad (4)$$

Here, we have denoted by \bar{s}_i the equilibria of the strain that acts as a source of x_i ; this means that, if x_i results from the mutation of a certain x_k , then $\bar{s}_i = \bar{x}_k$. At the same time,

$$\lambda_i = \rho_i - \delta - \mu c_i \quad (5)$$

where c_i is the number of "offsprings" of strain i .

Theorem 1: $\lambda_i > 0$ ensures the existence of the equilibrium point with $\bar{x}_i > 0$ and $\bar{x}_k > 0$ for all x_k that can be reached starting from x_i , otherwise $\bar{x}_k = 0$ for $\lambda_k < 0$. This point is locally stable if, additionally, $\lambda_k < 0$ for all other k .

Proof: The Jacobian of the system evaluated at a given equilibrium point can be decomposed as $J = D + \mu M_1$, where M_1 contains the off-diagonal elements of M , and thus only encodes the mutations between strains. The entries of

D are given by

$$d_{ii} = \rho_i - \delta - \mu c_i - 2\rho_i \bar{x}_i$$

The properties derived above for the constraints on the mutation patterns imply that M_1 can be thought of as the adjacency matrix of a directed acyclic graph (DAG) [13]; therefore, there exists a topological ordering of the strains that renders M_1 strictly upper triangular [14]. In other words, we can relabel the strains so that for every mutation from x_i to x_j , we have $i < j$. The Jacobian becomes upper triangular, and its eigenvalues will be given by the entries of D . At the origin, the i -th eigenvalue will correspond to λ_i from Eq. (5). On the other hand, the eigenvalues associated with non-zero coordinates are given by

$$\Delta_i = -\sqrt{\lambda_i^2 + 4\mu\rho_i \bar{s}_i}$$

and they are always negative. As a consequence, whenever a strain x_i is able to persist by itself – which translates into $\lambda_i > 0$ – then all of its offsprings will also persist, as seen from Eq. (4), even if they would be eradicated in isolation. If all other strains in the system are unable to persist in isolation, the eigenvalues associated to the equilibrium point where $\bar{x}_i > 0$, with $\bar{x}_k > 0$ if k corresponds to a offspring of i (that is, $\bar{s}_k = \bar{x}_i$) and $\bar{x}_k = 0$ otherwise, will be given by

$$\begin{aligned} -\lambda_i &< 0 \\ \Delta_k &< 0 & \bar{s}_k &= \bar{x}_i \\ \lambda_k &< 0 & \bar{s}_k &\neq \bar{x}_i \end{aligned}$$

and the equilibrium is thus asymptotically stable. \blacksquare

Theorem 2: If we explicitly separate the zero and non-zero equilibrium coordinates—so that the i -th element of an equilibrium point is either 0 or \bar{x}_i —then the set defined by

$$\Omega = \{x \in \mathbb{R}^n \mid 0 \leq x_i \leq \bar{x}_i \ \forall i\}$$

is positively invariant with respect to the system described by Eq. (3). Equivalently, for any given initial condition $x_0 \in \Omega$, the solution to (3) satisfies $x(t) \in \Omega \ \forall t > 0$.

Proof: Let us recall that

$$\dot{x} = f(x) = (f_1(x), \dots, f_n(x)),$$

and consider the boundaries of Ω , given by

$$\begin{aligned} B_i^{(1)} &= \{x \mid x_i = 0, \quad 0 < x_j < \bar{x}_j \quad \forall j \neq i\} \\ B_i^{(2)} &= \{x \mid x_i = \bar{x}_i, \quad 0 < x_j < \bar{x}_j \quad \forall j \neq i\} \end{aligned}$$

The invariance condition [15] translates into $f \cdot \hat{n} \geq 0$ along the boundaries above, where \hat{n} is a normal vector pointing towards Ω . We note that the normal vectors that correspond to each boundary are given by $\hat{n}_i^{(1)} = \hat{e}_i$ for $B_i^{(1)}$ and $\hat{n}_i^{(2)} = -\hat{e}_i$ for $B_i^{(2)}$, where \hat{e}_i is the i -th unitary vector, $(\hat{e}_i)_j = \delta_{ij}$, with δ_{ij} the Kronecker delta.

Choosing an initial condition x_0 along $B_i^{(1)}$, with $x_j = p_j \in [0, \bar{x}_j] \ \forall j \neq i$ we have

$$f(x_0) \cdot \hat{n}_i^{(1)} = f_i(x_0) = \mu \sum_{j \neq i}^{\eta} p_j m_{i,j} \geq 0 \quad \forall i$$

Similarly, for the case of $B_i^{(2)}$, we choose an initial condition x_0 with $x_i = \bar{x}_i$ and $x_j = p_j \in [0, \bar{x}_j] \ \forall j \neq i$; this yields

$$\begin{aligned} f(x_0) \cdot \hat{n}_i^{(2)} &= -f_i(x_0) \\ &= -\rho_i \bar{x}_i (1 - \bar{x}_i) + \delta \bar{x}_i + \mu c_i \bar{x}_i + \mu \sum_{j \neq i}^{\eta} m_{i,j} p_j \end{aligned}$$

Now, we use the fact that $(\bar{x}_1, \dots, \bar{x}_n)$ is an equilibrium point of the system, so that

$$\rho_i \bar{x}_i (1 - \bar{x}_i) - \delta \bar{x}_i - \mu c_i \bar{x}_i + \mu \sum_{j \neq i}^{\eta} m_{i,j} \bar{x}_j = 0$$

and

$$-\rho_i \bar{x}_i (1 - \bar{x}_i) + \delta \bar{x}_i + \mu c_i \bar{x}_i = \mu \sum_{j \neq i}^{\eta} m_{i,j} \bar{x}_j$$

Hence,

$$\begin{aligned} f(x_0) \cdot \hat{n}_i^{(2)} &= \mu \sum_{j \neq i}^{\eta} m_{i,j} (\bar{x}_j - p_j) \\ &\geq 0 \quad \forall i \end{aligned}$$

since $0 \leq p_j \leq \bar{x}_j \ \forall j \neq i$.

Therefore, Ω is positively invariant with respect to the system (3). \blacksquare

Corollary 1: Given the system (3) with $\mu = 0$, the equilibrium at the origin ($\bar{x}_k = 0$) is globally asymptotically stable when

$$\rho_i < \delta \quad \forall i \in \{1, \dots, n\}.$$

Proof: We have seen above that the origin is a locally asymptotically stable equilibrium point of (3) when $\rho_i < \delta + \mu c_i, \ \forall i$ simultaneously. In order to establish the global stability of the origin in Ω , let us choose a Lyapunov function

$$V(x) = \sum_i^{\eta} x_i$$

We note that $V \geq 0, \ \forall x \in \Omega$, and $V = 0$ iff $x = 0$. Now,

$$\begin{aligned} \dot{V}(x) &= \sum_i^{\eta} \dot{x}_i \\ &= \sum_i^{\eta} \rho_i x_i (1 - x_i) - \delta x_i \\ &= \sum_i^{\eta} (\rho_i - \delta) x_i - \sum_i^{\eta} \rho_i x_i^2 \end{aligned} \quad (6)$$

From the expression above, $\rho_i < \delta \ \forall i$ ensures that $\dot{V} \leq 0 \ \forall x \in \Omega$, and $\dot{V} = 0$ iff $x = 0$. Therefore, the origin is globally asymptotically stable under this condition. \blacksquare

Remark 1: The condition above arises trivially from considering all strains as independent of one another, in absence of mutations, and it is more restrictive than the condition found previously, since mutations have a stabilizing effect on the origin. However, Eq. (6) can be employed as a basis to establish a switching policy in order to ensure the eradication of the pathogen in the case with mutations under a set of different available therapies.

IV. SWITCHING THERAPIES

Based on the general model (2), the problem formulation can then be broadly described as the design of a switching policy for the gradual eradication of pathogenic strains. To formally state the problem we need the following definitions:

Definition 1: A switching policy is the cycling choice between therapies σ with a period T_σ , which can be represented by a piecewise constant function $\sigma(t) : \mathbb{R} \rightarrow \{1, 2, \dots, N\}$. $\sigma(t)$ remains constant for all $t \in [kT_\sigma, (k+1)T_\sigma)$.

Definition 2: A periodic cycling policy is the periodic switching between therapies i with regular intervals T_i . For example, for the case of two therapies with periods T_1 and T_2 , we have $\sigma(T_1) = 1$ and $\sigma(T_2) = 2$, then the periodic cycling policy sequence is

$$\sigma = \{\underbrace{\sigma=1}_{T_1}, \underbrace{\sigma=2}_{T_2}, \dots, \underbrace{\sigma=1}_{T_1}, \underbrace{\sigma=2}_{T_2}\}. \quad (7)$$

Next, we describe the design of switching policies of the system (2) in a discrete-time version. To this end, we will divide the analysis into two parts. The first is assuming the variants do not mutate that is $\mu = 0$, this is still an interesting biological scenario as the main goal is to eradicate different variants of a pathogenic micro-organism. The second part will consider mutation, as $\mu \neq 0$ for the case of not backward mutations, as from the evolution point of view, it is very difficult that this type of mutation occurs.

A. Switching Therapies Assuming No Mutations ($\mu = 0$)

Assuming that the variants do not present mutations, that is $\mu = 0$, we can re-parameterize the model (2) for a fixed period of treatment ($\sigma(t) = \sigma$) as follows:

$$\dot{x}_i(t) = b_{i,\sigma} x_i(t) \left(1 - \frac{x_i(t)}{a_{i,\sigma}}\right) \quad (8)$$

where $b_{i,\sigma} = \rho_{i,\sigma} - \delta$ and $a_{i,\sigma} = Kb_{i,\sigma}/\rho_{i,\sigma}$. Equation (8) has the conventional logistic form which can be solved analytically or by the nearly exact method [16], thus the recursive form of (2) is as follows:

$$z_i(k+1) = \frac{a_{i,\sigma} z_i(k)}{z_i(k) + (a_{i,\sigma} - z_i(k))e^{-b_{i,\sigma} T_\sigma}} \quad (9)$$

where k is the discrete-time step, and T_σ is the period where the therapy σ is provided.

Theorem 3: Let the dynamics in (2) without mutation ($\mu = 0$) and a periodic cycle (T_σ) for each of the therapies ($\sigma = 1, \dots, N$). The different variants will be eradicated if and only if the following condition is satisfied

$$\frac{\sum_{\sigma=1}^N \rho_{i,\sigma} T_\sigma}{T} < \delta \quad (10)$$

where $T = \sum_{\sigma=1}^N T_\sigma$.

Proof: Considering the initial condition $z_0 = z(0) = 0$ and the first two cycles of therapies $\sigma = 1, 2$ with their respective period $T_{\sigma=1,2}$, by construction, we have the Jacobian matrix $J_{\sigma=1,2}$ at the origin as follows:

$$J_{\sigma=1,2} = e^{b_{i,1}T_1 + b_{i,2}T_2} \quad (11)$$

In a similar vein, we can generalize the Jacobian $J_{\sigma=1,\dots,N}$ in the origin as follows,

$$J_{\sigma=1,\dots,N} = e^{\sum_{\sigma=1}^N b_{i,\sigma} T_\sigma} \quad (12)$$

as $b_{i,\sigma} = \rho_{i,\sigma} - \delta$ and we are interested in the stability of the origin, we check the exponential term to be less than 1, then

$$\sum_{\sigma=1}^N (\rho_{i,\sigma} - \delta) T_\sigma \leq 0 \quad (13)$$

$$\sum_{\sigma=1}^N \rho_{i,\sigma} T_\sigma \leq \delta T \quad (14)$$

$$\frac{\sum_{\sigma=1}^N \rho_{i,\sigma} T_\sigma}{T} < \delta \quad (15)$$

Remark 2: The condition (10) can additionally serve to design the duration of the therapies (T_σ) to eradicate all different variants during the course of an infection if the following inequality system has a solution

$$\begin{cases} \sum_{\sigma=1}^N \rho_{1,\sigma} T_\sigma < \delta T \\ \sum_{\sigma=1}^N \rho_{2,\sigma} T_\sigma < \delta T \\ \vdots \\ \sum_{\sigma=1}^N \rho_{n,\sigma} T_\sigma < \delta T. \end{cases}$$

This can be formulated as a feasibility problem in a linear programming framework. While this could provide a sufficient condition for a possible success of a cycling therapy, the unfeasible solution does not necessarily imply the failure of a switching trajectory to stabilize the origin.

Corollary 2: For a cycle of the therapies with equal time duration, the stability condition (10) can be further simplified to

$$\frac{\sum_{\sigma=1}^N \rho_{i,\sigma}}{N} < \delta$$

Proof: Following the Theorem 3, we have that the period of each therapy is equal, that is $T_1 = T_2 = \dots = T_N$. Then, $\sum_{\sigma=1}^N T_\sigma = NT_\sigma$. Therefore condition (10) becomes independent of T_σ . ■

Remark 3: The corollary 2 points out that in order to eradicate a variant i with cycling therapies, the average expansion of the variant i through the cycling should be less than its contraction.

B. Switching Therapies Assuming Mutations ($\mu \neq 0$)

For the case with mutation ($\mu \neq 0$), a condition similar to (10) is difficult to prove. Model Predictive Control (MPC) appears to be suitable for a sub-optimal application to the biomedical application, due to its robustness to disturbances, model uncertainties and the capability of handling constraints [6], [17], [18], [19]. Thus, the selection of therapies based on the MPC will be employed on similar reasoning as in our previous work based on switched linear systems [18]. In summary, if the total population size is small enough during a finite time of treatment, then there is a significant probability that the population becomes zero. Therefore, we consider the cost

$$J := c'x(t_f) \quad (16)$$

where c is the column vector with all ones. The final time, t_f , is the time point at which the cost function will be evaluated. This cost should be minimized under the action of the switching rule. The decision time to switch therapy is T_c . Thus, the control algorithm predicts the future dynamic behavior of the system over a prediction horizon T_p and computes an open-loop optimal control sequence over the prediction horizon. Then the first decision of the open-loop optimal control is applied. The problem is written as follows:

Problem 2: The internal variables of the controller will be denoted as $(\bar{x}, \bar{\sigma})$, with constraints $x(k) \in \Omega \subseteq R^n$ and $\sigma(\bullet) \in \mathcal{U} \subseteq \mathbb{N}_q^n$. Find

$$\min_{\bar{\sigma}} J(x(k), \bar{\sigma}(\bullet); T_c, T_p),$$

with

$$J(x(k), \bar{\sigma}(\bullet); T_p, T_c) := cx(t + T_p)$$

subject to:

$$\dot{\bar{x}}(\tau) = A_{\bar{\sigma}(\tau)}\bar{x}(\tau) \quad \bar{x}(\tau) = x(k)$$

$$\bar{\sigma}(\tau) \in \mathcal{U}, \quad \forall \tau \in [k, k + T_c]$$

$$\bar{\sigma}(\tau) = \bar{\sigma}(\tau + T_c), \quad \forall \tau \in [k + T_c, k + T_p]$$

$$\bar{x}(\tau) \in \Omega, \quad \forall \tau \in [k, k + T_p]$$

This MPC problem involves a nonlinear and complex optimization problem, the global optimization algorithm known as differential evolution [20] is applied here for the implementation of the algorithm without further tuning of the solver.

V. NUMERICAL SIMULATIONS

In a similar way to [18], simple illustrative examples are considered based on 4 genetic variants and two different therapies. Thus, $\eta = 4$, and 2 drug therapies, $N = 2$. The strain $i = 1$ is considered the Wild Type (WT) which is susceptible to most of the drugs. The Genotype 1 (G_1) is resistant to therapy 1 but it is susceptible to therapy 2. The Genotype 2 (G_2) is resistant to therapy 2, but it is susceptible to therapy 1. The Highly Resistant Genotype (R_G) is a genotype with a low replication rate, but it is resistant to all drug therapies.

Pathogen clearance rate is fixed, $\delta = 0.24 \text{ day}^{-1}$, which corresponds to a half life of slightly less than 3 days [21]. Typical mutation rates are of the order of $\mu = 10^{-4}$. The following mutation matrix is considered:

$$M_u = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 \\ 0 & 1 & 1 & 0 \end{bmatrix} \quad (17)$$

TABLE I
ILLUSTRATIVE SIMULATIONS SCENARIOS FOR DRUG RESISTANCE
BASED ON EQUATION (2)

Scenario	Therapy	WT(x_1)	G_1 (x_2)	G_2 (x_3)	R_G (x_4)
1	1	0.05	0.27	0.05	0.20
	2	0.05	0.05	0.27	0.20
2	1	0.01	0.3	0.1	0.3
	2	0.01	0.1	0.3	0.3
3	1	0.01	0.26	0.05	0.25
	2	0.01	0.15	0.38	0.24

Three different scenarios are proposed as in the Table I. The first scenario, the most ideal case, describes a stabilizable switched system with a full symmetry between G_1 and G_2 , in the sense that first therapy inhibits G_2 with the same intensity that therapy 2 inhibits G_1 . In practice, a small difference in relative replication ability is expected. The second scenario shows a system that can not be stabilized with symmetry between G_1 and G_2 (similar to Case 1) but there is a resistant genotype that can not be stabilized under switching. The third scenario is a switched system that can be stabilized under switching and it has full asymmetry for replication rates in G_1 and G_2 . In general, the finite set of possible

TABLE II
TOTAL PATHOGEN LOAD AT THE END OF TREATMENT OF 200 DAYS WITH
A POSSIBILITY TO SWITCH EVERY 20 DAYS.

Scenario	Optimal (Brute Force)	Optimal (DE Algorithm)	MPC
1	2.3615×10^{-5}	2.3615×10^{-5}	2.3615×10^{-5}
2	1.8851×10^3	1.8851×10^3	1.8851×10^3
3	0.1040	0.1040	0.1141

control values causes problems for many control techniques. Nevertheless in the cause of MPC, having a finite set of options may be an advantage in making the optimization easier to solve.

To compute optimal switching trajectories, we consider a “brute force” approach, which calculates all possible combinations of the therapies ($N_c = t_f/T_c$) and then finding the minimum for the cost function (16). However, this approach is computational unfeasible for checking $N_c > 15$. Thus, in order to check larger treatment combinations we consider the differential evolution algorithm [20].

Assuming a prediction horizon of 100 days (T_p), we consider an MPC strategy as discussed in Problem 2. Table II illustrates treatment scenarios of 200 days (t_f) with decision time to switch therapy of 20 days (T_c), that is $N_c = 10$,

2^{10} combinations. Based on the column of “brute force” results in the Table II, we can conclude that the DE algorithm can find optimal trajectories. While we can not guarantee that the DE algorithm will find the optimal solution for any example, it might find solutions very close to the optimal. In a similar fashion, the MPC was able to find optimal switching trajectories in cases 1 and 2 but not in the case 3. However, MPC finds a solution that is very close to the optimal.

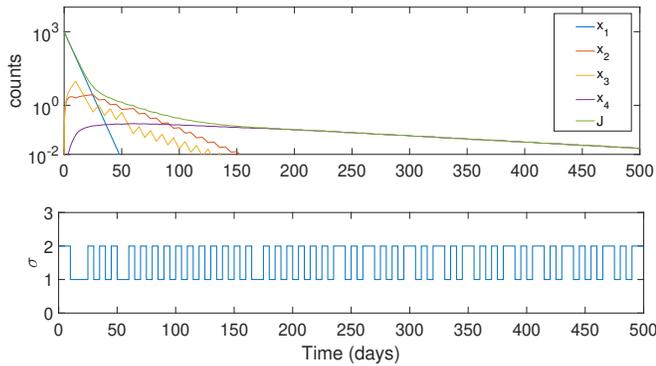


Fig. 2. MPC results for simulation scenario 3. This considers a simulation time of 500 days with a decision time of every 5 days. The wildtype (x_1) is rapidly eradicated. The genotypes 2 (x_2) and 3 (x_3) are gradually eradicated by switching between therapies. It can be observed that the switching rule does not have a clear pattern. The resistant genotype (x_4) is also eradicated due to the appropriate switching between the therapies. Total pathogen load is represented in the cost function J .

The advantage of the MPC would be the computational time, thus we could explore short decision times. Thus, in Fig. 2 we illustrate the performance of MPC for 500 days (t_f) with decision time to switch therapy of 5 days (T_c), that is $N_c = 100$, 2^{100} combinations. This scenario would not be computationally feasible for a “brute force” approach. The upper panel in Fig. 2 shows how the MPC strategy can decrease the pathogen load of the different genotypes. The lower panel in Fig. 2 presents the switching trajectory, which does not have any intuitive pattern, thus highlighting the potential of MPC and other control strategies.

VI. CONCLUSIONS

This paper introduced a switching logistic model with the potential to be the basis for scheduling antimicrobial therapies to mitigate resistance. Considering the case of absence of switching between treatments when backward mutations are forbidden, we derived conditions of global stability presented in Theorem 1. Assuming variants without mutations during treatments, conditions for which unstable zero-equilibrium of the logistic maps can be stabilized through a periodic switching signal are derived in Theorem 3 and Corollary 2. For the case with mutations, switching strategies based on receding horizon optimization such as the MPC were formulated in Problem 2. Numerical results highlighted that the MPC strategy will perform very close to optimal control policies while computational resources are largely decreased.

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