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ANALYSIS OF A CHEMOSTAT MODEL FOR ANTIMICROBIAL RESISTANT AND NON-RESISTANT ORGANISMS WITH DELAY

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Abstract

In this paper, we consider the dynamical properties of the time delayed chemostat model composed of the resource, antibiotic, and two bacteria (one is sensitive and the other is resistant by the antibiotic). First, we give a model and summarize several known results on the basic properties of the model such as the existence of the equilibrium and stability of the equilibrium by the Hopf bifurcation theory. Then numerical simulations are presented to illustrate the results of periodic solution.

1. Introduction

Many years ago, antibiotics have been critical in the fight against infectious disease caused by bacteria and other microbes. Disease-causing microbes that have become resistant to antibiotic drug therapy are an increasing public health problem. Nowadays, about 70 percent of the

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bacteria that cause infections in hospital are resistant to at least one of the drugs most commonly used for treatment [11]. Some organisms are resistant to all approved antibiotics and can only be treated with experimental and potentially toxic drugs. Microbial development of resistance, as well as economic incentives, has resulted in research and development in the search for new antibiotics in order to maintain a pool of effective drugs at all times. While the development of resistant strains is inevitable, the slack ways that we administer and use antibiotics has greatly exacerbated the process. In the face of a microbe’s inherent ability to develop antibiotic resistance, many societal, medical, and agricultural practices contribute to this process, foremost of which are discussed below.

Evidence also began to accumulate that bacteria could pass genes for drug resistance between strains and even between species. For example, antibiotic-resistance genes of staphylococci are carried on plasmid that can be exchanged with Bacillus, Streptococcus, and Enterococcus providing the means for acquiring additional genes and gene combinations. Some are carried on transposes, segments of DNA that can exist either in the chromosome or in plasmid. Once the resistance genes have developed, they are transferred directly to all the bacteria's progeny during DNA replication. This is known as vertical gene transfer or vertical evolution.

Several mechanisms have evolved in bacteria, which confer them with antibiotic resistance. These mechanisms can either chemically modify the antibiotic, render it inactive through physical removal from the cell, or modify target site so that, it is not recognized by the antibiotic. The most common mode is enzymatic inactivation of the antibiotic. An existing cellular enzyme is modified to react with the antibiotic in such a way that it no longer affects the microorganism. An alternative strategy utilized by many bacteria is the alteration of the antibiotic target site. These and other mechanisms are shown in Figure 1.

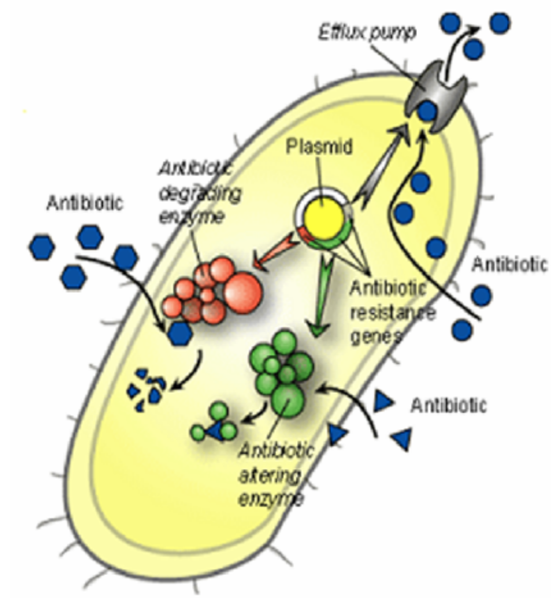

Figure 1. Bacteria's mechanisms.

One of the first models for phage-bacteria interaction was proposed by A. Campbell [2]. The next model was proposed by B. R. Levin et al. [6]. They attempt to analyze the model of bacteria and virulent bacteriophage. In 2002 and 2004, E. Beretta and F. Solinano [1] developed model for bacteria and virulent bacteriophage interaction with latency period.

In 2007, T. Puttasontiphot et al. [9] shown the model that improve the transferring of resistant bacteria to susceptible bacteria. In this paper, we will use this model to present the model of two bacteria of delay (latency period) incorporating the realistic through time death rate in linear stability analysis brings to characteristic equations with delay.

2. Model Construction

$$\frac{dS}{dt_1} = \frac{\psi_S C}{(1 + \gamma_a A)(K_S + C)}(\gamma' - S)S - \frac{\varepsilon_\gamma SR}{K_\gamma + S}$$

$$-\frac{\varepsilon_K AS}{K_K + A} - \omega_1 S, \tag{2.1}$$

$$\frac{dR}{dt_2} = \frac{\psi_R RC}{K_R + C} + \frac{\varepsilon_{\gamma\gamma} S(t-\tau)R(t-\tau)}{K_\gamma + S} - \omega_2 R, \tag{2.2}$$

$$\frac{dC}{dt_3} = (C_1 - C)\,\omega_3 - \frac{\varepsilon_S \psi_S SC}{(1+\gamma_a A)(K_S + C)} - \frac{\varepsilon_R \psi_R RC}{K_R + C}, \tag{2.3}$$

$$\frac{dA}{dt_1} = \omega_4 (A_1 - A). \tag{2.4}$$

We consider a chemostat model with variables $S(t)$, $R(t)$, $C(t)$, and $A(t)$, which present for the population of susceptible bacteria, the population of resistant bacteria, the concentration of the resource, and the concentration of the antibiotic, respectively.

The first term on the right hand side of Equation (2.1) is the growth rate of the susceptible population level as level S. The second term accounts for the reduction in the number of susceptible population level as its member is converted into a resistant strain due to the acquisition of an extra chromosomal element, or plasmid, from members of the resistant strain. Resistance can also be due to chromosomal mutation that renders the strain insensitive to the antibiotics [8]. The resistant bacteria are viruses, which attack the susceptible bacteria. The third term is the rate at which the susceptible bacteria are killed off by the antibiotic. The last term is then the rate of removal of S by natural means. The response functions used in Equations (2.1) and (2.2) are of the Holling's type generally assumed in many previous population models [4], [5]. In Equation (2.4), the antibiotic is removed naturally at the rate, that is proportional to its amount A at any time t.

Equation (2.2) describes the rate of change of the resistant population level R growing at the rate given by the first term, which assumes a Holling type saturating function of the substrate concentration C. The second term in Equation (2.2) accounts for the increase in R due to the development of resistance in the susceptible strain. The time elapsing from the instant of infection, i.e., when the virus injects the content of the virus head inside the bacterium, to the instant of the bacterium cell walllysis, at which ε_γ copies of assembled phages are released in chemostat solution, is called *latency time* [1] and is denoted by τ. This term needs the latent period of the infected bacteria in order to describe this phenomenon. So, this term has the latency time that is used in the second term in Equation (2.1). The last term is then naturally removed at the rate $\omega_2 R$.

Equation (2.3) describes the rate of change of the nutrient or substrate C. The second term on the right hand side accounts for its consumption by the susceptible bacteria S, while the last term accounts for that by the resistant R. Since S is sensitive to the presence of antibiotic A, the consumption rate by S is reduced as A increases, and thus, the factor $1 + \gamma_a A$ in the denominator of this term.

Since Equation (2.4) is autonomous and depends only on A, it can be easily solved for $A(t)$, which is found to tend eventually to A_1 as time progresses. We may therefore consider the above model in the event that A has reached the level A_1. We are thus reduced to the following three equations for $t \geq t_0$:

$$\frac{dS}{dt_1} = \frac{\psi_S C}{(1 + \gamma_a A_1)(K_S + C)}(\gamma' - S)S - \frac{\varepsilon_\gamma SR}{K_\gamma + S} - \frac{\varepsilon_K A_1 S}{K_K + A_1} - \omega_1 S, \quad (2.5)$$

$$\frac{dR}{dt_2} = \frac{\psi_R RC}{K_R + C} + \frac{\varepsilon_\gamma S_\tau R_\tau}{K_\gamma + S} - \omega_2 R, \quad (2.6)$$

$$\frac{dC}{dt_3} = (C_1 - C)\omega_3 - \frac{\varepsilon_S \psi_S SC}{(1 + \gamma_a A_1)(K_S + C)} - \frac{\varepsilon_R \psi_R RC}{K_R + C}, \quad (2.7)$$

with initial conditions

$$S(t_0) = S_{00},$$

$$R(t_0) = R_{00},$$

$$C(t_0) = C_{00}.$$

Therefore, our model consists of Equations (2.5)-(2.7).

3. Model Analysis

In order to apply the singular perturbation method to our system of Equations (2.5)-(2.7), we scale the dynamics of the three hierarchical components of the system by means of two small dimensionless positive parameters ε and δ, and introduce the following new system parameters.

Let $a_1 = \dfrac{\psi_S}{1+\gamma A}$, $a_2 = \dfrac{\varepsilon_K A}{K_K + A}$, $a_3 = \dfrac{\varepsilon_S \psi_S}{1+\gamma A}$, $a_4 = \varepsilon_R \psi_S$, $S = x$, $R = y$, $C = z$, $S(t-\tau) = x_\tau$, $R(t-\tau) = y_\tau$, we are led to the following system of differential equations:

$$\frac{dx}{dt} = f(x, y, z), \tag{3.1}$$

$$\frac{dy}{dt} = \varepsilon g(x, y, z), \tag{3.2}$$

$$\frac{dz}{dt} = \varepsilon\delta h(x, y, z), \tag{3.3}$$

with initial conditions

$$x(0) = x_0,$$

$$y(0) = y_0,$$

$$z(0) = z_0,$$

where

$$f(x, y, z) \equiv \frac{a_1 z}{(K_S + z)}(\gamma - x)x - \frac{\varepsilon_\gamma xy}{K_\gamma + x} - (a_2 + \omega_1)x, \tag{3.4}$$

$$g(x, y, z) \equiv \frac{\psi_R yz}{K_R + z} + \frac{\varepsilon_{\gamma\gamma} x_\tau y_\tau}{K_\gamma + x} - \omega_2 y, \tag{3.5}$$

$$h(x, y, z) \equiv (z_1 - z)\omega_3 - \frac{a_3 xz}{(K_S + z)} - \frac{a_4 yz}{K_R + z}. \tag{3.6}$$

First, we prove a result on the existence and uniqueness of the steady state solution (x_s, y_s, z_s), where $f(x_s, y_s, z_s) = g(x_s, y_s, z_s) = h(x_s, y_s, z_s) = 0$ for the system (3.1)-(3.3) with (3.4)-(3.6). This result yields the following delineating conditions [9].

Lemma 3.1. *The system of Equations* (3.1)-(3.3) *with* (3.4)-(3.6) *has a unique non-washout steady state solution* (x_s, y_s, z_s), $x_s > 0$, $y_s > 0$, $z_s > 0$, *provided that*

$$a_1\gamma - (a_2 + \omega_1) > 0, \tag{3.7}$$

$$\psi_R - \omega_2 > 0, \tag{3.8}$$

$$\varepsilon_{\gamma\gamma} - \omega_2 > 0, \tag{3.9}$$

$$\gamma - k_\gamma > 0, \tag{3.10}$$

$$a_1(\gamma - k_\gamma) - (a_2 + \omega_1) > 0. \tag{3.11}$$

Proof. see in [9]. □

4. Existence of Sustained Oscillation Dependent on Delay

In order to investigate the effect of delays on the possibility of periodic dynamics in our system, we now assume that x_s, y_s, z_s is the unique non-washout steady state of our model system.

Letting $X = x - x_s, Y = y - y_s, Z = z - z_s$, we will be led to the following linearized system of (3.1)-(3.3) with (3.4)-(3.6)

$$\begin{pmatrix} \dot{X} \\ \dot{Y} \\ \dot{Z} \end{pmatrix} = A \begin{pmatrix} X \\ Y \\ Z \end{pmatrix}, \tag{4.1}$$

where A is the corresponding Jacobian matrix evaluated at x_s, y_s, z_s, namely,

$$A = \begin{pmatrix} B_1 & -B_2 & B_3 \\ B_4 e^{-\lambda\tau} & B_5 + B_6 e^{-\lambda\tau} & B_7 \\ -B_8 & -B_9 & -B_{10} \end{pmatrix}, \tag{4.2}$$

where

$$B_1 = \frac{a_1 z_s(\gamma - 2x_s)}{K_S + z_s} - \frac{K_\gamma \varepsilon_\gamma y_s}{(K_\gamma + x_s)^2} - (a_2 + \omega_1);$$

$$B_2 = \frac{\varepsilon_\gamma x_s}{K_\gamma + x_s};$$

$$B_3 = \frac{a_1 x_s K_S(\gamma - x_s)}{(K_S + z_s)^2};$$

$$B_4 = \frac{\varepsilon_{\gamma\gamma} K_\gamma y_s}{(K_\gamma + x_s)^2};$$

$$B_5 = \frac{\psi_R z_s}{K_R + z_s} - \omega_2;$$

$$B_6 = \frac{\varepsilon_{\gamma\gamma} x_s}{K_\gamma + x_s};$$

$$B_7 = \frac{\psi_R K_R y_s}{(K_R + z_s)^2};$$

$$B_8 = \frac{a_3 z_s}{K_S + z_s};$$

$$B_9 = \frac{a_4 z_s}{K_R + z_s};$$

$$B_{10} = \omega_3 + \frac{a_3 K_S x_s}{(K_S + z_s)^2} + \frac{a_4 K_R y_s}{(K_R + z_s)^2}.$$

We may then write the associated characteristic equation of the model system as

$$F(\lambda) \equiv \lambda^3 + r_1\lambda^2 + r_2\lambda + r_3 + (r_4\lambda^2 + r_5\lambda + r_6)e^{-\lambda\tau} = 0, \tag{4.3}$$

where

$$r_1 = B_{10} - B_1 - B_5;$$

$$r_2 = B_1B_5 + B_3B_8 + B_7B_9 - B_1B_{10} - B_5B_{10};$$

$$r_3 = B_1B_5B_{10} - B_2B_7B_8 - B_3B_5B_8 - B_1B_7B_9;$$

$$r_4 = -B_6;$$

$$r_5 = B_1B_6 + B_2B_4 - B_6B_{10};$$

$$r_6 = B_1B_6B_{10} + B_3B_4B_9 + B_2B_4B_{10} - B_3B_6B_8.$$

According to the Hopf bifurcation theory, for a periodic solution to exist, it is necessary that Equation (4.3) has a pair of pure imaginary complex roots $\lambda = \pm i(\omega)$, for some value of τ. In order that such a pair can be found, one must have $F(i\omega) = 0$, that is,

$$(i\omega)^3 + r_1(i\omega)^2 + r_2 i\omega + r_3 + (r_4(i\omega)^2 + r_5(i\omega) + r_6)e^{-i\omega\tau} = 0. \tag{4.4}$$

Equating real and imaginary parts on the right of Equation (4.4) to zero, we obtain the following two equations

$$r_1\omega^2 - r_3 = r_5\omega\sin(\omega\tau) - (r_4\omega^2 - r_6)\cos(\omega\tau), \tag{4.5}$$

$$\omega^3 - r_2\omega = (r_4\omega^2 - r_6)\sin(\omega\tau) + r_5\omega\cos(\omega\tau). \tag{4.6}$$

Squaring both sides of Equations (4.5) and (4.6), then adding, one is led to

$$\varphi(\omega) = \omega^6 + (r_1^2 - 2r_2 + r_4^2)\omega^4 + (r_2^2 + 2r_4r_6 - 2r_1r_3 - r_5^2)\omega^2 + (r_3^2 - r_6^2) = 0. \tag{4.7}$$

Setting ω^2 in Equation (4.7), we arrive at the following equation

$$\phi(n) \equiv n^3 + pn^2 + qn + r = 0, \tag{4.8}$$

where

$$p = r_1^2 - 2r_2 + r_4^2;$$

$$q = r_2^2 + 2r_4r_6 - 2r_1r_3 - r_5^2;$$

$$r = r_3^2 - r_6^2.$$

We see that Equation (4.3) will have a pair of complex solutions $\lambda = \pm i(\omega)$, if Equation (4.8) has a positive real solution $n = \omega^2 > 0$.

For such a polynomial Equation (4.8), the following results have been proved by S. Ruan and J. Wei [10], and so we state them in the following three lemmas without proofs.

Lemma 4.1. *If* $r < 0$, *then Equation* (4.8) *has at least one positive root.*

Lemma 4.2. *If* $r \geq 0$, *then the necessary condition for Equation* (4.8) *to have positive real root is that* $\Delta \equiv p^2 - 3q \geq 0$.

Lemma 4.3. *If*

$$r \geq 0, \tag{4.9}$$

and

$$\Delta \geq 0, \tag{4.10}$$

then Equation (4.8) *has a positive root, if and only if* $n_1 > 0$ *and* $\phi(n_1) \leq 0$, *where*

$$n_1 = \frac{-p + \sqrt{\Delta}}{3}. \tag{4.11}$$

Proof. We note that $\phi'(n) = 0$ at $n = n_1$ and n_2 such that $n_{1,2} = \frac{-p \pm \sqrt{p^2 - 3q}}{3}$. The proof of this lemma can be seen in the work of S. Ruan and J. Wei [10]. □

Thus, by the above lemmas, we now suppose that Equation (4.8) has positive roots. Without loss of generality, we suppose that it has three positive roots denoted by $n_1, n_2,$ and n_3. Then, the followings will be positive roots of Equation (4.7).

$\omega_{11} = \sqrt{n_1}, \omega_{12} = \sqrt{n_2},$ and $\omega_{13} = \sqrt{n_3},$ or $\omega_{1k} = \sqrt{z_k}, k = 1, 2, 3,$ which again leads us to Equations (4.5) and (4.6) with ω is substituted by ω_{1k}.

Dividing Equations (4.5) and (4.6) when $\omega = \omega_{1k}$ and rearranging, we then arrive at the following expression for $\tan \omega_{1k}\tau$, provided $\cos \omega_{1k}\tau \neq 0$:

$$\tan(\omega_{1k}\tau) = \frac{(r_5 w_k)(r_1 w_k^2 - r_3) - (r_6 - r_4 w_k^2)(w_k^3 - r_2 w_k)}{(r_5 w_k)(w_k^3 - r_2 w_k) + (r_6 - r_4 w_k^2)(r_1 w_k^2 - r_3)}. \tag{4.12}$$

We are now in the position to state and prove the following theorem.

Theorem 4.4. *Suppose*

$$r_1 + r_4 > 0, r_3 + r_6 > 0, \textit{and } (r_1 + r_4)(r_2 + r_5) - (r_3 + r_6) > 0. \tag{4.13}$$

(a) *If* $r \geqslant 0$ *and* $\Delta < 0$, *then all roots of Equation* (4.3) *have nonzero real parts for all* $\tau \geqslant 0$.

(b) *If either* (i) $r < 0$, *or* (ii) $r \geqslant 0, \Delta \geqslant 0, n_1 > 0,$ *and* $\phi(n_1) \leqslant 0$, *then all roots of Equation* (4.3) *have negative real parts when* $\tau \in [0, \tau_0)$, *where*

$$\tau_0 = \min_{1 \leqslant k \leqslant 3}\{\tau_k^j, \tau_k^j > 0\}, \tag{4.14}$$

with

$$\tau_k^{(j)} = \frac{1}{w_k} \tan^{-1}\left[\frac{(r_5 w_k)(r_1 w_k^2 - r_3) - (r_6 - r_4 w_k^2)(w_k^3 - r_2 w_k)}{(r_5 w_k)(w_k^3 - r_2 w_k) + (r_6 - r_4 w_k^2)(r_1 w_k^2 - r_3)}\right], \tag{4.15}$$

where $k = 1, 2, 3, j = 1, 2, 3, \ldots.$

Proof. (a) By contradiction, if Equation (4.3) has a root with zero real part for some $\tau \geqslant 0,$ then this means that Equation (4.8) has a positive real root. By (4.2), the necessary condition of this is then that $\Delta \geqslant 0,$ which contradicts that the fact that $\Delta < 0.$ Therefore, all roots of Equation (4.3) have nonzero real parts for all $\tau \geqslant 0.$

(b) First, we observe that when $\tau = 0,$ Equation (4.3) reduces to

$$F(\lambda) \equiv \lambda^3 + r_1\lambda^2 + r_2\lambda + r_3 = 0. \tag{4.16}$$

Then, the Routh-Hurwitz criterion, all roots of Equation (4.16) have negative real parts since the conditions in (4.13) hold. This, therefore, implies that all roots $\lambda(\tau)$ of Equation (4.3) have negative real parts at the point $\tau = 0.$ We can deduce then, from the continuity of $\lambda(\tau),$ that all roots of Equation (4.3) will have negative real parts for values of τ in some open interval containing $\tau = 0.$ This means that all roots of Equation (4.11) have negative real parts for positive values of $\tau \in [0, \tau_c)$ for some $\tau_c > 0.$

However, τ_0 is defined by (4.14) to be the minimum of all the positive $\tau = \tau_k^{(j)}$ that solve Equation (4.12). Thus, τ_0 is the minimum of such positive τ's for which the real parts of some roots of Equation (4.3) vanish, provided (i) or (ii) holds. Therefore $\tau = \tau_0,$ which completes the proof. $\square$

Finally, for a Hopf bifurcation to occur, leading to a limit cycle surrounding the non-washout steady state $x_s, y_s, z_s,$ we also need to show that

$$\frac{dRe\lambda(\tau)}{d\tau}\Big|_{\tau=\tau_0} \neq 0. \tag{4.17}$$

This is done in the next theorem.

Theorem 4.5. *Suppose conditions* (i) *or* (ii) *in Theorem* 4.4 *hold, then* $\lambda = \pm iw_0$ *is a pair of purely imaginary roots of Equation* (4.3). *Moreover, if*

$$\phi'(n_0) \neq 0, \tag{4.18}$$

where

$$n_0 = w_0^2,\ w_0 = w_k|_{\tau=\tau_0}, \tag{4.19}$$

then Equation (4.17) *holds.*

Proof. The first part of this theorem is an immediate consequence of Theorem 4.4 and the definition of τ_0. To prove that (4.17) holds, we begin by writing $F(\lambda)$ in the form

$$F(\lambda) = F_1(\lambda) - F_2(\lambda)\exp^{-\lambda\tau}, \tag{4.20}$$

where $F_1 \equiv \lambda^3 + a\lambda^2 + b\lambda + d$ and $F_2 \equiv e - c\lambda$. Then, on $F = 0$, the total derivative of F with respect to τ is

$$\frac{dF}{d\tau} = [\dot{F}_1 - (\dot{F}_2 e^{-\lambda\tau})]\frac{d\lambda}{d\tau} + \lambda F_2 e^{-\lambda\tau} = 0, \tag{4.21}$$

where $\dot{F}_i \equiv \dfrac{dF_i}{d\lambda}$, $i = 1, 2$. Solving (4.22) for $\lambda' = \dfrac{d\lambda}{d\tau}$, we obtain

$$(\lambda')^{-1} = -\frac{\dot{F}_1 - (\dot{F}_2 e^{-\lambda\tau})}{\lambda F_2 e^{-\lambda\tau}}. \tag{4.22}$$

Also, on $F(iw) = 0$, we must have $F_1 = F_2 e^{-\lambda\tau}$, and thus,

$$Re(\lambda')^{-1}|_{\tau=\tau_0} = Re\left(-\frac{\dot{F}_1}{\lambda F_1} + \frac{\dot{F}_2}{\lambda F_2}\right)_{\tau=\tau_0}.$$

That is,

$$Re(\lambda')^{-1}|_{\tau=\tau_0} = Re\left(-\frac{\dot{F}_1\overline{F}_1}{\lambda\| F_1\|^2} + \frac{\dot{F}_2\overline{F}_2}{\lambda\| F_2\|^2}\right)_{\tau=\tau_0}. \tag{4.23}$$

Now, letting

$$R_1 = Re(F_1),\ R_2 = Re(F_2),$$

$$I_1 = Im(F_1),\ I_2 = Im(F_2),$$

at $\tau = \tau_0$, we see that for $F(iw) = 0$, we need to have

$$\phi(w) = R_1^2 + I_1^2 - R_2^2 - I_2^2 = 0, \tag{4.24}$$

or equivalently, (4.7) holds, which means

$$\|F_1\|^2 = R_1^2 + I_1^2 = R_2^2 + I_2^2 = \|F_2\|^2.$$

Equation (4.23) then becomes

$$Re(\lambda')|_{\tau=\tau_0} = \frac{[(R_1 \frac{dR_1}{dw} + I_1 \frac{dI_1}{dw}) - (R_2 \frac{dR_2}{dw} + I_2 \frac{dI_2}{dw})]_{w=w_0}}{w_0\|F_1\|^2}$$

$$= \frac{[\frac{d}{dw}(R_1^2 + I_1^2) - \frac{d}{dw}(R_2^2 + I_2^2)]_{w=w_0}}{2w_0\|F_1\|^2}.$$

That is,

$$Re(\lambda')|_{\tau=\tau_0} = \frac{\frac{d\phi}{dw}|_{w=w_0}}{2w\|F_1\|^2}. \tag{4.25}$$

Equivalently,

$$\left(\frac{dRe\lambda}{d\tau}\right)^{-1}\Big|_{\tau=\tau_0} = \frac{h'(n_0)}{\|F_1\|^2}. \tag{4.26}$$

Hence,

$$sign\left\{\frac{dRe\lambda}{d\tau}\Big|_{\tau=\tau_0}\right\} = sign\left\{\left(\frac{dRe\lambda}{d\tau}\right)^{-1}\Big|_{\tau=\tau_0}\right\} = sign\{h'(n_0)\}.$$

Since $h'(n_0) \neq 0$, it is either positive or negative. Therefore, $\frac{dRe\lambda}{d\tau}|_{\tau=\tau_0}$ is either positive or negative as well. That is, $\frac{dRe\lambda}{d\tau}|_{\tau=\tau_0} \neq 0$, which completes our proof. □

In summary, the above analysis provides the proof of the following.

Theorem 4.6. *If conditions* (4.9), (4.10), (4.11), (4.13), *and* (4.18) *hold, then a Hopf bifurcation occurs in our model system* (3.1)-(3.3) *with* (3.4)-(3.6) *for a positive composite delay* $\tau = \tau_0$ *given by Equation* (4.13) *and* (4.14). *The non-washout steady state* x_s, y_s, z_s *is stable for* $\tau < \tau_0$, *and loses its stability at* $\tau = \tau_0$. *Furthermore, there will be a positive number* ε *such that the model system under study possesses periodic solutions for values of* $\tau \in (\tau_0, \tau_0 + \varepsilon)$.

In such a case that $\tau \in (\tau_0, \tau + \varepsilon)$, the periodic solution is a limit cycle, that bifurcates from the steady state (x_s, y_s, z_s), whose radius increases with increasing τ [3], [7].

Figure 2 shows numerical simulations of the model system under study, when the parametric values, given in the figure caption, have been chosen so that the conditions listed in Theorem 4.6 are satisfied.

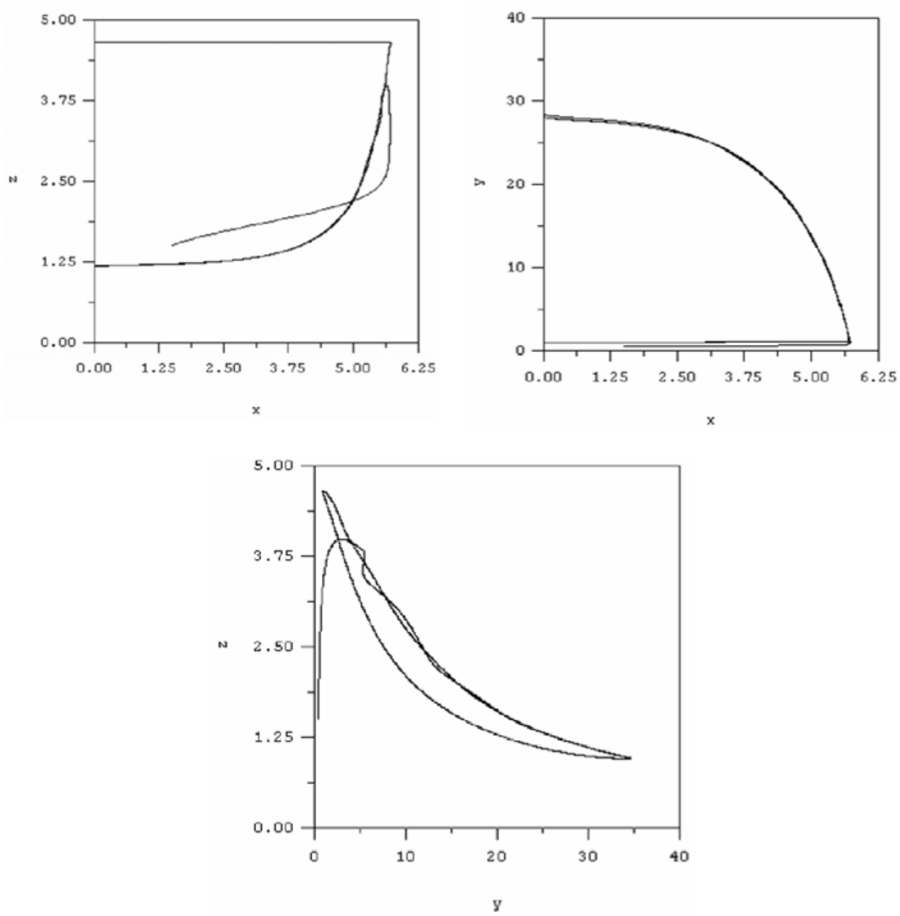

Figure 2. Computer simulation of the model Equations (3.1)-(3.3) with (3.4)-(3.6), where $\varepsilon = 1.0$, $\delta = 1.0$, $z_1 = 5.0$, $\varepsilon_\gamma = 0.5$, $\psi_R = 1.69$, $\gamma = 5.9$, $\omega_1 = 0.3$, $\omega_2 = 0.85$, $\omega_3 = 0.685$, $K_S = 2.01$, $K_\gamma = 0.3$, $K_R = 5.0$, $a_1 = 0.079245863$, $a_2 = 0.077777778$, $a_3 = 0.006339669$, $a_4 = 0.507$, $x_0 = 1.5$, $y_0 = 0.5$, and $z_0 = 1.5$, showing the solution trajectory tending towards a closed limit cycle. Here, the solution trajectory is projected onto (a) the (x, z)-plane, (b) the (x, y)-plane, and (c) the (y, z)-plane.

Figure 3 shows a numerical simulation of the model system (3.1)-(3.3) with (3.4)-(3.6), with parametric values chosen to satisfy the inequalities identified in Theorem 4.6. Here, $\varepsilon = 0$, $\delta = 1$, $z_1 = 5.0$, $\varepsilon_\gamma = 0.5$, $\psi_R = 1.69$, $\gamma = 5.9$, $\omega_1 = 0.3$, $\omega_2 = 0.85$, $\omega_3 = 0.685$, $K_S = 2.01$, $K_\gamma = 0.3$, $K_R = 5.0$, $a_1 = 0.079245863$, $a_2 = 0.077777778$, $a_3 = 0.006339669$, $a_4 = 0.507$, $x_0 = 1.5$, $y_0 = 0.5$, and $z_0 = 1.5$. The solution trajectory, projected onto the three phase-planes, is seen in this case to tend towards a closed limit cycle as predicted for Theorem 4.6.

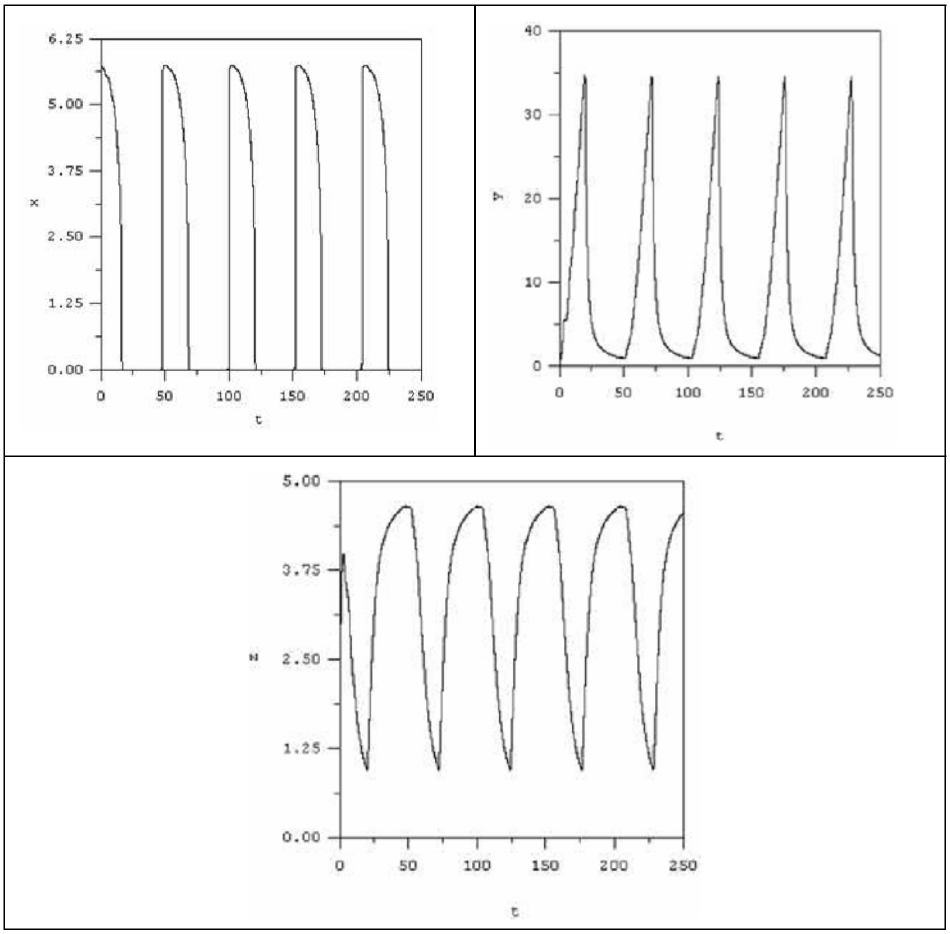

Figure 3. Time courses of (a) susceptible bacteria (x), (b) resistant bacteria (y) and (c) nutrient (z) of the case seen in figure, exhibiting periodic oscillation.

5. Conclusion

In this paper, we have studied the time delayed chemostat model (2.1)-(2.4) for two kinds of bacteria based on antibiotic, in which the steady state is reduced by a factor, which depends on the latency delay τ. In our study, we have modified the model proposed by Puttasontiphot et al. [9] which has been reported to give good qualitative agreement with the experimental observations. By incorporating the delay τ and also taking into account, the delay in the action of changing susceptible population to resistant bacteria, we have been able to investigate the possibility of different dynamic behavior permitted by our model, which is dependent on the delays. It is found that the system is stable for sufficiently small composite delay τ. As τ becomes large, the system can exhibit oscillatory behavior. The resulting characteristic equation, once linearized around the steady state, also contains this factor (see (4.3)). In general, the linear stability analysis, when the system is dependent of delay is much more difficult than the case of delay independent system. Therefore, our main purpose is to discuss the stability of the delay differential equation with delay dependent parameters. In many delay differential equations, we know that the large time delay usually plays destabilizing role. In other words, if a steady state exists and is unstable for $\tau = \tau_0$, then it remains unstable for $\tau > \tau_0$. From the Hopf bifurcation theory, we have derived conditions for existence of periodic solutions and provided numerical simulations to illustrate these periodic solutions. In Figure 2 and Figure 3, we used $z_1 = 5.0$, $\varepsilon_\gamma = 0.5$, $\psi_R = 1.69$, $\gamma = 5.9$, $\omega_1 = 0.3$, $\omega_2 = 0.85$, $\omega_3 = 0.685$, $K_S = 2.01$, $K_\gamma = 0.3$, $K_R = 5.0$, $a_1 = 0.079245863$, $a_2 = 0.077777778$, $a_3 = 0.006339669$, $a_4 = 0.507$, $x_0 = 1.5$, $y_0 = 0.5$, and $z_0 = 1.5$.

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References

[1] E. Beretta and F. Solinano, Analysis of a chemostat model for bacteria and virulent bacteriophage, Discrete and Continuous Dynamical Systems, 2 (2002), 495-520.

[2] A. Campbell, Conditions for existence of bacteriophage, Evolution 15 (1961), 153-165.

[3] D. D. Hassard, N. D. Kazarinoff and Y. H. Wan, Theory and Applications of Hopf Bifurcation, Cambridge University Press, Cambridge, (1981), 498-499.

[4] C. S. Holling, The components of predation as revealed by a study of small mammal predation of the European pine sawfly, Canad. Entomol. 91 (1959), 293-320.

[5] C. S. Holling, Some characteristics of simple types of predation and parasitism, Canad. Entomol 91 (1959), 385-398.

[6] B. R. Levin, F. M. Stewart and L. Chao, Resource-limited growth, competition and predation: A model and experinment studies with bacteria and bacteriophage, American Naturalist, 111 (1997), 3-24.

[7] J. E. Marsden and M. McCracken, The Hopf Bifurcation and its Applications, Springer-Verlag, New York, (1976), 410-412.

[8] S. J. Peacock, S. Mandal and ICJW, Bowler, Preventing Staphylococcus aureus infection in the remal unit, Q. J. Med. 95 (2002), 405-410.

[9] T. Puttasontiphot, Y. Lenbury, C. Rattanakul, S. Rattanamongkonkul, J. R. Hotchkiss and P. S. Crooke, Dynamic processes permitting stable coexistence of antimicrobial resistant and non-resistant organisms in a gastrointestinal tract model, Scienceasia 33 (2007), 197-206.

[10] S. Ruan and J. Wei, On the zeros of a third degree exponential polynomial with applications to a delayed model for the control of testosterone section, IMA J. Math. Appl. Med. Biol. 18(1) (2001), 41-52.

[11] K. Todar, Bacterial Resistance to Antibiotic (2008), 1-4.

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