Stability and persistence of delayed resistant and sensitive bacterial strains interaction under impulsive drug treatment

Pailin Chayapham, Yongwimon Lenbury

***Abstract*—**Drug resistance occurs when living organisms such as bacteria, viruses, fungi and parasites change in ways that render the medications used incapable of curing the disease or medical conditions they cause. The microorganisms which have become resistant to most antimicrobials are commonly referred to as "superbugs". This development is a major concern to patients and physicians because a resistant infection may be vital, being able to spread to others, and impose huge costs to individuals and society. Here, we consider a model of the dynamic interaction between sensitive and resistant strains of pathogens in a nutrient limiting environment of the gastrointestinal tract. A delay τ in the process of conversion from a sensitive strain to a resistant strain is incorporated by addition of a delay in the rate equation of the resistant strain with an exponential factor to account for the probability that a resistant bacteria survives from the time $t-\tau$ to the time *t*. The system is analyzed for the stability of its various equilibrium solutions. The model is then expanded to take into account the effect of periodic drug treatment leading us to a system of delayed impulsive differential equations. Conditions are discovered under which the system is persistent, and stability of the susceptible strain free equilibrium and the bacterial free equilibrium can be expected.

Keywords—Drug resistance, Conversion delay, Impulsive drug treatment, Stability, Persistence.

I. Introduction

DRUG resistance, or chemical resistance, is a consequence of evolution by means of natural selection, which results in the change in the inherited characteristics of living organisms over successive generations [1]. Resistance to drugs or chemicals or toxins is a response to pressures imposed on any biological population and individual organisms may vary in the extent to which they are sensitive to the drug used. Those with greater fitness may be more capable of surviving drug treatment. Drug-resistant traits are consequently inherited by the offspring of the resistant individuals, giving rise to a population that is more drug-resistant. Drug resistance increases in severity if the drug in use is not capable of making sexual reproduction or cell-division or horizontal gene transfer impossible in the entire target population. This can be seen in some cancer cells which may develop resistance to the drugs used in chemotherapy [1].

According to [2] about 70 percent of the microorganisms that cause infections are resistant to at least one of the drugs commonly used for treatment. Some microbes are resistant to all approved antibiotics and doctors are forced into treatment using experimental and potentially toxic drugs. In a recent study [2], 25% of bacterial pneumonia patients were discovered to be resistant to penicillin. Moreover, an additional 25% of patients have acquired resistance to more than one antibiotic. The microorganisms which have become resistant to most antimicrobials are commonly referred to as "superbugs". A major part of the problem is the increasing use, and misuse, of existing antibiotics, while one of the factors that contributes to the increasing spread of such bacteria, making previously manageable problems of resistance more serious, is global travel.

Increasing number of research reports and articles reflects the gravity of the situation which necessitates the continual search for new antibiotics in order to maintain a supply of effective drugs at all times. It is commonly acknowledged that the development of resistant strains is unavoidable, but the slack ways that antibiotics are administered and used has greatly exacerbated the situation [3]. Unless we can detect and contain antibiotic resistance as soon as it emerges, society could be faced with infections that we may have no hope of curing.

Several models [4]-[7] have been proposed to assist the physicians in the attempt to contain the development of antibiotic resistance. In 2007, Puttasontiphot et al. [8] proposed and analyzed a mathematical model of antimicrobial resistance in the gastrointestinal tract which involves the resistant strain, sensitive strain, and the amount of available nutrients. The model did not take into account the delay in the process by which the sensitive bacteria are converted into the resistant population. However, there have been reported evidence [9], [10] that there is a time delay in the process of plasmid transfer which converts a susceptible into a resistant member of the microbial population. Although Sirinukunwattana et al. later incorporated the delays in their model of antibiotic resistance [11], it was assumed that the nutrients are abundantly available so that the process which they modelled was not nutrient-limited.

P. Chayapham is with the Department of Mathematics, Faculty of Science, Mahidol University, Rama 6 Road, Bangkok 10400 and the Centre of Excellence in Mathematics, CHE, 328 Si Ayutthaya Road, Bangkok 10400 THAILAND (e-mail: pailin26@hotmail.com).

Y. Lenbury is with the Department of .Mathematics, Faculty of Science, Mahidol University, Rama 6 Road, Bangkok 10400 and the Centre of Excellence in Mathematics, CHE, 328 Si Ayutthaya Road, Bangkok 10400 Thailand (corresponding author, phone: 662-201-5448; fax: 662-201-5343; e-mail: scylb@yahoo.com).

In this paper, we consider a nutrient limited situation of antibiotic resistance with conversion delay. A delay τ in the process of conversion from a sensitive strain to a resistant strain is incorporated by addition of a delay in the rate equation of the resistant strain with an exponential factor to account for the probability that a resistant bacteria survives from the time $t-\tau$ to the time *t*. The model is analyzed for the stability of its 4 equilibrium solutions conditional on the delay. The model is then expanded to take into account the effect of periodic drug treatment leading us to a system of delayed impulsive differential equations. Conditions are discovered under which the system is persistent, and stability of the resistant strain free equilibrium and the sensitive strain free equilibrium can be expected. Persistence of the bacterial free equilibrium, and the susceptible bacteria free equilibrium, are of great relevance clinically since such information can benefit a physician in the attempt to treat or contain the developing symptoms at the risk of drug resistance development.

II. Referenced Model

As in [8], we shall let $x(t)$ be the density of bacteria sensitive to antibiotics, $y(t)$ the density of bacteria resistant to antibiotics, and $z(t)$ the concentration of nutrients available in the environment, such as the gastrointestinal tract, for bacterial growth.

In the work by Andrup et al. [9] on the kinetics of conjugative transfer, a study was carried out of the plasmid pXO16 from Bacillus thuringiensis subsp. Israelensis. It was discovered that the conjugative transfer takes about 3 to 4 min. The mating complex was found to consist of one donor and one recipient cell. Having donated the plasmid, Andrup et al. [9] reported that the donor needs a "period of recovery" of approximately 10 min before it can redonate the plasmid. Moreover, it was found that during short observation period when the recipient cells were in excess compared with the donors, the process of conjugation could be reasonably described by a kinetic model analogous to the Michaelis-Menten model for enzyme catalysis [9].

Taking the above report into account, we may then construct the following model system, based on the core model in [8], which incorporates the time delay in the plasmid transfer.

$$x' = \frac{a_1 x(t) z(t)(\gamma - x(t))}{K_s + z(t)} - a_2 x(t) - \frac{\varepsilon_r x(t) y(t)}{k_\gamma + x(t)} - \omega_1 x(t) \tag{1}$$

$$y' = \frac{\varphi_R y(t) z(t)}{K_R + z(t)} + \frac{\varepsilon_r e^{-\mu_1 \tau} x(t-\tau) y(t-\tau)}{k_\gamma + x(t-\tau)} - \omega_2 y(t) \tag{2}$$

$$z' = \omega_3 z^* - \frac{a_3 x(t) z(t)}{K_S + z(t)} - \frac{a_4 y(t) z(t)}{K_R + z(t)} - \omega_3 z \tag{3}$$

with initial condition

$$\big(x(t), y(t), z(t)\big) = \big(\varphi_1(t), \varphi_2(t), \varphi_3(t)\big) \in C_3^+,$$

$$\varphi_i(0) > 0, \ i = 1, 2, 3$$

where $C_3^+ = C\big([-\tau, 0], \Re_3^+\big)$.

The first term on the right of (1) is the growth rate of sensitive population, the second term is the rate of removal due to remaining level of drug in the system, and the third term is the rate of conversion of sensitive into the resistant member, assuming the Michaelis-Menten dynamics as suggested by Andrup et al. [9]. The delay observed in [9]-[10] is incorporated in this conversion term by the time delay τ with the factor $e^{-\mu_1 \tau}$ to take into account the probability that a resistant bacteria survives from the time $t-\tau$ to the time *t*. In the second equation, the first term on the right corresponds to the growth rate of the resistant strain. In order to differentiated between the two strains, the growth rate of the sensitive population has been assumed to take a logistic growth form while that of the resistant population grows exponentially with the population size. The second term on the right of (2) is the rate of increase due to conversion of the sensitive strain through plasmid transfer. In the third equation, the first term is the rate of increase of available nutrients, the second is the rate of its consumption by the sensitive bacteria, and the third is that by to the resistant strain. The last terms in the three equations are the respective removal rates due to natural means.

The following result can be shown concerning the system's equilibrium solutions which satisfy $x' = y' = z' = 0$.

Lemma 1 If

$$\varphi_R > \omega_2 \tag{4}$$

$$\omega_2 > \varepsilon_r e^{-\mu_1 \tau} \tag{5}$$

$$(z^* - \tilde{z})\omega_3 - \frac{a_4 \tilde{y} \tilde{z}}{K_R + \tilde{z}} < 0 \tag{6}$$

$$(z^* - z_\gamma)\omega_3 - \frac{a_3 \gamma z_\gamma}{K_S + z_\gamma} + \frac{a_4 (a_2 + \omega_1)(K_\gamma + \gamma) z_\gamma}{\varepsilon_r (K_R + z_\gamma)} > 0 \tag{7}$$

where

$$\tilde{y} = \frac{K_\gamma}{\varepsilon_r}\left(\frac{\gamma \tilde{z}}{K_S + \tilde{z}} - a_2 - \omega_1\right) \tag{8}$$

$$\tilde{z} = \frac{K_R \omega_2}{\varphi_R} \tag{9}$$

$$z_\gamma = \frac{K_R K_\gamma \omega_2 + \gamma K_R (\omega_2 - \varepsilon_r e^{-\mu_1 \tau})}{K_\gamma (\varphi_R - \omega_2) + (\varphi_R - \omega_2 + \varepsilon_r e^{-\mu_1 \tau})\gamma} \tag{10}$$

then, our delayed differential equation model (1)-(3) possesses 4 physically meaningful equilibriums:

1. $E^* = (0, 0, z^*)$
2. $E_0 = (0, y_0, z_0)$, where

$$y_0 = \frac{(z^* - z_0)\omega_3 \varphi_R}{a_4 \omega_2} \tag{11}$$

$$z_0 = \frac{\omega_2 K_R}{\varphi_R - \omega_2} \tag{12}$$

3. $E_1 = (x_1, 0, z_1)$, where

$$x_1 = \frac{(z^* - z_1)\omega_3 (K_S + z_1)}{a_3 z_1} \tag{13}$$

$$z_1 = \frac{(\omega_1 + a_2)K_S}{a_2(\gamma - x_1) - (a_2 + \omega_1)} \tag{14}$$

4. $E_2 = (x_2, y_2, z_2)$ satisfying

$$x_2 = \left[(z^* - z_2)\omega_3 + \frac{a_4 y_2 z_2}{K_R + z_2} \right] \frac{K_S + z_2}{a_3 z_2} \tag{15}$$

$$y_2 = \left[\frac{a_1 z_2 (\gamma - x_2)}{K_S + z_2} - a_2 - \omega_1 \right] \frac{K_\gamma + x_2}{\varepsilon_r} \tag{16}$$

$$z_2 = \frac{K_R \omega_2 K_\gamma + (\omega_2 - \varepsilon_r e^{-\mu_1 \tau}) K_R x_2}{K_\gamma (\varphi_R - \omega_2) + (\varphi_R - \omega_2 + \varepsilon_r e^{-\mu_1 \tau}) x_2} \tag{17}$$

Proof

This has been shown in our work in [12], but included here for completeness.

It is straight forward to verify that $E_i, i = 1, 2, .., 4,$ satisfy $x' = y' = z' = 0$ with $\tau = 0$.

We next observe from (1) that if $x = \gamma$ then $x' \le 0$ and so $x \le \gamma$. Also, from (3), with $\tau = 0$, that if $z = z^*$, then $z' \le 0$. Therefore, we have $z \le z^*$. Thus, $y_0 \ge 0$. When $y_0 = 0$, we have the equilibrium E_0. The equilibrium E_1 then corresponds to the case $y_0 > 0$. Inequality (4) gives $z_0 > 0$.

For E_1, (13) and (14) yield

$$\begin{aligned} &\Im_1(z_1) \equiv \left[a_1 z^* K_S \omega_3 + K_S a_3 (a_2 + \omega_1) \right] \\ &+ \left[a_3 (a_2 + \omega_1) - \gamma a_1 a_3 + (z^* - K_S) a_1 \omega_3 \right] z_1 - \omega_3 z_1^2 = 0 \end{aligned} \tag{18}$$

$\Im_1(z_1)$ is a quadratic function with $\Im_1(z_1 = 0) > 0$ and $\Im_1(z_1) \to -\infty$ as $z_1 \to \infty$. Thus, (18) has a positive solution $z_1 > 0$.

For E_2, Eq. (15) and (17) yield

$$\Im_2(z_2) \equiv (z^* - z_2)\omega_3 - \frac{a_3 x_2 z_2}{K_S + z_2} + \frac{a_4 y_2 z_2}{K_R + z_2} = 0 \tag{19}$$

From (17), we see that as $x_2 \to 0$, $z \to \tilde{z}$, and by (16)

$$y \to \tilde{y} = \frac{K_\gamma}{\varepsilon_r} \left(\frac{\gamma \tilde{z}}{K_S + \tilde{z}} - a_2 - \omega_1 \right)$$

So, as $x_2 \to 0$,

$$\Im_2 \to (z^* - \tilde{z})\omega_3 - \frac{a_4 \tilde{y} \tilde{z}}{K_R + \tilde{z}} < 0 \tag{20}$$

by (6). As $x_2 \to \gamma^-$,

$z \to z_\gamma$,

and by (17)

$$y \to y_\gamma = -\frac{(a_2 + \omega_1)(K_\gamma + \gamma)}{\varepsilon_r} < 0$$

So, as $x_2 \to \gamma^-$, we have

$$\Im_2 \to (z^* - z_\gamma)\omega_3 - \frac{a_3 \gamma z_\gamma}{K_S + z_\gamma} + \frac{a_4 (a_2 + \omega_1)(K_\gamma + \gamma) z_\gamma}{\varepsilon_r (K_R + z_\gamma)} > 0$$

by (7). Hence, by the Intermediate Value Theorem, there is a $z_2, 0 < z_2 < z_\gamma$, such that $\Im_2 = 0$. This means, the E_2 is a positive equilibrium, which completes the proof. □

In what follows, we shall use the notation

$u_\tau \equiv u(t - \tau)$

We next use the comparison theorem to show the solutions to the delay model system (1)-(3) are bounded under suitable conditions in [12], which is presented here for completeness.

Theorem 1 There is an $M > 0$ such that for any solution $(x(t), y(t), z(t))$ of (1)-(3) with positive initial values, $x(t) \le M$, $y(t) \le M$, $z(t) \le M$ for all large *t*, provided

$$a_2 + \omega_1 > a_1 \gamma \tag{21}$$

Proof

We let

$$w \equiv e^{-\mu_1 \tau} x_\tau + y(t) + \frac{\varphi_R}{a_4} z(t)$$

and

$h = \min(a_2 + \omega_1 - a_1 \gamma, \omega_2, \omega_3) > 0$.

The derivative of *w* along positive solutions of (1)-(3) can be derived as follows.

$$\begin{aligned} w' = &\left[\frac{e^{-\mu_1 \tau} a_1 x_\tau z_\tau (\gamma - x_\tau)}{K_S + z_\tau} - e^{-\mu_1 \tau} a_2 x_\tau \right. \\ &\left. - \frac{\varepsilon_\gamma e^{-\mu_1 \tau} x_\tau y_\tau - \omega_1 x_\tau}{K_\gamma + x_\tau} \right] + \left[\frac{\varphi_R yz}{K_R + z} + \frac{\varepsilon_\gamma e^{-\mu_1 \tau} x_\tau y_\tau}{K_\gamma + x_\tau} - \omega_2 y \right] \\ &+ \left[\frac{\varphi_R}{a_4} \right] (z^* - z)\omega_3 - \frac{\varphi_R}{a_4} \frac{a_3 xz}{K_S + z} - \frac{\varphi_R}{a_4} \frac{a_4 yz}{K_R + z} \\ &\le e^{-\mu_1 \tau} (a_1 \gamma - a_2 - \omega_1) x_\tau - \omega_2 y - \frac{\omega_3 \varphi_R}{a_4} z + \frac{\varphi_R z^*}{a_4} \\ &\le \frac{\varphi_R z^*}{a_4} - hw(t) \end{aligned}$$

due to (21).

We consider the following comparison equation

$$w_1' = \frac{\varphi_R z^*}{a_4} - h w_1(t)$$

which gives

$$w_1 = \frac{\varphi_R z^*}{a_4 h} + k e^{-ht} \to \frac{\varphi_R z^*}{a_4 h} \equiv M \text{ as } t \to \infty. \tag{22}$$

If $(x(t), y(t), z(t))$ is a solution of (1)-(3) with the initial conditions $x(\theta) > \phi_1(\theta) > 0$, $y(\theta) > \phi_2(\theta) > 0$, and $z(\theta) > \phi_3(\theta) > 0$, there then exists an *M*, depending only on the

model parameters, such that $w(t) < w_1(t)$, by the Comparison Theorem. Consequently, by the definition of w and (22), each solution with positive initial values is uniformly bounded. □

III. Stability System Equilibriums

In this section, we investigate the stability property of each of the 4 equilibriums given above.

Bacteria Free Equilibrium E^*:

By linearizing the system (1)-(3) about E^* and finding its Jacobian matrix J^* at E^*, we can prove the following [12].

Theorem 2 If

$$\omega_2 > \frac{\varphi_R z^*}{K_R + z^*} \tag{23}$$

$$a_2 + \omega_1 > \frac{a_1 \gamma z^*}{K_S + z^*} \tag{24}$$

then E^* is locally asymptotically stable for $\tau \geq 0$.

Proof

By linearizing the model system about E^*, we can write the characteristic equation of the model system from its Jacobian matrix J^* at E^* and find that the eigenvalues to be

$\lambda_1 = -\omega_3 < 0,$

$$\lambda_2 = \frac{\varphi_R z^*}{K_R + z^*} - \omega_2,$$

and

$$\lambda_3 = \frac{a_1 \gamma z^*}{K_S + z^*} - \left(a_2 + \omega_1\right).$$

λ_2 is negative by (23), and λ_3 is negative by (24). Thus, all eigenvalues of J^* are negative which means the equilibrium E^* is locally asymptotically stable. □

Susceptible Bacteria Free Equilibrium E_0:

Finding the Jacobian matrix J_0 of (1)-(3) at E_0, one can show the following theorem which has been shown in [12], given again here for completeness.

Theorem 3 If

$$\frac{\varepsilon_r y_0}{K_\gamma} + \omega_1 + a_2 > \frac{\gamma a_1 z_0}{K_S + z_0} \tag{25}$$

then E_0 is locally asymptotically stable for $\tau \geq 0$.

Proof

The eigenvalues of J_0 are

$$\lambda_1 = \frac{\gamma a_1 z_0}{K_S + z_0} - \frac{\varepsilon_\gamma y_0}{K_\gamma} - \omega_1 - a_2 < 0$$

which is negative due to (25), and $\lambda_{1,2}$ that satisfy

$$\lambda^2 + A\lambda + B = 0$$

where

$$A = \frac{a_4 K_R y_0}{\left(K_R + z_0\right)^2} + \omega_3 > 0$$

and

$$B = \frac{a_4 \varphi_R K_R y_0 z_0}{\left(K_R + z_0\right)^3} > 0$$

Therefore, $\lambda_{1,2}$ are both negative. Thus, all eigenvalues of J_0 are negative and hence, the equilibrium E_0 is locally asymptotically stable. □

Resistant Bacteria Free Equilibrium E_1:

Similarly, we can prove the asymptotic stability of E_1 which has been shown in [12], given again here for completeness.

Theorem 4 If

$$\omega_2 > \frac{\varphi_S z_1}{K_R + z_1} + \frac{\varepsilon_\gamma e^{-\mu_1 \tau} x_1}{K_\gamma + x_1} \tag{26}$$

then E_1 is locally asymptotically stable for $\tau \geq 0$.

Proof

Two of the eigenvalues of the Jacobian matrix J_1 at E_1 are $\lambda_{1,2}$ satisfying

$$\lambda^2 + A\lambda + B = 0$$

where

$$A = \frac{a_1 x_1 z_1}{K_S + z_1} + \frac{a_3 K_S x_1}{\left(K_S + z_1\right)^2} + \omega_3 > 0$$

$$B = \frac{a_1 x_1 z_1}{K_S + z_1}\left(\frac{a_3 K_S x_1}{\left(K_S + z_1\right)^2} + \omega_3\right) + \frac{a_3 z_1}{K_S + z_1}\frac{a_1 K_S x_1 (\gamma - x_1)}{\left(K_S + z_1\right)^2} > 0$$

Therefore, $\lambda_{1,2}$ are both negative. The other eigenvalues of J_1 can be solved from

$$\lambda = \frac{\varphi_R z_1}{K_R + z_1} + \frac{\varepsilon_\gamma e^{-(\mu_1 + \lambda)\tau} x_1}{K_\gamma + x_1} - \omega_2 \tag{27}$$

which is negative if $\tau = 0$ due to (26).

Now, suppose $\mathrm{Re}\,\lambda$ can be positive for some $\tau \geq 0$, then there must be a value of $\tau > 0$ at which $\mathrm{Re}\,\lambda = 0$, so that $\lambda = iw$, where ω is real. Substituting this into (27), one obtains

$$iw - \frac{\varphi_R z_1}{K_R + z_1} - \frac{\varepsilon_\gamma x_1 e^{-\mu_1 \tau}}{K_\gamma + x_1}(\cos w\tau - i \sin w\tau) + \omega_2 = 0$$

Equating real and imaginary parts of the above equation to zero, we have

$$w = -\frac{\varepsilon_\gamma x_1 \sin w\tau e^{-\mu_1 \tau}}{K_\gamma + x_1} \tag{28}$$

and

$$\omega_2 - \frac{\varphi_R z_1}{K_R + z_1} = \frac{\varepsilon_\gamma x_1 \cos w\tau e^{-\mu_1 \tau}}{K_\gamma + x_1} \tag{29}$$

Squaring (28)-(29) and adding, we obtain,

$$w^2 = \left(\frac{\varepsilon_\gamma x_1 e^{-\mu_1 \tau}}{K_\gamma + x_1}\right)^2 - \left(\omega_2 - \frac{\varphi_R z_1}{K_R + z_1}\right)^2 < 0 \qquad (30)$$

due to (26).

Thus, (30) has no real solution and therefore, $\mathrm{Re}\,\lambda < 0$ for all $\tau \geq 0$, which means the equilibrium E_1 is locally asymptotically stable. □

Endemic Equilibrium E_2:

Considering the Jacobian matrix J_2 of (1)-(3) at E_2, we can sate the following results which have been shown in [12], given again here for completeness.

Theorem 5 If

$$\frac{a_1 x_2 z_2}{K_S + z_2} > \frac{\varepsilon_\gamma x_2 y_2}{K_\gamma + x_2} \qquad (31)$$

and

$$(c_3 c_7 + c_2 c_8) c_4 + (c_1 c_7 - c_2 c_6) c_5 > 0 \qquad (32)$$

where

$$c_1 = \frac{a_1 x_2 z_2}{K_S + z_2} - \frac{\varepsilon_\gamma x_2 y_2}{(K_\gamma + x_2)^2},\ c_2 = \frac{\varepsilon_\gamma x_2}{K_\gamma + x_2},$$

$$c_3 = \frac{a_1 K_S x_2 (\gamma - x_2)}{(K_S + z_2)^2}, c_4 = \frac{\varepsilon_\gamma K_\gamma y_2}{(K_\gamma + x_2)^2},$$

$$c_5 = \frac{\varphi_R K_R y_2}{(K_R + z_2)^2},\ c_6 = \frac{a_3 z_2}{K_S + z_2}$$

$$c_7 = \frac{a_4 z_2}{K_R + z_2},\ c_8 = \frac{a_3 K_S x_2}{(K_S + z_2)^2} + \frac{a_4 K_R y_2}{(K_R + z_2)^2} + \omega_3$$

then E_2 is locally asymptotically stable for $\tau = 0$.

Proof

For $\tau = 0$, the characteristic equation of J_2 at E_2 can be written as

$$\lambda^3 + C_1 \lambda^2 + C_2 \lambda + C_3 = 0 \qquad (33)$$

where

$C_1 = c_1 + c_8$,

$C_2 = c_2 c_4 + c_1 c_8 + c_3 c_6 + c_5 c_7$,

$C_3 = (c_3 c_7 + c_2 c_8) c_4 + (c_1 c_7 - c_2 c_6) c_5$

In the case that $\tau = 0$, it is clear that C_1 and C_2 are positive, while C_3 is positive since (28) holds. Therefore, by the Routh-Hurwitz criteria, E_2 is locally asymptotically stable for $\tau = 0$. □

Turning our attention to the case where $\tau > 0$, we rely on the work of Culshaw and Ruan [13] and write $\lambda(\tau) = \alpha(\tau) + i\varpi(\tau)$ where $\alpha(\tau)$ and $\varpi(\tau)$ are real. The characteristic equation is now written as

$$\lambda^3 + B_1 \lambda^2 + B_2 \lambda + B_4 + (B_5 \lambda + B_6) e^{-\lambda \tau} = 0 \qquad (34)$$

where

$B_1 = C_1, B_2 = c_1 c_8 + c_3 c_6 + c_5 c_7$,

$B_4 = (c_1 c_7 - c_2 c_6) c_5$

$B_5 = c_2 c_4$,

$B_6 = (c_3 c_7 + c_2 c_8) c_4$

Substituting $\lambda(\tau) = \alpha(\tau) + i\varpi(\tau)$ in (30), we obtain $(\alpha(\tau) + i\varpi(\tau))^3 + B_1 (\alpha(\tau) + i\varpi(\tau))^2 + \mathrm{B}_2 (\alpha(\tau) + i\varpi(\tau))$ and

$$B_4 + e^{-\alpha\tau} (\cos \varpi\tau - i \sin \varpi\tau)(B_5(\alpha + i\varpi) + B_6) = 0 \qquad (35)$$

From Theorem 5, we know that E_2 is locally asymptotically stable for $\tau = 0$, which means $\alpha(0) < 0$. By continuity of the function $\alpha(\tau)$, we are assured that $\alpha(\tau) < 0$ for values of τ such that $0 < \tau < \tau_c$ for some $\tau_c > 0$. That is E_2 remains locally asymptotically stable for these values of τ.

Now, suppose $\alpha(\tau_c) = 0$ for some $\tau_c > 0$, and $\alpha(\tau) < 0$ for values of $0 < \tau < \tau_c$. Then, E_2 may lose its stability at $\tau = \tau_c$, at which point $\lambda(\tau) = i\varpi(\tau_c)$. However, $i\varpi$ is a solution of (33) if and only if

$$-i\varpi^3 - B_1 \varpi^2 + iB_2 \varpi + B_4 + (B_5 i\varpi + B_6)(\cos \varpi\tau - i \sin \varpi\tau) = 0 \qquad (36)$$

Equating the real and imaginary parts in (36) to zero, we obtain

$$B_1 \varpi^2 - B_4 = B_6 \cos \varpi\tau + B_5 \varpi \sin \varpi\tau \qquad (37)$$

$$-\varpi^3 + B_2 \varpi = -B_5 \varpi \cos \omega\tau + B_6 \sin \varpi\tau \qquad (38)$$

Squaring and adding (35) and (36), one obtains

$$\left(B_1 \varpi^2 - B_4\right)^2 + \left(B_2 \varpi - \varpi^3\right)^2 = B_6^2 + B_5^2 \varpi^2 \qquad (39)$$

Letting $k = \varpi^2$ in (39) leads to the equation in *k* as follows.

$$P(k) \equiv k^3 + d_1 k^2 + d_2 k + d_3 = 0 \qquad (40)$$

where

$d_1 = B_1^2 - 2B_2$, $d_2 = B_2^2 - 2B_1 B_4 - B_5^2$,

$d_3 = B_4^2 - B_6^2$

Thus, we state may prove the following results [12].

Lemma 2 Let $\tau > 0$. Under the assumptions (31)-(32) in Theorem 5, suppose (40) has no positive solutions. Then, all solutions of (33) have negative real parts.

Proof

Since (40) has no positive solutions, any real ω cannot be a solution of (33). This means there is no τ_k such that $\lambda(\tau_k) = i\omega(\tau_k)$. Since Theorem 5 ensures that $\lambda(0) = 0$, λ remains negative for all τ by the continuity of $\lambda(\tau)$. □

Lemma 3 Let $K_1 = \dfrac{-d_1 + \sqrt{d_1^2 - 3d_2}}{3}$, and $d_3 > 0$.

i) If $d_2 < 0$ and $P(K_1) < 0$, (40) has a positive solution.

ii) If $d_1^2 - 3d_2 < 0$, (40) has no positive solutions.

Proof

i) Since it is given that $d_2 < 0$, we have

$$\sqrt{d_1^2 - 3d_2} > |d_1|$$

Thus, K_1 is real and positive. From (40), we have $P(0) = d_3 > 0$, with the given fact that $P(K_1) < 0$, by the Intermediate Value Theorem, (40) has a positive solution, say K^*. That is, $P(K^*) = 0$.

ii) If $d_1^2 - 3d_2 < 0$, then $d_2 > \frac{d_1^2}{3} > 0$, which means $P'(k) = 3k^2 + 2d_1 k + d_2 = 0$ has no real solution.

Noting that $P'(0) = d_2 > 0$, we therefore know that the quadratic polynomial $P'(k)$ is strictly positive on the real line. Since $P(0) = d_3 > 0$, the function $P(k)$ does not vanish anywhere on the positive real line, and hence (40) has no positive solution. □

Consequently, we have the next result concerning the stability of the equilibrium solution E_2 [12].

Theorem 6

If the equilibrium E_2 exists, (31)-(32) hold, and

$$d_1^2 - 3d_2 < 0 \tag{41}$$

then E_2 is locally asymptotically stable for $\tau \geq 0$.

Proof

When $\tau = 0$, Theorem 5 states that all eigenvalues of J_2 have negative real parts, provided (31) and (32) hold. By part ii) of Lemma 2, (40) has no positive solutions under the assumption (41).

IV. System Under Impulsive Drug Treatment

From the delayed system (10)-(3), we have construct in [14] an impulsive system to describe the periodic drug intakes, and arrive at the following model system.

$$x'(t) = \frac{a_1 x(t) z(t)\left(\gamma - x(t)\right)}{K_S + z(t)} - a_2 x(t) - \frac{\varepsilon_\gamma x(t) y(t)}{K_\gamma + x(t)} - \omega_1 x(t), t \neq nT \tag{42}$$

$$y'(t) = \frac{\psi_R y(t) z(t)}{K_R + z(t)} + \frac{\varepsilon_\gamma e^{-\mu_1 \tau} x(t-\tau) y(t-\tau)}{K_\gamma + x(t-\tau)} - \omega_2 y(t), t \neq nT \tag{43}$$

$$z'(t) = \left(z^* - z(t)\right)\omega_3 - \frac{a_3 x(t) z(t)}{K_S + z(t)} - \frac{a_4 y(t) z(t)}{K_R + z(t)}, t \neq nT \tag{44}$$

$$x(t^+) = (1-\mu)x(t), \quad t = nT, \quad n = 1, 2, \ldots \tag{45}$$

$$y(t^+) = y(t), \quad t = nT, \quad n = 1, 2, \ldots \tag{46}$$

$$z(t^+) = z(t), \quad t = nT, \quad n = 1, 2, \ldots \tag{47}$$

where $\left(x(t), y(t), z(t)\right) = \left(\varphi_1(t), \varphi_2(t), \varphi_3(t)\right) \in C_3^+$, such that $\varphi_i(0) > 0$, $i = 1, 2, 3$, with $C_3^+ = C\left(\left[-\tau, 0\right], \Re_3^+\right)$, and $x(t^+), y(t^+)$, and $z(t^+)$ being the right limits of $x(t), y(t)$, and $z(t)$ at time t, respectively. T is the period and μ $\left(0 < \mu < 1\right)$ represents the killing effort, or strength of prescribed drug.

Next, we discuss the stability behavior of the bacteria free equilibrium as well as the susceptible bacteria free equilibrium of (42)-(47), which corresponds to the desirable situation where both susceptible and resistant bacterial populations become extinct.

In order to investigate the stability of the system's equilibriums, we need the following result on the positivity of the solutions, the proof of which is quite straight forward and therefore it is stated without proof [14].

Lemma 4

Suppose $\boldsymbol{X}(t) = (x(t), y(t), z(t))$ is a solution of (42)-(47) with $\boldsymbol{X}(0^+) \geq 0$, then $\boldsymbol{X}(t) \geq 0$ for all $t \geq 0$. Moreover, $\boldsymbol{X}(t) > 0$ for all $t \geq 0$ if $\boldsymbol{X}(0^+) > 0$.

The stability of the bacterial free equilibrium $(0, 0, z^*)$ has already been established in [14] and we state the result here without proof.

Theorem 7 The bacterial free solution $(0, 0, z^*)$ of (10)-(15) is globally stable for $\tau \geq 0$ provided

$$a_2 + \omega_1 > a_1 \gamma \tag{48}$$

and

$$\omega_2 > \psi_R \tag{49}$$

Next, to investigate the stability of the susceptible strain free equilibrium we let

$$R_0 \equiv \frac{a_1 K_\gamma \gamma}{K_\gamma (a_2 + \omega_1) + \varepsilon_\gamma y_0},$$

$$a = \frac{\gamma a_1 z_0}{K_S + z_0} - a_2 - \frac{\varepsilon_\gamma y_0}{K_\gamma} - \omega_1,$$

$$b = \frac{\varphi_R e^{-\mu_1 \tau} y_0}{K_\gamma},$$

$$c = \frac{\varphi_R k_R y_0}{(K_R + z_0)^2},$$

$$d = \frac{a_3 z_0}{K_S + z_0},$$

$$e = \frac{a_4 z_0}{K_R + z_0},$$

and

$$f = \frac{a_4 K_R y_0}{\left(K_R + z_0\right)^2} + \omega_3$$

then the following theorem show that the sensitive strain free equilibrium $E_0 = (0, y_0, z_0)$ is asymptotically stable under suitable conditions on the system parameters.

Theorem 8 Suppose

$$\alpha \equiv \frac{-f+\sqrt{f^2-4ce}}{2},$$

$$\beta \equiv \frac{f+\sqrt{f^2-4ce}}{2} < c, \tag{52}$$

and

$$R_0 < 1. \tag{53}$$

The susceptible bacteria free equilibrium solution is locally asymptotically stable provided

$$\frac{1}{T} > \frac{\alpha}{\ln\left(1+\alpha/\beta\right)^{-1}} \tag{54}$$

Proof

The Jacobian matrix of (42)-(44) at E_0 can be written as

$$J_0 = \begin{bmatrix} a & 0 & 0 \\ b & 0 & c \\ -d & -e & -f \end{bmatrix}$$

The eigenvalues of J_0 are

$\lambda_1 = a$

which is negative due to (53), and

$$\lambda_2 = \frac{-f+\sqrt{f^2-4ce}}{2} = \alpha$$

$$\lambda_3 = \frac{-f-\sqrt{f^2-4ce}}{2} = -\beta$$

which are both negative since e, f, and c are all positive, by their definitions above. The corresponding eigenvectors are

$$\begin{pmatrix} 1 \\ \delta_1 \\ \delta_2 \end{pmatrix}, \begin{pmatrix} 0 \\ 1 \\ \alpha/c \end{pmatrix}, \text{ and } \begin{pmatrix} 0 \\ 1 \\ -\beta/c \end{pmatrix},$$

where the exact expressions for δ_1 and δ_2 are not relevant to our analysis which follows.

Using the above eigenvectors as its columns, we form the transformation matrix:

$$P = \begin{pmatrix} 1 & 0 & 0 \\ \delta_1 & 1 & 1 \\ \delta_2 & \alpha/c & -\beta/c \end{pmatrix}$$

and let

$$L_0 = \begin{pmatrix} e^{at} & 0 & 0 \\ 0 & e^{\alpha t} & 0 \\ 0 & 0 & e^{-\beta t} \end{pmatrix}$$

Then, the fundamental solution of the linearized system of (42)-(44) is

$$\varphi(t) = PL_0 = \begin{pmatrix} e^{at} & 0 & 0 \\ \delta_1 e^{at} & e^{\alpha t} & e^{-\beta t} \\ \delta_2 e^{at} & \alpha e^{\alpha t}/c & -e^{-\beta t}\beta/c \end{pmatrix}$$

when $t = nT$, the linearization of (45)-(47) yields

$$\begin{pmatrix} x(t^+) \\ y(t^+) \\ z(t^+) \end{pmatrix} = \begin{pmatrix} 1-\mu & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} x(t) \\ y(t) \\ z(t) \end{pmatrix}$$

According to the Floquet's theorem, the stability of E_0 is determined by the eigenvalues of

$$L = \begin{pmatrix} 1-\mu & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} \varphi(T)$$

$$= \begin{pmatrix} (1-\mu)e^{aT} & 0 & 0 \\ \delta_1 e^{aT} & e^{\alpha T} & e^{-\beta T} \\ \delta_2 e^{aT} & \alpha e^{\alpha T}/c & -e^{-\beta T}\beta/c \end{pmatrix}$$

The eigenvalues $\eta_i, i = 1,2,3,$ of L are such that

$$|\eta_1| = \left|(1-\mu)e^{aT}\right| < 1,$$

since $a < 0$ due to (53),

$$|\eta_2| = \left|(1+\frac{\alpha}{\beta})e^{\alpha T}\right| < 1,$$

Due to the inequality (54), and

$$|\eta_3| = \left|-e^{-\beta T}\beta/c\right| < 1$$

since (52) holds. Therefore, Floquet theory of impulsive differential equations assures that E_0 is locally asymptotically stable. □

To investigate the system's persistence, we need to first show the boundedness of the system's solutions.

Theorem 9 There is an $M > 0$ such that the solutions of (42)–(47) satisfies $x(t) \le M$, $y(t) \le M$, $z(t) \le M$ for all $t \ge 0$ provided

$$a_2 + \omega_1 - a_1\gamma > 0 \tag{55}$$

Proof

We define

$$\underset{\sim}{W}(s) = W(t) \equiv e^{-\mu_1\tau}x_\tau + y(t) + \frac{\varphi_R}{a_4}z_\tau, s = t-\tau$$

Then, with $\dot{(.)}$ being the derivative with respect to s,

$$D^+\underset{\sim}{W} = e^{-\mu_1\tau}\dot{x}_\tau + \dot{y}(t) + \frac{\varphi_R}{a_4}\dot{z}_\tau$$

$$= \frac{e^{-\mu_1\tau}a_1 z_\tau x_\tau(\gamma - x_\tau)}{K_S + z_\tau} - a_2 x_\tau e^{-\mu_1\tau} - e^{-\mu_1\tau}\omega_1 x_\tau$$

$$-\omega_2 y + \frac{a_3 z_1}{\varphi_R} - \frac{\varphi_R\omega_3 z^*}{a_4} - \frac{\varphi_R\omega_3 z}{a_4} \tag{56}$$

Using (55), Eq. (56) leads us to

$$\dot{\underset{\sim}{W}}(s) < \frac{\varphi_R\omega_3 z^*}{a_4} - \xi\left(e^{-\mu_1\tau}x_\tau + y + \frac{\varphi_R}{a_4}z_\tau\right)$$

$$= \rho - \xi W, \text{ if } s \ne nT$$

where $\xi = \min(a_2 + \omega_1 - a_1\gamma, \omega_2, \omega_3)$, which is positive due to (55), and $\rho = \frac{\varphi_R \omega_3 z^*}{a_4}$.

If $s = nT$, we obtain

$$\underset{\sim}{W}(s^+) = e^{-\mu_1\tau}(1-\mu)x_\tau + y(t) + \frac{\varphi_R}{a_4} z_\tau \le \underset{\sim}{W}(s)$$

Thus,

$$\begin{aligned}\underset{\sim}{W}(s) &= \underset{\sim}{W}(0)\exp\int_0^{t-\tau}(-\xi)du + \int_0^{t-\tau}\rho\exp\left(\int_u^{t-\tau}(-\xi)dv\right)du \\ &\le \underset{\sim}{W}(0)\exp\int_0^{s}(-\xi)du + \int_0^{s}\rho\exp\xi(u-s)du \\ &= \underset{\sim}{W}(0)e^{-\xi s} + \rho e^{-\xi s}\int_0^s \exp\xi u du \\ &= \underset{\sim}{W}(0)e^{-\xi s} + \rho e^{-\xi s}\left(\frac{e^{\xi s}-1}{\xi}\right) \\ &\le \underset{\sim}{W}(0)e^{-\xi s} + \frac{\rho}{\xi} \\ &\to \frac{\rho}{\xi} \quad \text{as } s \to \infty.\end{aligned}$$

Therefore,

$$W(t) = \underset{\sim}{W}(s) \le \frac{\rho}{\xi} \equiv M \quad \text{as } t \to \infty$$

Thus, W is bounded, and hence so are the solutions $x(t), y(t),$ and $z(t)$ of (42)-(47). □

Next, persistence of the impulsive delay system (42)-(47) is shown in the following theorem. On the basis of the Theorem 9, we can let $M^* > 0$ be the least upper bound of $x(t), y(t),$ and $z(t)$.

Theorem 10 Under the conditions $0 < x(0) < \gamma$, $y(0) > 0$, $z(0) > 0$, and (55) such that $x(t) \le M^*$, $y(t) \le M^*$, $z(t) \le M^*$ for all $t \ge 0$, the impulsive delay system model (42)-(47) is persistent.

Proof

From (44), we have

$$z'(t) > \omega_3 z^* - \left(\omega_3 + \frac{a_3 M^*}{K_S} + \frac{a_4 M^*}{K_R}\right) z$$

We compare the above with the equation

$$c_3' = \omega_3 z^* - \left(\omega_3 + \frac{a_3 M^*}{K_S} + \frac{a_4 M^*}{K_R}\right) c_3$$

which yields

$$\lim_{t\to\infty} c_3 = \frac{\omega_3 z^*}{\left(\omega_3 + \frac{a_3 M^*}{K_S} + \frac{a_4 M^*}{K_R}\right)}$$

Hence, by the Comparison Theorem, there exist $t_1 > 0$ and $\varepsilon_3 > 0$ such that

$$z(t) \ge c_3(t) > \frac{\omega_3 z^*}{\left(\omega_3 + \frac{a_3 M^*}{K_S} + \frac{a_4 M^*}{K_R}\right)} - \varepsilon_3 = m_3 > 0 \text{ for all } t \ge t_1$$

From (42), we have

$$x'(t) > \frac{a_1 m_3(\gamma - M^*)}{K_S + M^*} x - (a_2 + \omega_1 + \frac{\varepsilon_\gamma M^*}{K_\gamma})x$$

We thus have

$$x'(t) \ge q(t) - px(t), t \ne nT$$
$$x(t^+) = (1-\mu)x(t), t = nT$$

where

$$p = a_2 + \omega + \frac{\varepsilon_\gamma M^*}{K_\gamma} > 0$$

and

$$q(t) = \frac{m_3(\gamma - M^*)}{K_S + M^*} x(t)$$

Integrating, we obtain

$$\begin{aligned}x(t) &\ge (1-\mu)x(0)\exp(\int_0^t(-p)ds) \\ &\quad + \int_0^t[(1-\mu)\exp(\int_s^t(-p)d\theta)q(s)]ds \\ &\ge (1-\mu)e^{-pt}x(0) + \int_0^t[(1-\mu)\,\mathrm{e}^{-p(t-s)}\,q(s)]ds \\ &\ge (1-\mu)e^{-pt}[x(0) + \int_0^t \mathrm{e}^{ps}\,q(s)ds]\end{aligned}$$

From our earlier observation, we have $x(t) < \gamma$, easily proved by contradiction. Since M^* is the least upper bound, we have $\gamma > M^*$. Therefore $q(t) > 0$, and so there exists a $t_2 > t_1$ and $\varepsilon_1 > 0$ such that

$$0 < \varepsilon_1 < \liminf_{t\to\infty} q(t) \text{ for all } t \ge t_2$$

Hence,

$$\begin{aligned}x(t) &> (1-\mu)e^{-pt}[x(0) + \int_0^t \mathrm{e}^{ps}\,\varepsilon_1 ds] \\ &> (1-\mu)e^{-pt}[x(0) + \varepsilon_1(\frac{\mathrm{e}^{ps}-1}{p})] \\ &> (1-\mu)e^{-pt}[x(0) - \frac{\varepsilon_1}{p}] + (1-\mu)\frac{\varepsilon_1}{p} > (1-\mu)\frac{\varepsilon_1}{p}\end{aligned}$$

So, we have

$$x(t) > (1-\mu)\frac{\varepsilon_1}{p} \equiv m_1 > 0 \text{ for } t \ge t_2$$

Then, from (43) we then have

$$y'(t) \ge \frac{\varepsilon_\gamma e^{-\mu_1\tau} m_1}{K_\gamma + M^*} y(t-\tau) - \left(\omega_2 - \frac{\varphi_R m_3}{K_R + M^*}\right) y$$

We thus have

$$y'(t) \ge q(t) - py(t), t \ne nT$$
$$y(t^+) = y(t), t = nT$$

where

$$p = \omega_2 - \frac{\varphi_R m_3}{K_R + M^*}$$

and

$$q(t) = \frac{\varepsilon_\gamma e^{-\mu_1 \tau} m_1}{K_\gamma + M^*} y(t-\tau)$$

If ω_2 is sufficiently large, $p > 0$, since m_3 can be arbitrarily small.

Integrating, we obtain

$$\begin{aligned} y(t) &\geq y(0) \exp y(\int_0^t (-p) ds) \\ &\quad + \int_0^t [\exp(\int_s^t (-p) d\theta) q(s)] ds \\ &\geq e^{-pt} y(0) + \int_0^t [\mathrm{e}^{-p(t-s)} q(s)] ds \\ &\geq e^{-pt} [y(0) + \int_0^t \mathrm{e}^{ps} q(s) ds] \end{aligned}$$

Since $q(t) > 0$, there exist $t_3 > t_2$ and $\varepsilon_2 > 0$ such that

$$0 < \varepsilon_2 < \liminf_{t \to \infty} q(t) \text{ for all } t \geq t_2$$

Therefore,

$$\begin{aligned} y(t) &> e^{-pt} [y(0) + \int_0^t \varepsilon_2 \mathrm{e}^{ps} ds] \text{ for all } t > t_3 \\ &= e^{-pt} \left[y(0) + \varepsilon_2 \left(\frac{e^{pt} - 1}{p} \right) \right] \\ &> e^{-pt} \left[y(0) - \frac{\varepsilon_2}{p} \right] + \frac{\varepsilon_2}{p} \end{aligned}$$

Since ε_2 can be arbitrarily small, this yields $y(t) > \frac{\varepsilon_2}{p}$ as $t \to \infty$. This completes the proof. □

V. Discussion And Clinical Interpretation

We have thus constructed and analyzed a model of microbial resistance to drugs in order to illustrate how a delay in the process of plasmid transfer can effect the dynamic behavior of the system. We have found that under suitable conditions, the susceptible strain may win out and the resistant population can vanish, corresponding to the case where E_1 is stable, which is the desirable outcome. The more favorable outcome in the treatment of diseases is, in fact, for the equilibrium E^* to be stable, in which case both strains of the bacterial population vanish.

If we define the reproduction numbers as

$$R_1 = \frac{\varphi_R z^*}{\omega_2 (K_R + z^*)},$$

$$R_2 = \frac{a_1 \gamma z^*}{(a_2 + \omega_1)(K_S + z^*)}$$

then Theorem 2 assures that the equilibrium E^* will be asymptotically stable if $R_1 < 1$, and $R_2 < 1$, and both the susceptible and resistant population will become extinct provided their densities are initially not very much different from the equilibrium.

We have also analyzed a model of drug resistance with time delay under impulsive drug intake, which results in periodic removal of the susceptible bacterial strain or both strains. The model is investigated in terms of the global asymptotic stability of the bacterial free solution. If we let

$$R_3 = \frac{a_1 \gamma}{a_2 + \omega_1}$$

$$R_4 = \frac{\varphi_R}{\omega_2}$$

then, Theorem 7 implies that, under suitable conditions, the system can be free of both bacterial strains, provided

$$R_3 < 1 \quad (57)$$

as well as

$$R_4 < 1 \quad (58)$$

The equilibrium $E^*(0, 0, z^*)$ of (10)-(15) is then globally asymptotically stable for all $\tau \geq 0$.

We note here that if the above 2 inequalities are satisfied then we also have $R_1 < 1$, and $R_2 < 1$. This means that if the bacteria free equilibrium E^* of the delayed system under impulsive drug treatment is globally asymptotically stable, then the bacteria free equilibrium E^* of the system without ant drug treatment will be locally asymptotically stable.

The asymptotic stability of the susceptible strain free equilibrium for the system under drug treatment can be stated in terms of the basic reproduction number R_0, defined by (53), known as the average number of new susceptible bacterial particles that arise from each reproducing bacteria. Assuming that (52) holds, then Theorem 8 assures us that the susceptible bacteria free equilibrium will be locally asymptotically stable for all $\tau \geq 0$ if

$$R_0 < 1$$

and, as in (54),

$$\frac{1}{T} > \frac{\alpha}{\ln(1 + \alpha/\beta)^{-1}}$$

In other words, for the Floquet Theorem to apply (from the proof of Theorem 8), we need to satisfy (54) which puts a restriction on the frequency of the drug treatment $\frac{1}{T}$ conditional on the drug efficacy μ. Inequality (54) gives a very useful and applicable guideline for physicians administering the drug. In particular, it informs us that the frequency of drug applications must exceed the quantity on the right of (54) which depend on μ. If the drug's strength is higher, μ being larger, then the prescribed drug could be taken less frequently. Once the susceptible strain vanishes, the resistant strain, by equation (43) could eventually get eliminated by natural immunological responses, provided of course that there is no additional infection by foreign resistant strain.

Finally, considering the conditions (27), (48), (49), (52) and (55) which involve the delay τ, we see that the delay in the conjugative plasmid transfer does play an important role in the stability or instability of the system.

VI. Conclusion

According to WHO [15], antimicrobial resistance, which refers to the ability of microorganisms to enable a disease to withstand treatment by antimicrobial medicines, is increasingly being detected. Whether it is a drug used to treat common bacterial infections, or the complex combinations now being used to fight HIV infection, resistance is spreading at an alarming pace. Medicines which are once effective in fighting against malaria and tuberculosis have now become virtually useless in many parts of the world [15]. Drug resistance has become a major public health risk and it is feared that its spread can seriously threaten any advances in our ability to medicate and cure diseases.

Our analysis has yielded quite valuable discoveries that can assist the physicians facing with the threat of antibiotic resistance, to be able to make appropriate adjustments in the attempt to contain the worsening degree of drug resistance.

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