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Josephine N. A. Tetteh [*] **Sorin Olaru** [**] **César Parra-Rojas** [*]
Esteban A. Hernandez-Vargas [***,*]

[*] *Frankfurt Institute for Advanced Studies, Frankfurt, Germany.*
[**] *Laboratory of Signals and Systems, CentraleSupelec, Université Paris-Saclay, Gif-sur-Yvette, France*
[***] *Instituto de Matemáticas, UNAM, Unidad Juriquilla, Mexico.*

Abstract: Drug resistant pathogens are a global public health threat and their control have become a challenging task. In this paper, a mathematical model which describes the general dynamics of microbial resistance is employed. Utilizing a two-strain bacterial population, notions from control engineering and positive switched systems are used to develop control strategies aimed at minimizing the appearance of drug resistant bacteria within the host. Based on the Lyapunov function argument, a switching strategy can be found to ensure stability of the eradication equilibrium under given conditions. Numerical simulations compare switching under different feedback controls and validate the use of the switching strategy in general for the proposed model of bacterial resistance mitigation.

Keywords: Bacterial resistance, switched positive systems, two-strain bacteria

1. INTRODUCTION

The alarming increase in morbidity and mortality rates attributed to drug-resistant infections has raised global concern in control and prevention of resistance related infections. Proposed treatment strategies to tackle this problem have been the subject of investigation of several mathematical modelling evaluations. Tackling resistance, however, will stem from understanding the mechanisms leading to resistance evolution at within-host level.

In the literature, studies of infections have been conducted using the notion of switched positive dynamical systems (Di Giamberardino and Iacoviello, 2018; Hernandez-Vargas et al., 2011). A switched positive system generally refers to a hybrid dynamical system consisting of a family of continuous-time subsystems and a rule which brings about the switching between them. Interest in switched systems has increased recently due to their applications in diverse areas such as economics, engineering and biology to mention a few (Liberzon, 2003). The feedback stabilization of such systems has received a lot of attention and numerous tools have been developed to make such analysis. In particular, the use of control Lyapunov functions have gained wide popularity in studying the stabilization of both linear and nonlinear switched systems (Zhao et al., 2012; El-Farra et al., 2005). Studies show that for switched systems, control Lyapunov functions provide a robust feedback solution for achieving stability (Blanchini et al., 2015). The notion of switched positive systems has also been applied in the context of infections (Di Giamberardino and Iacoviello, 2018; Hernandez-Vargas et al., 2011) and in epidemiological systems (Rami et al., 2013).

In this work, we use a mathematical model which captures the mechanisms of resistance described in Hernandez-Vargas and Olaru (2019). This model describes the interaction between genetic bacterial strains and helps tailor appropriate interventions. Employing notions in control engineering and positive switched systems, we develop a control technique based on Lyapunov functions to minimize the appearance of drug resistant bacteria within the host. The rest of this paper is organised as follows: description of the model in Section 2, analysis of the model without switching in Section 3, Lyapunov stability analysis in Section 4 and description and simulations of the switched system in Section 5. The paper ends with a conclusion in Section 6.

2. RESISTANCE MODELLING

This paper considers a particular case of the mathematical model proposed in Hernandez-Vargas and Olaru (2019) for describing the global dynamics of antibiotic resistance. The switched system is as follows

$$\begin{aligned}\dot{x}_i(t) &= \rho_{i,\sigma(t)} x_i(t)\left(1-\frac{x_i(t)}{K}\right) - \delta x_i(t) \\ &\quad +\mu \sum_j \left(M_{j,i}x_j(t) - M_{i,j}x_i(t)\right)\end{aligned} \tag{1}$$

defined for all $t \geq 0$, and where $x_i : i = 1, 2, 3, ..., n$ with n represent different bacterial strains, μ is the mutation rate, δ is the bacterial clearance, ρ_i is the proliferation rate of the strain i, $M_{i,j}$ is the mutation from strain i to strain j, K defines the maximum carrying capacity and $\sigma(t)$ denotes the switching signal based on the treatment policy such that $\sigma(t) = \sigma_j$ for $j \in \{1, 2, \cdots, N\}$ with

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N representing the number of treatment policies. Further qualitative characterisation of the model with and without switching is considered in the subsequent sections.

3. MODEL ANALYSIS WITHOUT SWITCHING

Here we consider the model where there is no switch between therapies. With the use of therapy, it is possible for a strain susceptible to one drug to generate resistant strains which are susceptible to another drug by a phenomenon known as collateral sensitivity Pál et al. (2015). Over time, the newly developed susceptible strains can also generate strains which are resistant to the current drug but susceptible to a different drug. This continuous occurrence of resistant and susceptible strains can eventually lead to the appearance of resistant strains susceptible to the initial drug used.

Our aim is to illustrate a hypothetical scenario of this phenomenon using a two-strain bacterial population, x_1 and x_2, where each strain represents a family of strains sharing the same susceptibility to a given drug. Assuming that each mutation changes the susceptibility of the bacteria from one family to the other, the connection between the families can be written by the following symmetric matrix:

$$M = \begin{bmatrix} 0 & 1 \\ 1 & 0 \end{bmatrix}.$$

Taking $K = 1$, the system of equations (1) can be rewritten according to the above assumptions as:

$$\dot{x}_1 = [-\delta + \rho_1 (1 - x_1)]\, x_1 + \mu(-x_1 + x_2) \tag{2a}$$

$$\dot{x}_2 = [-\delta + \rho_2 (1 - x_2)]\, x_2 + \mu(x_1 - x_2). \tag{2b}$$

All parameters and initial conditions are assumed to be non-negative so that $x_1(0) \geq 0$ and $x_2(0) \geq 0$.

3.1 Equilibrium points and stability

Equilibrium points The substitution method is used to find the equilibrium points of the system. Equating the right hand side of Eqns (2) to zero, an expression for x_2 in terms of x_1 is obtained from Eqn (2b) which is substituted into Eqn (2a) to obtain a quartic polynomial, $H(x_1)$ described explicitly as :

$$H(x_1) = \frac{x_1\left(-\mu\rho_1 x_1(\delta+\mu)\right)}{\mu^2} + \frac{x_1\left(\rho_1\left(\delta+\mu-\rho_2\right)+\rho_2(\delta+\mu)-\delta(\delta-2\mu)\right)}{\mu} - \frac{x_1\left(\rho_2\left(\rho_1\left(x_1-1\right)\left(2x_1(\delta+\mu)-\mu\right)+x_1(\delta+\mu)^2+\rho_1^2\left(x_1-1\right)^2 x_1\right)\right)}{\mu^2}$$

and

$$x_2(x_1) = \frac{\delta x_1 + \mu x_1 + \rho_1 x_1^2 - \rho_1 x_1}{\mu}.$$

$H(x_1)$ and $x_2(x_1)$ are plotted on the same axis. The intersection of $H(x_1)$ with the abscissa gives the x_1-components of the equilibrium points. The coordinates of these intersection points to the curve $x_2(x_1)$ give the corresponding x_2-components and hence characterize the equilibrium points. This is illustrated in Fig. 1(a), which shows four equilibrium points: the trivial equilibrium point $E_1(0,0)$, where both populations are zero, two others E_2, E_3 and a coexistence equilibrium at $E_4(k_1, k_2)$, where both populations are positive.

Depending on the parameter values, only two or all four equilibrium points are admissible: the origin (which always exists) and (under certain conditions) a coexistence equilibrium in the positive orthant. The points (E_2 and E_3) are not admissible because the values of x_1 and x_2 are negative at E_2 and E_3 respectively. Hence, the only biologically meaningful equilibrium points are the origin E_1 and the positive coexistence equilibrium at E_4. A vector field plot of system (2) depicts these equilibrium points and gives a hint of the nature of their stability. This is shown in Fig. 1(b). Fig. 1(c) illustrates the dependence of E_4 on parameter values.

Stability The origin, $E_1(0,0)$ is a common equilibrium point which always exists independent of the parameters thus, making it the point of interest from the stability point of view. Since $E_1(0,0)$ is a common equilibrium point, once its stability is addressed, the stability of E_4 can be inferred. The Jacobian matrix for Eqn (2) is

$$J_{(x_1,x_2)} = \begin{pmatrix} -\delta - \mu + \rho_1 - 2\rho_1 x_1 & \mu \\ \mu & -\delta - \mu + \rho_2 - 2\rho_2 x_2 \end{pmatrix}$$

with eigenvalues

$$\lambda_{1,2} = \frac{1}{2}\left[-2\delta - 2\mu + G(x_1,x_2)\right] \pm \sqrt{4\mu^2 - G(x_1,x_2)^2} \tag{3}$$

where $G(x_1,x_2) = 2\rho_1 x_1 + \rho_1 - 2\rho_2 x_2 + \rho_2$

At the origin, the trace and determinant of the Jacobian matrix are:

$\tau = -2(\delta+\mu) + \rho_1 + \rho_2,$

$\Delta = \delta^2 + \mu(-\rho_1 - \rho_2) + \delta(2\mu - \rho_1 - \rho_2) + \rho_1\rho_2.$

Thus, for stability of $E_1(0,0)$, the restriction of $\tau < 0$ and $\Delta > 0$ is satisfied by the conditions:

$$\text{C1} : \mu > \frac{(\delta-\rho_1)(\delta-\rho_2)}{-2\delta+\rho_1+\rho_2} = \mu_c \text{ and C2} : 2\delta > \rho_1 + \rho_2 \tag{4}$$

where μ_c is a critical mutation rate.

It follows that whenever both $\rho_1 > \delta$ and $\rho_2 > \delta$, then $\mu_c > 0$ and $-2\delta+\rho_1+\rho_2 > 0$. The former is a contradiction to C2 and consequently E_1 is not stable. However, when both $\rho_1 < \delta$ and $\rho_2 < \delta$, then $-2\delta+\rho_1+\rho_2 < 0$ and $\mu_c < 0$. Thus E_1 is stable for any value of $\mu > 0$. Furthermore, if either $\rho_1 > \delta$ and $\rho_2 \leq \delta$ or $\rho_1 \leq \delta$ and $\rho_2 > \delta$ but their sum $(\rho_1 + \rho_2)$ still satisfies C2, then $(\delta-\rho_1)(\delta-\rho_2) < 0$ and $-2\delta+\rho_1+\rho_2 < 0$ so $\mu_c > 0$. The origin is not always stable in this case and there exist some values of μ which make E_1 stable.

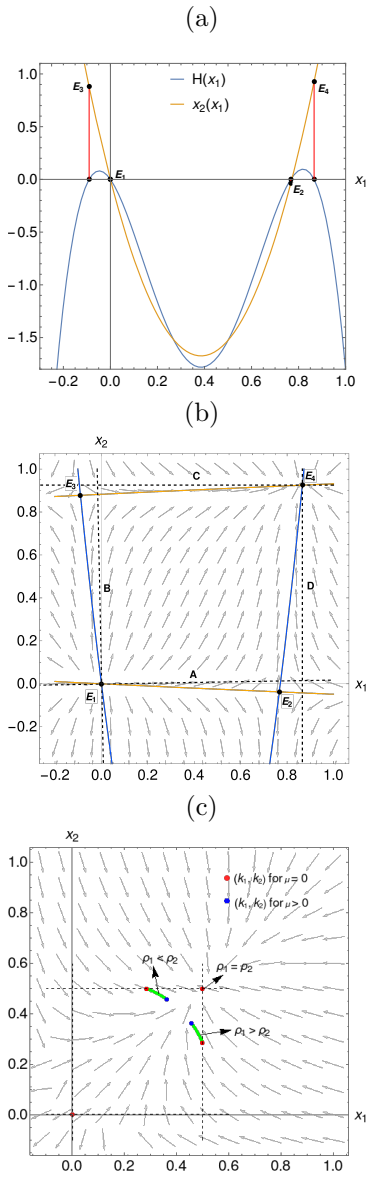

Fig. 1. Graphical view of equilibrium points for system (2). (a) Equilibrium points as a result of substitution method. Red lines: trace of intersection points to $x_2(x_1)$ curve. (b) Vector fields around the four equilibrium points; two with non-negative coordinates (E_1 and E_4) and two with negative components (E_2 and E_3). (c) Dependence of E_4 on parameters. Red dots represent the value of E_4 for $\mu = 0$ and blue dots for $\mu > 0$. The green lines show the translation of equilibrium point (k_1, k_2) from $\mu = 0$ to $\mu > 0$. If $\rho_1 = \rho_2$, E_4 is unchanged for both $\mu = 0$ and $\mu > 0$.

Proposition 1. The stability of E_4 is complementary to that of E_1 in that when E_1 is stable, E_4 does not exist but whenever E_4 exists, E_1 is unstable. In addition, the points E_2 and E_3 are saddles if they exist.

Note that the evolution of E_2 and E_3 as a function of changes in μ could lead to the escape of trajectories from the positive orthant and thus, a study of the positivity of the solutions is necessary. The feasible region of state space is required to be positive since the system is based on populations. The following subsection investigates the positivity of solutions by means of the invariance of the feasible region.

3.2 Set-theoretic characterisation of behaviour

The notion of positive systems relates to the positivity of solutions of the system. We aim to prove the positivity of the system (2) by means of the invariance of the state-space region of biological interest.

Proposition 2. (Positivity of solutions). Solutions of the system with non-negative μ remain non-negative for any positive initial conditions in $\mathbb{R}^2$ and for all time $t > 0$. □

Proof: Let $x_i(t) > 0 \; \forall \; t > 0$ and non-negative values of μ. From system (2) we have;

$$\dot{x}_i \geq x_i \left(-\delta - \mu + \rho_i(1 - x_i)\right)$$

with solution

$$x_i(t) \geq \frac{(\rho_i - \delta)}{\rho_i \left(1 + \left(\frac{(\rho_i - \delta)}{x_0} - 1\right) e^{-t(\rho_i - \delta - \mu)}\right)} \tag{5}$$

for all $\rho_i \geq 0$, $\delta \geq 0$.

When $\rho_i > \delta$, it follows $\frac{(\rho_i - \delta)}{\rho_i} > 0$.

When $\rho_i \leq \delta$ all components are converging monotonically and $\lim_{t \to \infty} x_i(t) = 0$.

This proves that system (2) is non-negative $\forall t > 0$. ■

Let us now consider the region of invariance with respect to system (2) .

Definition 1. (Blanchini (1999)). A set $X \in \mathbb{R}^n$ is positively invariant with respect to the system $\dot{x} = f(x(t))$ if $\forall \; x_0 \in X$, the solution $x(t, x_0)$ satisfies $x(t, x_0) \in X \; \forall \; t > 0$.

Proposition 3. Given a set of positive parameters: ρ_i, δ and μ, the set

$$\Omega = \left\{(x_1, x_2) \in \mathbb{R}^2 \mid 0 \leq x_1 \leq k_1, 0 \leq x_2 \leq k_2\right\} \tag{6}$$

is positively invariant with respect to system (2) above. □

Proof: Consider the general dynamical system

$$\dot{x} = F(x) \tag{7}$$

with $F : \mathbb{R}^2 \to \mathbb{R}^2$ and let $\mathcal{X}$ be the set of all initial conditions in $\mathbb{R}^2$. Following Nagumo's theorem, assume that for each initial condition in $\mathcal{X}$, there is a globally unique solution and let $\Omega \subseteq \mathcal{X}$ be a closed and convex set. The boundary of the set Ω is denoted as $\partial\Omega$ and the tangent cone of Ω at x is denoted as $\mathcal{T}_{\Omega(x)}$. Then, the set Ω is positively invariant for the system if and only if

$$F(x) \in \mathcal{T}_{\Omega(x)}, \; \forall \; x \in \partial\Omega,$$

Thus, if for every $x \in \partial\Omega$, the derivative $\dot{x}(t)$ points inside the set Ω, then the trajectory $x(t)$ remains in Ω (Blanchini, 1999).

In the particular case of Ω in Eqn (6) and $\dot{x}_i$ in Eqn (2) with $F(x) = \begin{bmatrix} f_1(x) \\ f_2(x) \end{bmatrix}$, $\partial\Omega$ is defined by the four line segments (see Fig. 1);
$A = \{(x_1, x_2) \mid 0 < x_1 < k_1, x_2 = 0\}$,
$B = \{(x_1, x_2) \mid x_1 = 0, 0 < x_2 < k_2\}$,
$C = \{(x_1, x_2) \mid 0 < x_1 < k_1, x_2 = k_2\}$ and
$D = \{(x_1, x_2) \mid x_1 = k_1, 0 < x_2 < k_2\}$.

To show that all points along $\partial\Omega$ point inwards, one has to use normals that point inside Ω by using the dot product. However, we recall Proposition 2, where it was shown that the system is positive and hence the points along the boundaries defined by A and B are proved to point inside Ω. Thus, it remains to show that points along C and D also point inside Ω.

For C, x_2 is constant and x_1 changes from 0 to k_1 with the normal vector $\boldsymbol{n_C} = (0, -1)$. For any point $p \in [0, k_1]$, let $X = \begin{bmatrix} p \\ k_2 \end{bmatrix}$ be the initial conditions. Then,

$$\begin{aligned} F(X)^T.\boldsymbol{n_C} &= F\left(\begin{bmatrix} p \\ k_2 \end{bmatrix}\right)^T \cdot \begin{pmatrix} 0 \\ -1 \end{pmatrix} \\ &= \left[f_1\left(\begin{bmatrix} p \\ k_2 \end{bmatrix}\right)\ f_2\left(\begin{bmatrix} p \\ k_2 \end{bmatrix}\right)\right] \cdot \begin{pmatrix} 0 \\ -1 \end{pmatrix} \\ &= -f_2\left(\begin{bmatrix} p \\ k_2 \end{bmatrix}\right), \forall p. \end{aligned}$$

It remains to show now that

$$F(X)^T.\boldsymbol{n_C} = -f_2\left(\begin{bmatrix} p \\ k_2 \end{bmatrix}\right) \geq 0, \forall p \in [0, k_1]. \tag{8}$$

From Eqn (2b),

$$\dot{x}_2 = [-\delta + \rho_2(1 - x_2)]\, x_2 + \mu(-x_1 + x_2). \tag{9}$$

Since (k_1, k_2) are roots of the system (2),

$$\dot{x}_2 = [-\delta + \rho_2(1 - k_2)]\, k_2 + \mu(-k_1 + k_2) = 0. \tag{10}$$

Thus,

$$\begin{aligned} [-\delta + \rho_2(1 - k_2) - \mu]\, k_2 + \mu k_1 &= 0 \\ [-\delta + \rho_2(1 - k_2) - \mu]\, k_2 &= -\mu k_1 \end{aligned} \tag{11}$$

Now from Eqn (8),

$$\begin{aligned} -f_2\left(\begin{bmatrix} p \\ k_2 \end{bmatrix}\right) &= -\left[\rho_2 k_2\,(1 - k_2) - \delta k_2 - \mu k_2 + \mu p\right] \\ &= -\left[\rho_2 k_2\,(1 - k_2) - \delta k_2 - \mu k_2\right] - \mu p \\ &= -(-\mu k_1) - \mu p \quad \text{from Eqn (11)} \\ &= \mu(k_1 - p) > 0 \quad \text{when } p \in (0, k_1) \end{aligned}$$

The value of the dot product being positive, the vector fields point in the same direction as a normal field (i.e. inside the domain Ω).

For D, x_1 is constant and x_2 changes from 0 to k_2 with the normal vector $\boldsymbol{n_D} = (-1, 0)$. Based on the same reasoning, similar results are obtained:

$$F(X)^T.\boldsymbol{n_D} = f_1\left(\begin{bmatrix} k_1 \\ p \end{bmatrix}\right) > 0, \forall p \in [0, k_2].$$

and the vector fields point inside the domain.

Eventually, since all points along $\partial\Omega$ point inwards, the set Ω is positively invariant with respect to system (2). ■

Corollary 1. In the case when there is no mutation, that is when $\mu = 0$, along the boundaries C and D,

$$f_2\left(\begin{bmatrix} p \\ k_2 \end{bmatrix}\right) = 0 \text{ and } f_1\left(\begin{bmatrix} k_1 \\ p \end{bmatrix}\right) = 0$$

respectively. Therefore the set Ω is positively invariant with respect to system (2). ■

The invariant region Ω bounded by the line segments A, B, C, D is illustrated in Fig. 1.

4. LYAPUNOV STABILITY ANALYSIS

We have established that all solutions of the system with positive initial conditions are positive and remain in the positively invariant region Ω for all $t > 0$. We have also shown that the system converges to either the origin or the coexistence equilibrium point. However, the convergence of interest is the one at the origin which indicates the eradication of both strains of bacteria.

The stability of the origin is analysed in this section using Lyapunov's theory on stability of dynamical systems. The following lemma from Khalil (2002) states Lyapunov's stability theorem for a general system of ordinary differential equations.

Theorem 1. (Lyapunov theorem stability (Khalil, 2002)). Let $\bar{x}$ be an equilibrium point for the system (7) and $D \subset \mathbb{R}^n$ be a domain containing $\bar{x}$. Let $V : D \to \mathbb{R}$ be a continuously differentiable function such that

$$V(\bar{x}) = 0 \text{ and } V(x) > 0 \text{ in } D \setminus \{\bar{x}\} \tag{12}$$

$$\dot{V}(x) \leq 0 \text{ in } D \tag{13}$$

Then, $\bar{x}$ is stable. Moreover, if

$$\dot{V}(x) < 0 \text{ in } D \setminus \{\bar{x}\} \tag{14}$$

then $\bar{x}$ is asymptotically stable. A continuously differentiable function $V(x)$ satisfying these conditions is called a Lyapunov function. ■

Using a Lyapunov function, we can determine the Lyapunov stability of the equilibrium point, E_1 for system (2).

Theorem 2. The system (2) under the conditions (4) has $\bar{x} = 0$ as stable equilibrium with a domain of attraction $\Omega_D = \{(x_1, x_2) \in \Omega \mid (x_1, x_2) \neq (k_1, k_2)\}$. □

Proof: Starting from the positive invariance of $\Omega \subset \mathbb{R}^2$, we construct a candidate Lyapunov function in the form

$$V(x) = (x_1 - \bar{x}_1)^2 + (x_2 - \bar{x}_2)^2. \tag{15}$$

Over the domain Ω_D, $V(x)$ is continuously differentiable, $V(\bar{x}) = 0$ and $V(x) > 0$ for all $x \neq \bar{x}$. Thus $V(x)$ is a valid Lyapunov candidate. The derivative, $\dot{V}(x)$ of the Lyapunov function $V(x)$ is calculated along the trajectories as

$$\dot{V}(x) = 2(x_1 - \bar{x}_1)\dot{x}_1 + 2(x_2 - \bar{x}_2)\dot{x}_2 \tag{16}$$

Clearly, $\dot{V}(x) = 0$ for $x = (0, 0)$ and $x = (k_1, k_2)$. Next, we consider the Lyapunov stability of the origin and develop Eqn (15) for $x \in \Omega_D$ and the equilibrium point $\bar{x} = (0, 0)$

$$\begin{aligned} \dot{V}(x) &= 2x_1\dot{x}_1 + 2x_2\dot{x}_2 \\ &= 2x_1\left[(-\delta + \rho_1\,(1 - x_1))x_1 + \mu(-x_1 + x_2)\right] \\ &+ 2x_2\left[(-\delta + \rho_2\,(1 - x_2))x_2 + \mu(x_1 - x_2)\right] \\ &= 2x_1^2(\rho_1 - \delta) + 2x_2^2(\rho_2 - \delta) \\ &- 2(\rho_1 x_1^3 + \rho_2 x_2^3) - 2\mu(x_1 - x_2)^2 \end{aligned}$$

Let μ be expressed in terms of the critical mutation rate μ_c from Eqn (4) as $\mu = \mu_c + \epsilon$. Substituting this into $\dot{V}(x)$ yields:

$$\dot{V}(x) = 2x_1^2(\rho_1 - \delta) + 2x_2^2(\rho_2 - \delta) - 2\left(\rho_1 x_1^3 + \rho_2 x_2^3\right)$$
$$-2(x_1 - x_2)^2\left(\frac{(\delta - \rho_1)(\delta - \rho_2)}{-2\delta + \rho_1 + \rho_2} + \epsilon\right)$$
$$= -2\rho_1 x_1^3 - 2\rho_2 x_2^3 - 2\epsilon x_1^2 - 2\epsilon x_2^2 + 4\epsilon x_1 x_2$$
$$+\frac{2(\delta - \rho_1)^2 x_1^2 + 2(\delta - \rho_2)^2 x_2^2 + 4(\delta - \rho_1)(\delta - \rho_2)x_1 x_2}{-2\delta + \rho_1 + \rho_2}$$
$$= -2\rho_1 x_1^3 - 2\rho_2 x_2^3 - 2\epsilon(x_1 - x_2)^2$$
$$+\frac{2((\delta - \rho_1)x_1 + (\delta - \rho_2)x_2)^2}{-2\delta + \rho_1 + \rho_2}$$

When C1 is satisfied then $\frac{2((\delta-\rho_1)x_1+(\delta-\rho_2)x_2)^2}{-2\delta+\rho_1+\rho_2} < 0$. When C2 is satisfied then $\epsilon > 0$ and $-2\epsilon(x_1 - x_2)^2 < 0$.

Therefore satisfying both conditions (4) ensures that $\dot{V}(x) < 0,\ \forall\, x \in \Omega$. ■

When any of the conditions (4) are not satisfied, there exists at least one combination of $(x_1, x_2) \in \Omega_D$ which makes the expression (16) non-negative, thus invalidating the stability of the origin over this domain.

5. SWITCHING TO SCHEDULE THERAPIES

5.1 Model description with therapies

By considering the switched system (2), we introduce here a mechanism for improving the stabilisation and the rate of convergence of the system (2) when more than one treatment policy is employed.

Definition 2. A switching signal is defined as the consecutive choice between therapies at the rate T and is represented by a piecewise constant function

$$\sigma(t) : \mathbb{R} \to \{\sigma_1, \sigma_2, \ldots, \sigma_N\}$$

such that $\sigma(t)$ is constant for all switch times

$$t_k \in [kT, (k+1)T)$$

and for $k = 0, 1, 2, \ldots$

The objective next is to employ switching for the gradual eradication of resistant strains in a system on the long term based on a feedback decision. We denote a periodic switching as the switching between therapies at regular intervals.

5.2 Switching based on control Lyapunov function

The use of the Lyapunov function serves as a tool for improving the convergence. Based on the Lyapunov function argument, we can have a switching strategy which ensures the stability of the origin under a given choice of the parameters.

Proposition 4. The system (2) has the origin as a stable equilibrium if $\forall x \in \Omega_D$ there exists at least one therapy σ_i such that $\dot{V}(x, \sigma_i) < 0$. □

Proof. Let the Lyapunov function defined as in Eqn (15) be with respect to the dynamics of system (2) changing $V(x)$ into $V(x, \sigma)$. If for every $x \in \Omega_D$ there is at least one therapy σ_i that yields $\dot{V}(x, \sigma_i) < 0$ at any switching time, we can construct a switching policy by choosing the therapy such that

$$\sigma(t) = \arg\min_{\sigma_i} \dot{V}(x, \sigma_i).$$

This constructive solution proves the existence of a switching policy $\sigma(t)$, such that $\dot{V}(x, \sigma(t)) < 0, \forall x \in \Omega_D$. ■

Hence, the system has a stable equilibrium at the origin if there exists a $\rho_{i,\sigma}$ which makes $\dot{V}(x, \sigma) < 0$. Thus, given two configurations both with the common equilibrium point $(0, 0)$, a policy based on the Lyapunov function derivative can be used to stabilize the system provided that at least one of the configurations guarantees $\dot{V}(x(t), \sigma(t)) < 0$. In addition, switching based on the Lyapunov function derivative can lead to faster convergence than periodic switching. In the following, some scenarios of these conditions are discussed.

5.3 Discussion on switching therapies

If the switching system (2) has a common Lyapunov function, then the system is asymptotically stable at the origin for any switching signal $\sigma(t)$. To illustrate this, we consider three different scenarios with different proliferation rates and under two treatment policies (see Table 1). For all simulations, an initial condition vector $x = [10^3, 10]$ is chosen and the following parameter values are used: $\delta = 0.25, K = 10^5$, $T = 10$ days and $\mu = 10^{-4}$.

Table 1. Proliferation rates for bacterial strains under therapy combinations

Case	Therapy	x_1	x_2	E_1
1	1	$\rho_{1,1} = 0.2$	$\rho_{2,1} = 0.1$	Stable
	2	$\rho_{1,1} = 0.1$	$\rho_{2,1} = 0.2$	Stable
2	1	$\rho_{1,1} = 0.5$	$\rho_{2,1} = 0.1$	Unstable
	2	$\rho_{1,1} = 0.1$	$\rho_{2,1} = 0.2$	Stable
3	1	$\rho_{1,1} = 0.35$	$\rho_{2,1} = 0.1$	Unstable
	2	$\rho_{1,1} = 0.1$	$\rho_{2,1} = 0.35$	Unstable

In case 1, both subsystems are asymptotically stable at the origin. Therefore, any switching policy leads to eradication of both strains. In case 2, the first subsystem is unstable at the origin but the second is stable. Switching periodically between therapies will not stabilize the entire system unconditionally. In cases 1 and 2, switching based on the Lyapunov function argument not only ensures convergence to the origin but also achieves convergence at a faster rate compared to switching periodically between policies. We can see in Fig. 2(a) and 2(b) switching results for cases 1 and 2 respectively. For case 3, the two subsystems are not stable at the origin and thus, using the policies independently does not lead to eradication. However, switching between the two policies periodically leads to a convergence at the origin. Moreover, the Lyapunov switching converges to such a periodic stabilizing sequence implicitly and additionally ensures a better convergence of the closed-loop system (see Fig. 2(c)).

For this last case, subsystems a priori unstable at the origin can be brought to convergence under the Lyapunov switching argument based on feedback. Moreover, an analysis of the Lyapunov function derivative shows that a sliding mode can occur at the intersection of the two configuration as shown in Fig. 3(b). Thus, the feedback switching can be seen as a reaching law to the sliding surface. Once the sliding mode is reached, the control can be completed with a sliding law defined based on periodic switching.

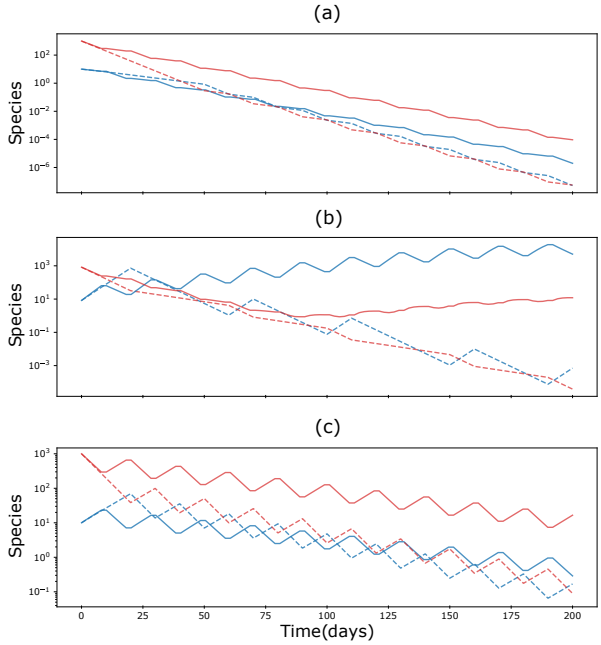

Fig. 2. Illustration of therapy switching for all three cases. (a) Case 1; (b) Case 2; (c) Case 3. Solid lines: periodic switching. Dashed lines: Lyapunov based switching. Blue lines: strain x_1. Red lines: strain x_2.

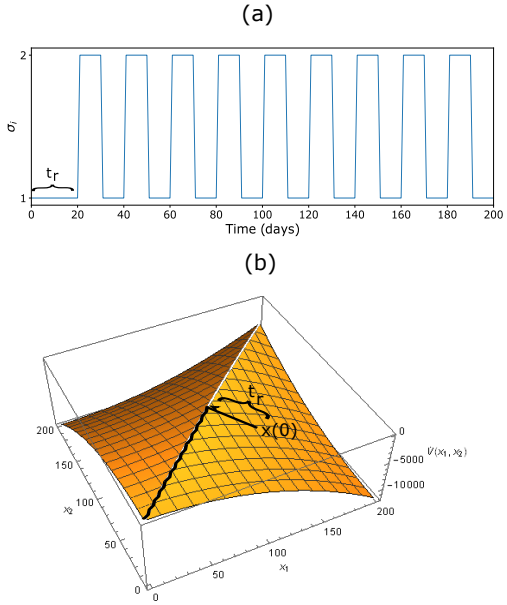

Fig. 3. A sliding mode for case 3 occurs at the intersection of $\dot{V}(x_1, x_2)$ for therapy 1 and 2 when the minimum of $\dot{V}(x_1, x_2)$ for each pair (x_1, x_2) with respect to both therapies is plotted. The right hand side shows the values of $\dot{V}(x_1, x_2)$ under therapy 1 and the left hand side shows the values of $\dot{V}(x_1, x_2)$ under therapy 2. t_r denotes the time to reach the sliding mode.

6. CONCLUSION

Switching therapies can be considered as a mechanism for improving the stabilisation and rate of convergence of a positive system when more than one treatment policy is used. For the particular case of antibiotic resistance infections, switching can be employed for the gradual eradication of resistant strains on the long term based on a feedback decision. Our numerical simulations suggest that switching between therapies based on the switching rule from the Lyapunov function leads to a better convergence at the origin than an open-loop periodic switching.

A key biological aspect of the proposed control-theoretical approach is that in a first stage one needs to identify the distribution of the bacterial population. Based on this initial information, a switching trajectory (see Fig. 3(a)) can be computed to indirectly define a sliding mode (see Fig. 3(b)). Once on the sliding mode, a periodic switching between therapies can be employed to eradicate the bacterial colony. In conclusion, this approach can be used as an instrument in the future to guide therapies to tackle bacterial resistance with a minimal collection of information.

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