

Drug Resistant and Wild-type Strains Interaction: Investigating Effects of Conversion Delays for Possible Control Strategies

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Abstract—Drug resistance arises when a drug such as an antimicrobial or an antineoplastic loses its effectiveness in curing a disease or health condition. The increasing threat of drug resistance is compromising medical care worldwide. To provide deeper understanding of possible measures to avoid the endemicity of drug resistant strains, many models have been proposed and analyzed on the dynamics of co-circulating wild-type and drug resistant viruses. We aim to add to these works by considering a model which incorporates the effects of delay in the evolution of resistant strain, as well as the role of the immune response and the target cells availability on the suppression of the peak load of resistant virus. The model is analyzed to discover possible impacts of delays on the system's dynamic behaviour, persistence of the two strains, and the global stability. Oscillatory behaviour and the role of delays as possible control parameters are also investigated.

Keywords—Drug resistance, Cost of resistance, maturation delays effects, global stability, uniform persistence.

I. INTRODUCTION

ONE of the most outstanding advances in the history of human health is the discovery of antimicrobial agents which are medicines used to treat infections caused by bacteria, fungi, parasites, and viruses. Capable of decreasing suffering from illnesses and even save lives, antimicrobial agents have been hailed as "miracle drugs" that are our leading weapons in the treatment of infectious diseases. When penicillin was discovered and applied, survival rate of patients increased. But antibiotic resistance rapidly arose at a faster rate than that of human's ability to develop new drugs.

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Antimicrobial resistance refers to the ability of certain microorganisms to withstand attack by drugs. Rapid and relentless rise in resistant pathogens creates serious concerns by threatening lives and wasting limited healthcare resources.

Many drugs and antibiotics that were formally effective in fighting infections are no longer effective because of the development of resistant strains which poses a serious threat to public health. Many intervention measures have been devised in order to limit the emergence and spread of antimicrobial-resistant bacteria such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococci*, and multidrug-resistant *Gram-negative bacilli* [1]. However, these pathogens still recover and continue to spread at dangerous pace. Viral infections like HIV-1 are able to rapidly produce resistant strains, causing life-long infection, and resistance to Influenza-A drugs is rising. Understanding drug resistant infections is therefore at the forefront of concentrated research [1].

Many mass-action models [1-6] have been used to study the activity of a virus or bacterial species within a host, describing the interaction between strains, the cells they infect and the attempts of the body's immune response to remove the infection. Of particular interest is the impact of drug administration on the dynamics of co-circulating wild-type and drug resistant viruses. In 2007, Puttasontiphot *et al.* [6] investigated bacteria-antibiotic dynamics in a chemostat exposed to antimicrobial selection pressure. To support the model derivation, experimental data were collected, first from a culture of *Enterococcus faecalis* ATCC 29212 and *Serratia marcescens* ATCC 43861 growing in 1% Mueller-Hinton Broth II in the absence of antibiotics, and then from a culture of *Bacteroides Fragilis* with BMS-284756 for the antibiotic. Their full model involves the density of a sensitive strain S , that of a resistant strain R , the concentration of the limiting resource, or substrate, and the effective antibiotic level.

We, on the other hand, consider a situation in which the resource is abundant so that we may take the interactions of the two strains to be independent of the substrate concentration. We further incorporate the delay τ in the evolution of the resistant strain as well as the time it takes before the resistant members become mature enough to reproduce or transmit the chromosomal elements known as plasmids to affect the conversion of sensitive to resistant strain. Our referenced model is thus written as follows.

$$\frac{dS}{dt} = \psi_S S(t) - H(S(t))S(t)R(t-\tau) - d_S S(t) - kS(t) + I \tag{1}$$

$$\frac{dR}{dt} = \psi_R (r - R(t))R(t-\tau) + H(S(t))S(t)R(t-\tau) - d_R R(t-\tau) \tag{2}$$

where the first term on the right of (1) is the growth rate of the sensitive strain, the second term accounts for the conversion of sensitive members to resistant ones.

The function $H(S)$ in this second term is the response function of the sensitive population to the conversion attempts of the resistant population. In [6], the response was assumed to take the form of a Holling type function:

$$H(S) = \frac{\epsilon_r}{K_r + S} \tag{3}$$

In this paper, we shall let $H(S)$ be a general continuous function and investigate the effect different formulations of $H(S)$ have on the dynamic behaviour of the model.

The third term on the right of (1) is the death rate, while the fourth term is the killing rate of S by administered drugs. We also assume that the host is being infected by the sensitive strain at the constant rate I .

The first term on the right of equation (2) is the growth rate of the resistant strain. Here, we have taken into account the ‘‘cost of resistance’’ which corresponds to the phenomena that the resistant strain is less fit in the absence of treatment due to being out competed by the wild type strain [7]. According to this concept, naturally we expect the wild type strain to be stable with a higher transmission rate than the drug resistant strain. Furthermore, it was suggested in [7] and [8] that a decrease in the peak load of resistant virus could be attributed to the cytotoxic lymphocytes’ response or a lack of target cells that limits the resistant virus from replicating. We incorporate this effect by using the logistic growth term for the resistant strain, so that its growth rate decreases as the current density rises to its carrying capacity r .

The second term on the right of (2) corresponds to the increase in the resistant population from conversion of the sensitive members. The last term is the death rate of the resistant population. The evolution of this strain has an intrinsic delay of τ in time which accounts for the delay in the responses of the host and the immune system to the resistant strain.

We shall first give a result on uniform persistence, then study the global stability in the case that the cost of resistance parameter $\gamma = \frac{1}{r}$ is relatively low. Finally, we investigate the effect of delay τ on the oscillatory behaviour of the solution when γ is rather high (low capacity r).

II. UNIFORM PERSISTENCE

Frequently, the strictly positive solutions of biological model eventually approach the boundary of non-zero zone. Such a situation is interpreted as extinction of populations. Thus, the question that arises is of specifying the condition that each initially strictly positive solution is at some positive distance away from the boundary as time evolves [9]. In this part, we provide the restrictions to guarantee that each strictly positive solution is uniformly bounded away from the boundary, in other words, uniformly persistence.

Letting

$$f(S) \equiv \psi_R r - \omega_R + H(S)S, \tag{4}$$

$$\omega_S = d_S + k > 0, \tag{5}$$

$$\omega_R = d_R > 0, \tag{6}$$

and

$$\psi_R r \geq \omega_R, \tag{7}$$

we investigate some properties of the solutions of (1) and (2), and the equilibrium point (S_b, R_b) which, by definition, satisfies the following system:

$$I = (H(S_b)R_b + \omega_S - \psi_S)S_b, \tag{8}$$

$$R_b = \frac{1}{\psi_R} f(S_b). \tag{9}$$

In what follows, \mathbb{R} denotes the set of real numbers. We now state and prove our first result.

Theorem 1 Let $H(\cdot)$ be a non-decreasing function, $\omega_S \geq \psi_S$, and (S, R) be a bounded positive solution of (1) and (2). Define

$$R_m = \liminf_{t \rightarrow +\infty} R(t), \quad R_M = \limsup_{t \rightarrow +\infty} R(t),$$

$$S_m = \liminf_{t \rightarrow +\infty} S(t), \quad S_M = \limsup_{t \rightarrow +\infty} S(t).$$

Then,

$$R_m \leq R_b \leq R_M, \tag{10}$$

and

$$S_m \leq S_b \leq S_M. \tag{11}$$

Proof $f(\cdot)$ is monotonically increasing from the hypothesis that $H(\cdot)$ is non-decreasing. For any bounded positive solution (S, R) of (1) and (2), we can construct a full time solution (S, \mathcal{R}) by using an ω -limit set of (S, R) such that

$$R_M = \mathcal{R}(0) = \max_{t \in \mathbb{R}} \mathcal{R}(t),$$

$$R_m \leq \min_{t \in \mathbb{R}} \mathcal{R}(t),$$

$$S_m \leq S(t) \leq S_M, \forall t \in \mathbb{R}.$$

(Please see [10-12] for details on full time solutions and their applications.)

Accordingly, from (2), we have

$$0 = \dot{\mathcal{R}}(0) = \psi_R (r - R_M) \mathcal{R}(-\tau) + H(\mathcal{S}(0)) \mathcal{S}(0) \mathcal{R}(-\tau) - \omega_R \mathcal{R}(-\tau), \quad (12)$$

and

$$R_M = \mathcal{R}(0) = \frac{1}{\psi_R} f(\mathcal{S}(0)). \quad (13)$$

First, we will show that $R_M \geq R_b$, that is

$$\frac{1}{\psi_R} f(\mathcal{S}(0)) \geq \frac{1}{\psi_R} f(S_b).$$

Since $f(\cdot)$ is monotonically increasing, we need to prove that $\mathcal{S}(0) \geq S_b$.

For the sake of contradiction, we assume that $\mathcal{S}(0) < S_b$.

Consequently, $R_M < R_b$. Since $S_m \leq \mathcal{S}(0)$, it follows that $S_m < S_b$.

We construct another full time solution $(\mathcal{S}, \mathcal{R})$ by using ω -limit set of (S, R) such that

$$\begin{aligned} S_m &= \mathcal{S}(0) = \min_{t \in \mathbb{R}} \mathcal{S}(t), \\ S_M &\geq \max_{t \in \mathbb{R}} \mathcal{S}(t), \\ R_m &\leq \mathcal{R}(t) \leq R_M \quad \forall t \in \mathbb{R}. \end{aligned}$$

Again, it follows that $\dot{\mathcal{S}}(0) = 0$.

From (1), we have

$$I = (\omega_s - \psi_s + H(S_m) \mathcal{R}(-\tau)) S_m, \quad (14)$$

Since we already have $S_m \leq \mathcal{S}(0) < S_b$, and $R_M < R_b$, (16) becomes

$$\begin{aligned} I &= (\omega_s - \psi_s + H(S_m) \mathcal{R}(-\tau)) S_m \\ &< (\omega_s - \psi_s + H(S_b) R_b) S_b = I. \end{aligned} \quad (15)$$

This contradiction implies that $\mathcal{S}(0) \geq S_b$, and thus $R_M \geq R_b$.

In addition, it follows that

$$S_M \geq \mathcal{S}(0) \geq S_b.$$

The other half of the proof is similar, but we need to construct a full time solution in an appropriate way to yield $R_m \leq R_b$ and $S_m \leq S_b$. ■

Remark 2 It is physically meaningful that the equilibrium is bounded in the range of all bounded positive solutions, and the numbers of both microbial strains in the body should adjust to some levels and remain steady when we are healthy.

Corollary 3 Theorem 1 yields the following inequalities

$$\frac{1}{\psi_R} f(S_m) \leq R_m \leq R_M \leq \frac{1}{\psi_R} f(S_M), \quad (16)$$

$$(\omega_s - \psi_s + H(S_M) R_m) S_m \leq I \leq (\omega_s - \psi_s + H(S_m) R_M) S_m \quad (17)$$

Proof We initially verify (16) by constructing a full time solution (\mathbf{S}, \mathbf{R}) such that

$$\begin{aligned} R_m &= \mathbf{R}(0) = \min_{t \in \mathbb{R}} \mathbf{R}(t), \\ R_M &\geq \max_{t \in \mathbb{R}} \mathbf{R}(t), \\ S_m &\leq \mathbf{S}(t) \leq S_M, \quad \forall t \in \mathbb{R}. \end{aligned}$$

Hence, $S_m \leq \mathbf{S}(0)$, and, from (2), we arrive at

$$\frac{1}{\psi_R} f(S_m) \leq R_m. \quad (18)$$

From the proof of Theorem 1, $\mathcal{S}(0) \leq S_M$, which implies

$$R_M \leq \frac{1}{\psi_R} f(S_M), \quad (19)$$

in (13). Then, it is clear that

$$\frac{1}{\psi_R} f(S_m) \leq R_m \leq R_M \leq \frac{1}{\psi_R} f(S_M).$$

In order to verify (17), we again construct a full time solution $(\mathcal{S}, \mathcal{R})$ such that

$$\begin{aligned} S_M &= \mathcal{S}(0) = \max_{t \in \mathbb{R}} \mathcal{S}(t), \\ S_m &\leq \min_{t \in \mathbb{R}} \mathcal{S}(t), \\ R_m &\leq \mathcal{R}(t) \leq R_M, \quad \forall t \in \mathbb{R}. \end{aligned}$$

Since $R_m \leq \mathcal{R}(-\tau)$, we obtain

$$\begin{aligned} [\omega_s - \psi_s + H(S_M) R_m] S_M &\leq [\omega_s - \psi_s + H(S_M) \mathcal{R}(-\tau)] S_M \\ &= I. \end{aligned} \quad (20)$$

By the definition of $\mathcal{R}(t)$, $\mathcal{R}(-\tau) \leq R_M$, and from (14), we have

$$\begin{aligned} I &= (\omega_s - \psi_s + H(S_m) \mathcal{R}(-\tau)) S_m \\ &\leq [\omega_s - \psi_s + H(S_m) R_M] S_m. \end{aligned} \quad (21)$$

According to (20) and (21), we therefore obtain

$$[\omega_s - \psi_s + H(S_M) S_m] S_M \leq I \leq [\omega_s - \psi_s + H(S_m) R_M] S_m. \quad \blacksquare$$

Remark 4 Under the assumptions of Theorem 1, uniform persistence of the system (1)-(2) physically represents the fact that our body will not be free of infection. It is reported that the bacterial populations colonize the mammalian digestive tract since birth, assisting in that life form's efficient digestion and nutrients' absorption [13].

Lemma 5 By the assumptions in Theorem 1, the following conditions are equivalent./

- i) $R_M = R_b$ ii) $S_m = S_b$ iii) $R_m = R_b$ iv) $S_M = S_b$

Proof To prove that i) implies ii), assume that $R_M = R_b$. Then from the second inequality in (16),

$$I \leq [\omega_s - \psi_s + H(S_m)R_m]S_m = [\omega_s - \psi_s + H(S_m)R_b]S_m. \tag{22}$$

Since $H(\cdot)$ is non-decreasing, it follows that $[\omega_s - \psi_s + H(S_m)R_b]S_m \leq [\omega_s - \psi_s + H(S_b)R_b]S_b = I$. (24)

Consequently, by (22) and (25), $S_m = S_b$.

To show that ii) implies iii), we suppose $S_m = S_b$. We construct a full time solution (\mathbf{S}, \mathbf{R}) such that, as before,

$$R_m = \mathbf{R}(0) = \min_{t \in \mathbb{R}} \mathbf{R}(t),$$

$$R_M \geq \max_{t \in \mathbb{R}} \mathbf{R}(t),$$

$$S_m \leq \mathbf{S}(t) \leq S_M, \forall t \in \mathbb{R}.$$

It follows from (18) that

$$R_b = \frac{1}{\psi_R} f(S_b) = \frac{1}{\psi_R} f(S_m) \leq R_m$$

However, we have $R_m \leq R_b$. Hence, we must have $R_m = R_b$.

To show that iii) implies iv), we consider the first inequality of (17),

$$[\omega_s - \psi_s + H(S_M)R_b]S_M = [\omega_s - \psi_s + H(S_M)R_m]S_M \leq I. \tag{24}$$

Since $H(\cdot)$ is non-decreasing,

$$I = [\omega_s - \psi_s + H(S_b)R_b]S_b \leq [\omega_s - \psi_s + H(S_M)R_b]S_M, \tag{25}$$

Hence, $S_M = S_b$.

Now, to show that iv) implies i), suppose $S_M = S_b$. From (9) and (16), we have

$$R_b = \frac{1}{\psi_R} f(S_b) = \frac{1}{\psi_R} f(S_M) \geq R_M.$$

Again, since $R_M \geq R_b$, we have $R_M = R_b$. ■

Remark 6 Every non-constant periodic solution of (1) and (2) must oscillate around the basal level (S_b, R_b) ; otherwise, one of the cases in Lemma 5 is satisfied which forces all strictly bounded positive solutions to converge to (S_b, R_b) .

III. GLOBAL STABILITY IN THE CASE $\omega_s > \psi_s$

In this section, we consider the case where the composite removal rate $\omega_s = d_s + k$ of the sensitive population is greater than its growth rate ψ_s . We first state and prove the following theorem on the stability of the equilibrium (S_b, R_b) .

Theorem 7 Let $\omega_s > \psi_s$, and (S, R) be a bounded positive solution of (1) and (2). Define

$$L_1 = \frac{1}{\psi_R} \sup_{S \in [S_b, \infty)} f'(S), \tag{26}$$

$$L_2 = \frac{1}{\psi_R} \sup_{S \in [0, S_b)} f'(S), \tag{27}$$

$$L_3 = \frac{H(S_b)S_b}{(\omega_s - \psi_s)}. \tag{28}$$

Then,

$$R_M - R_b \leq L_1 (S_M - S_b), \tag{29}$$

$$R_b - R_m \leq L_2 (S_b - S_m), \tag{30}$$

$$S_b - S_m \leq L_3 (R_M - R_b), \tag{31}$$

$$S_M - S_b \leq L_3 (R_b - R_m). \tag{32}$$

If $L_1 L_2 L_3^2 < 1$ then every bounded positive solution of (1) and (2) converges to a positive equilibrium.

Proof Note that although $f(\cdot)$ is monotonically increasing, (26) is well-defined because $S(t)$ is bounded. By constructing a full time solution $(\mathcal{S}, \mathcal{R})$ such that

$$R_M = \mathcal{R}(0) = \max_{t \in \mathbb{R}} \mathcal{R}(t),$$

$$R_m \leq \min_{t \in \mathbb{R}} \mathcal{R}(t),$$

$$S_m \leq \mathcal{S}(t) \leq S_M, \forall t \in \mathbb{R},$$

we again have $R_M = \mathcal{R}(0) = \frac{1}{\psi_R} f(\mathcal{S}(0))$, and $\mathcal{S}(0) \geq S_b$.

The mean value theorem implies that $\frac{f(\mathcal{S}(0)) - f(S_b)}{\mathcal{S}(0) - S_b} \leq \sup_{S \in [S_b, \infty)} f'(S)$. As a result,

$$R_M - R_b = \frac{1}{\psi_R} (f(\mathcal{S}(0)) - f(S_b))$$

$$\leq L_1 (\mathcal{S}(0) - S_b) \leq L_1 (S_M - S_b).$$

We now construct a full time solution $(\mathcal{S}, \mathcal{R})$ such that

$$S_m = \mathcal{S}(0) = \min_{t \in \mathbb{R}} \mathcal{S}(t),$$

$$S_M \geq \max_{t \in \mathbb{R}} \mathcal{S}(t),$$

$$R_m \leq \mathcal{R}(t) \leq R_M \quad \forall t \in \mathbb{R}.$$

With (8) and (14), we have

$$S_b - S_m = \frac{1}{(\omega_s - \psi_s)} (H(S_m)\mathcal{R}(-\tau)S_m - H(S_b)R_b S_b)$$

$$\leq \frac{H(S_b)S_b}{\omega_s - \psi_s} (R_M - R_b) = L_3 (R_M - R_b).$$

In the same way, (30) and (32) can be proven. Hence, by (29)-(32),

$$R_M - R_m \leq L_1 L_2 L_3^2 (R_M - R_m). \tag{33}$$

If $L_1 L_2 L_3^2 < 1$, then $R_M - R_m = 0$. By Lemma 5, the solution (R, S) converges to (S_b, R_b) .

IV. GLOBAL STABILITY WHEN $\omega_s = \psi_s$

In this case, the system (1)–(2) becomes

$$\dot{S} = -H(S(t))S(t)R(t-\tau) + I, \tag{34}$$

$$\begin{aligned} \dot{R} = & \psi_R(r - R(t))R(t-\tau) \\ & + H(S(t))S(t)R(t-\tau) - \omega_R R(t-\tau). \end{aligned} \tag{35}$$

The positive equilibrium of the system is given by

$$I = H(S_b)S_bR_b, \tag{36}$$

$$R_b = \frac{1}{\psi_R} f(S_b). \tag{37}$$

Lemma 8 Let $\psi_R r - \omega_R > 0$, and (S, R) be a bounded positive solution of (34) and (35). Also, let H be bounded such that

$$\underline{H} = g.l.b. H(S), \tag{38}$$

$S \in \mathbb{R}$

$$\bar{H} = l.u.b. H(S). \tag{39}$$

$S \in \mathbb{R}$

The evolution $S(t)$ is bounded by the recursive sequences, namely $\{m_k\}$ and $\{M_k\}$, such that

$$\begin{aligned} m_k & \leq S(t) \leq M_k, \\ m_k & = \underline{h}(M_k), \quad M_{k+1} = \bar{h}(m_k), \end{aligned} \tag{40}$$

for which

$$M_0 = \frac{S_b f(S_b) H(S_b) R_M}{\underline{H}(\psi_R r - \omega_R) R_m}, \tag{41}$$

$$\underline{h}(x) \equiv \frac{S_b f(S_b) H(S_b) R_m}{\bar{H} f(x) R_M}, \tag{42}$$

$$\bar{h}(x) \equiv \frac{S_b f(S_b) H(S_b) R_M}{\underline{H} f(x) R_m}. \tag{43}$$

Proof We shall use mathematical induction. M_0 is generated by minoring the resistant population time derivative in (35) as follows:

$$\begin{aligned} \dot{R} & \geq [-\psi_R R(t) + \psi_R r - \omega_R]R(t-\tau_R) \\ & \geq -\psi_R R_M R(t) + (\psi_R r - \omega_R) R_m. \end{aligned}$$

Hence, for any arbitrary t such that $t_0 \leq t$,

$$\begin{aligned} R(t) & \geq e^{-\psi_R R_M(t-t_0)} R(t_0) \\ & \quad + \frac{(\psi_R r - \omega_R) R_m}{\psi_R R_M} \left(1 - e^{-\psi_R R_M(t-t_0)}\right). \end{aligned}$$

Since $R(t)$ is a bounded evolution, we can take the limit as $t_0 \rightarrow -\infty$. Then,

$$R(t) \geq \frac{(\psi_R r - \omega_R) R_m}{\psi_R R_M}. \tag{44}$$

Referring to (42), the sensitive population time derivative in (34) is majored as follows:

$$\dot{S} \leq \frac{-\underline{H}(\psi_R r - \omega_R) R_m S(t)}{\psi_R R_M} + I.$$

Therefore, for any arbitrary $t_0 \leq t$,

$$\begin{aligned} S(t) & \leq e^{\frac{-\underline{H}(\psi_R r - \omega_R) R_m (t-t_0)}{\psi_R R_M}} S(t_0) \\ & \quad + \frac{I \psi_R R_M}{\underline{H}(\psi_R r - \omega_R) R_m} \left[1 - e^{\frac{-\underline{H}(\psi_R r - \omega_R) R_m (t-t_0)}{\psi_R R_M}} \right]. \end{aligned}$$

We can take the limit as $t_0 \rightarrow -\infty$ since $S(t)$ is a bounded evolution. Hence,

$$S(t) \leq \frac{I \psi_R R_M}{\underline{H}(\psi_R r - \omega_R) R_m} = \frac{S_b f(S_b) H(S_b) R_M}{\underline{H}(\psi_R r - \omega_R) R_m} \equiv M_0$$

Next, we suppose that there exists a $k \in \mathbb{N}$ such that $S(t) \leq M_k$ for all t . Then, the resistant population time derivative in (35) is majored as follows:

$$\begin{aligned} \dot{R} & \leq [-\psi_R R(t) + f(M_k)]R(t-\tau_R) \\ & \leq -\psi_R R_m R(t) + f(M_k) R_M. \end{aligned}$$

For any arbitrary $t_0 \leq t$,

$$R(t) \leq e^{-\psi_R R_m(t-t_0)} R(t_0) + \frac{f(M_k) R_M}{\psi_R R_m} \left(1 - e^{-\psi_R R_m(t-t_0)}\right)$$

Taking the limit as $t_0 \rightarrow -\infty$, we obtain

$$R(t) \leq \frac{f(M_k) R_M}{\psi_R R_m}. \tag{45}$$

Considering (4.1), it follows from (45) that

$$\dot{S} \geq \frac{-\bar{H} f(M_k) R_M S(t)}{\psi_R R_m} + I.$$

Hence, for any arbitrary $t_0 \leq t$,

$$\begin{aligned} S(t) & \geq e^{\frac{-(\bar{H} f(M_k) R_M)(t-t_0)}{\psi_R R_m}} S(t_0) \\ & \quad + \frac{I \psi_R R_m}{\bar{H} f(M_k) R_M} \left[1 - e^{\frac{-(\bar{H} f(M_k) R_M)(t-t_0)}{\psi_R R_m}} \right] \end{aligned}$$

Taking the limit as $t_0 \rightarrow -\infty$, we find

$$\begin{aligned} S(t) & \geq \frac{I \psi_R R_m}{\bar{H} f(M_k) R_M} \\ & = \frac{S_b f(S_b) H(S_b) R_m}{\bar{H} f(M_k) R_M} \equiv \underline{h}(M_k) \equiv m_k. \end{aligned} \tag{46}$$

From (46), the resistant population time derivative in (35) is minored as follows:

$$\dot{R} \geq -\psi_R R_M R(t) + f(m_k) R_m.$$

Therefore, for any arbitrary $t_0 \leq t$,

$$\begin{aligned} R(t) & \geq e^{-\psi_R R_M(t-t_0)} R(t_0) \\ & \quad + \frac{f(m_k) R_m}{\psi_R R_M} \left(1 - e^{-\psi_R R_M(t-t_0)}\right). \end{aligned}$$

Taking the limit as $t_0 \rightarrow -\infty$, it follows that

$$R(t) \geq \frac{f(m_k)R_m}{\psi_R R_M} \tag{47}$$

Referring to (47), the susceptible population time derivative in (34) is majored as follows:

$$\dot{S} \leq \frac{-H f(m_k)R_m}{\psi_R R_M} S(t) + I.$$

Therefore, for any arbitrary $t_0 \leq t$,

$$S(t) \leq e^{\frac{-H f(m_k)R_m(t-t_0)}{\psi_R R_M}} S(t_0) + \frac{I\psi_R R_M}{H f(m_k)R_m} \left(1 - e^{\frac{-H f(m_k)R_m(t-t_0)}{\psi_R R_M}} \right).$$

Taking $t_0 \rightarrow -\infty$, then

$$S(t) \leq \frac{I\psi_R R_M}{H f(m_k)R_m} = \frac{S_b f(S_b)H(S_b)R_M}{H f(m_k)R_m} \equiv \bar{h}(m_k) \equiv M_{k+1}. \blacksquare$$

Lemma 9 Under the assumptions of Lemma 8, $\{m_k\}$ is a bounded monotone increasing sequence, and $\{M_k\}$ is a bounded monotone decreasing sequence.

Proof Considering (40), we can write

$$m_{k+1} = \underline{h}(\bar{h}(m_k)),$$

and

$$M_{k+1} = \bar{h}(\underline{h}(M_k)).$$

where $\underline{h}(x)$ and $\bar{h}(x)$ are both monotone decreasing functions. Therefore, $\underline{h}(\bar{h}(x))$ and $\bar{h}(\underline{h}(x))$ are monotone increasing functions. We prove the hypothesis by induction.

In the initial step,

$$\begin{aligned} M_0 &= \frac{S_b f(S_b)H(S_b)R_M}{H(\psi_R r - \omega_R)R_m} \\ &\geq \frac{S_b f(S_b)H(S_b)R_M}{H(\psi_R r - \omega_R + H(m_0)m_0)R_m} \\ &= \frac{S_b f(S_b)H(S_b)R_M}{Hf(m_0)R_m} = \bar{h}(m_0) = M_1 \end{aligned}$$

Next, assume there exists an integer $k \in \mathbb{N}$ such that $M_k \leq M_{k-1}$. Then,

$$M_{k+1} = \bar{h}(\underline{h}(M_k)) \leq \bar{h}(\underline{h}(M_{k-1})) = M_k$$

Moreover,

$$m_k = \underline{h}(M_k) \geq \underline{h}(M_{k-1}) = m_{k-1}$$

Thus, $M_k \geq M_{k+1}$ and $m_k \leq m_{k+1}$ for all $k \geq 0$. \blacksquare

Lemma 10 Under the assumptions of Lemmas 8-9,

$$\sqrt{\frac{R_b S_b R_M}{M_*}} \leq R_m \leq R_b \leq R_M \leq \sqrt{\frac{R_b S_b R_M}{m_*}}$$

Proof According to Lemmas 8-9, we now have that $m_* \leq S_m \leq S_b \leq S_M \leq M_*$.

Again, we construct a full time solution (\mathbf{S}, \mathbf{R}) such that

$$R_m = \mathbf{R}(0) = \min_{t \in \mathbb{R}} \mathbf{R}(t),$$

$$R_M \geq \max_{t \in \mathbb{R}} \mathbf{R}(t),$$

$$S_m \leq \mathbf{S}(t) \leq S_M, \forall t \in \mathbb{R}.$$

Subsequently,

$$R_m = \frac{1}{\psi_R} f(\mathbf{S}(0)) = \frac{R_b}{f(S_b)} f(\mathbf{S}(0)). \tag{48}$$

Since $\bar{h}(m_*) = M_*$, and

$$\begin{aligned} S_b f(S_b) &= M_* f(m_*) \frac{R_m}{R_M} \frac{H}{H(S_b)} \\ &\leq M_* f(m_*) \frac{R_m}{R_M} \leq M_* f(\mathbf{S}(0)) \frac{R_m}{R_M}. \end{aligned} \tag{49}$$

As a result of (48) and (49),

$$\frac{R_b S_b R_M}{M_* R_m} \leq \frac{R_b}{f(S_b)} f(\mathbf{S}(0)) = R_m.$$

Therefore,

$$\sqrt{\frac{R_b S_b R_M}{M_*}} \leq R_m.$$

Similarly, $R_M \leq \sqrt{\frac{R_b S_b R_M}{m_*}}$ is proven \blacksquare

Theorem 11 Define

$$L_4 = \frac{S_b}{R_b}, \tag{50}$$

and

$$L_5 = \frac{M_*}{R_b}. \tag{51}$$

Then,

$$S_b - S_m \leq L_4 (R_M - R_b), \tag{52}$$

and

$$S_M - S_b \leq L_5 (R_b - R_m). \tag{53}$$

Under the assumptions of Lemmas 8-9, every bounded positive solution of (34) and (35) converges to the positive equilibrium if $L_1 L_2 L_4 L_5 < 1$, where L_1 and L_2 are defined as (26) and (27), respectively.

Proof In order to prove (52), a full-time solution $(\mathcal{S}, \mathcal{R})$ is constructed such that

$$S_m = \mathcal{S}(0) = \min_{t \in \mathbb{R}} \mathcal{S}(t),$$

$$S_M \geq \max_{t \in \mathbb{R}} \mathcal{S}(t),$$

$$R_m \leq \mathcal{R}(t) \leq R_M \quad \forall t \in \mathbb{R}.$$

Consequently,

$$S_m = \frac{I}{H(S_m)\mathcal{R}(-\tau)}.$$

Recall that $S_m \leq S_b$, so that $R_b \leq \mathcal{R}(-\tau)$. Therefore,

$$\begin{aligned} S_b - S_m &= \frac{I(H(S_m)\mathcal{R}(-\tau) - H(S_b)R_b)}{H(S_m)H(S_b)R_b\mathcal{R}(-\tau)} \\ &\leq \frac{I(\mathcal{R}(-\tau) - R_b)}{H(S_b)R_b\mathcal{R}(-\tau)} \\ &= \frac{S_b}{\mathcal{R}(-\tau)}(\mathcal{R}(-\tau) - R_b) \leq \frac{S_b}{R_b}(R_M - R_b). \end{aligned}$$

The inequality (53) can be proven in the same way by constructing a full time solution $(\mathcal{O}, \mathcal{R})$ such that

$$\begin{aligned} S_M &= \mathcal{O}(0) = \max_{t \in \mathbb{R}} \mathcal{O}(t), \\ S_m &\leq \min_{t \in \mathbb{R}} \mathcal{O}(t), \\ R_m &\leq \mathcal{R}(t) \leq R_M, \forall t \in \mathbb{R}. \end{aligned}$$

We conclude from (37), (38), (52), and (53) that

$$R_M - R_b \leq L_1 L_2 L_4 L_5 (R_M - R_b).$$

When $L_1 L_2 L_4 L_5 < 1$, $R_M = R_b$. Thus, by Lemma 5, bounded solutions of (34)-(35) converge to (S_b, R_b) . ■

V. OSCILLATION AND DELAY EFFECT

Linearizing the system (1)–(2) about the basal levels (S_b, R_b) , we are led to the following associated characteristic equation.

$$\lambda^2 + a\lambda + be^{-\lambda\tau} + c = 0, \tag{54}$$

where

$$a = \psi_R R_b + R_b [H'(S_b)S_b + H(S_b)] + (\omega_S - \psi_S), \tag{55}$$

$$b = H(S_b)S_b R_b [H'(S_b)S_b + H(S_b)], \tag{56}$$

$$c = \psi_R R_b [R_b (H'(S_b)S_b + H(S_b)) + (\omega_S - \psi_S)]. \tag{57}$$

Considering (54) with (55)-(57), Martin *et al.* [14] provided certain sufficient conditions,

$$\psi_R R_b + R_b [H'(S_b)S_b + H(S_b)] + (\omega_S - \psi_S) > 0, \tag{58}$$

$$(\psi_R r - \omega_R) [H'(S_b)S_b + H(S_b)] + \psi_R (\omega_S - \psi_S) < 0, \tag{59}$$

so that the system (1)–(2) will have asymptotically stable solution if

$$\tau < \tau_0,$$

where

$$\tau_0 = \frac{1}{\omega} \arctan \left(\frac{a\omega}{(c - \omega^2)} \right),$$

It will have oscillating solution if $\tau > \tau_0$ and

$$\omega^2 = \frac{-a^2 + 2c + \sqrt{(-a^2 + 2c)^2 - 4(c^2 - b^2)}}{2}.$$

In order to investigate the effect of delays, let t_0 and t_1 , such that $t_0 < t_1$, be two (large enough) consecutive zeros of $R - R_b$ with $R(t) > R_b$ for all $t \in (t_0, t_1)$. Then, there is a point $t_* \in (t_0, t_1)$ such that $R(t_*) = \max_{t \in [t_0, t_1]} R(t) > R_b$. It follows that $\dot{R}(t_*) = 0$, and

$$R(t_*) = \frac{R_b}{f(S_b)} f(S(t_*)).$$

Definition 12 Let t_0 and t_1 , such that $t_0 < t_1$, be two (large enough) consecutive zeros of $R - R_b$ with $R(t) > R_b$ for all $t \in (t_0, t_1)$. Then, there is a point $t_* \in (t_0, t_1)$ such that $R(t_*) = \max_{t \in [t_0, t_1]} R(t) > R_b$. If $t_0 \geq t_* - 2\tau$, we say that R is **oscillating rapidly** in the interval (t_0, t_1) . In the case $R(t) < R_b$ for all $t \in (t_0, t_1)$, we let $t_* \in (t_0, t_1)$ be the point such that $R(t_*) = \min_{t \in [t_0, t_1]} R(t) < R_b$ and define the rapid oscillation in the same way.

An oscillating solution (S, R) of (34) and (35) is called **eventually rapidly oscillating** around the basal levels if R is oscillating rapidly in every (but finite number of) intervals constructed by two consecutive zeros of $R - R_b$.

If R is not oscillating rapidly, we say R is **slowly oscillating**.

The existence of rapidly oscillating solutions have been discussed by Gyori and Trofimchuk [12] for Nicholson blowflies equations, Giang *et al.* [10] for nonlinear population models, and Giang *et al.* [11] for glucose-insulin interaction model with delays.

Lemma 13 Suppose $F(S) \equiv H(S)S$ is continuously differentiable and $\omega_R > \psi_R r$. If (S, R) is an eventually rapidly oscillating solution of (1)-(2), then

$$R_M - R_b \leq L_3 (1 - e^{-2\psi_R r R_m \tau}) (S_M - S_b), \tag{60}$$

$$R_b - R_m \leq L_4 (1 - e^{-2\psi_R r R_m \tau}) (S_b - S_m), \tag{61}$$

where

$$\begin{aligned}
 L_3 &= \frac{R_M}{\psi_R r R_m} \sup_{S \in [S_b, \infty)} F'(S), & &\leq \frac{S_b}{\omega_s - \psi_s} L_2 L_4 \left(1 - e^{-2\psi_R r R_m \tau}\right)^2 L_3 (S_M - S_b) \\
 L_4 &= \frac{R_M}{\psi_R r R_m} \sup_{S \in [0, S_b)} F'(S), & &\leq \frac{S_b^2}{(\omega_s - \psi_s)^2} L_1 L_2 L_3 L_4 \left(1 - e^{-2\psi_R r R_m \tau}\right)^2 (R_b - R_M) \\
 & & &\leq (R_b - R_M).
 \end{aligned}$$

Proof We construct a full time solution $(\mathcal{S}, \mathcal{R})$ such that

$$\begin{aligned}
 R_M &= \mathcal{R}(0) = \max_{t \in \mathbb{R}} \mathcal{R}(t), \\
 R_m &\leq \min_{t \in \mathbb{R}} \mathcal{R}(t), \\
 S_m &\leq \mathcal{S}(t) \leq S_M, \quad \forall t \in \mathbb{R}.
 \end{aligned}$$

As before, we have $R_M = \mathcal{R}(0) = \frac{1}{\psi_R} f(\mathcal{S}(0))$, and $\mathcal{S}(0) \geq S_b$. From (2), we have

$$\begin{aligned}
 e^{\psi_R r R_m t} R(t) &\leq e^{\psi_R r R_m t_0} R(t_0) \\
 &+ \int_{t_0}^t e^{\psi_R r R_m s} H(\mathcal{S}) \mathcal{S}(s) R(s - \tau) ds
 \end{aligned}$$

Let $t = 0$ and $t_0 (\leq 0)$ be the first time in negative axis that $R(t_0) = R_b$. It follows that

$$R_M - R_b \leq L_3 \left(1 - e^{\psi_R r R_m t_0}\right) (S_M - S_b).$$

By the definition of the fast oscillation, we have $t_0 > -2\tau$. Hence, we obtain (60) and the proof of (61) is similar. ■

Theorem 12 If

$$\begin{aligned}
 \frac{S_b^2}{(\omega_s - \psi_s)^2} L_1 L_2 L_3 L_4 \left(1 - e^{-2\psi_R r R_m \tau}\right)^2 &\leq 1, & (62) \\
 \omega_s - \psi_s &> 0,
 \end{aligned}$$

and

$$\omega_R - \psi_R r > 0,$$

then, every rapidly oscillating solution of (1), (2) converges to the positive equilibrium.

Proof From (31) and (32), we have

$$S_M - S_b \leq L_1 \frac{S_b}{\omega_s - \psi_s} (R_b - R_m), \tag{63}$$

$$S_b - S_m \leq L_2 \frac{S_b}{\omega_s - \psi_s} (R_M - R_b). \tag{64}$$

Hence, from (60)-(61) and (63)-(64),

$$\begin{aligned}
 R_b - R_m &\leq L_4 \left(1 - e^{-2\psi_R r R_m \tau}\right) (S_b - S_m) \\
 &\leq L_4 \left(1 - e^{-2\psi_R r R_m \tau}\right) L_2 \frac{S_b}{\omega_s - \psi_s} (R_M - R_b)
 \end{aligned}$$

since (62) holds. Thus, we have $R_b = R_m$.

Similarly, we can show that $R_M = R_b$, and that $S_M = S_b = S_m$. Therefore, the solution converges to (S_b, R_b) . ■

VI. CONCLUSION

We have shown that the system is uniformly persistent when the response function $H(\cdot)$ is a non-decreasing function of S . Further, the equilibrium state (S_b, R_b) is globally stable in the case that the removal rate $\omega_s = d_s + k$ of the sensitive strain is greater than its specific growth rate.

One crucial underlying assumption that ensures persistence and stability is that the ‘‘cost of resistance’’ γ is low enough so that its inverse, the carrying capacity r , is high enough for $\psi_R r$ to exceed the death rate ω_R of the resistant strain. If the cost of resistance is sufficiently high then the persistence or stability of the system could be lost, leading to extinction of one strain or both, unless certain conditions on the delay τ are satisfied.

The main advantage of modelling and analysis is that we may quantitatively investigate the possible strategies for therapy and control in terms of the complex dynamics of competing bacterial or viral strains. Clinically, it is difficult to assess pharmaco-dynamic effects of therapy regimens due to the complexity in repeatedly determining the viral load at the site of infection and antibiotic concentrations during the dosing interval [15]. Using dynamic models of sensitive-resistant strains interactions can overcome these difficulties. Through the above model development and analysis, we gain insightful information that could prove useful in designing empiric therapy and monitoring strategies.

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