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Large time behavior of nonautonomous differential systems modeling antibiotic-resistant bacteria in rivers

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RESEARCH ARTICLE

Large time behavior of non-autonomous differential systems modeling antibiotic resistant bacteria in rivers

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Abstract

In this paper, we study a general non-autonomous model for bacterial dynamics in rivers. The mathematical model is represented by a non-autonomous system of non-linear ordinary differential equations. We show the existence of a bounded positive invariant and attracting set. By using the Lyapunov function method, we establish global stability of steady state solutions of the associated autonomous system. Second, the existence of positive periodic solutions of the non-autonomous system is proven using a continuation theorem based on coincidence degree theory.

KEYWORDS:
Periodic solutions, Global dynamics, Coincidence degree, Antibiotic resistance

1 | INTRODUCTION

Antibiotic resistant bacteria have been found to exist in rivers around the globe[1,2]. In many cases, their prevalence has been found to be higher downstream of human activities such as hospitals, sewage treatment plants, or agricultural settings[3,4,5,6]. There are therefore worries that antibiotic resistant genes may contaminate drinking water[7,8] and, given that infectious diseases caused by antibiotic resistant bacteria are among the most urgent global public health problems[9], this is a concern.

Mathematical modeling can be used to understand the dynamics of antibiotic resistant bacteria in the water systems to make predictions about potential ways to counter this problem. In this context, we refer to the paper[10] where the authors have developed a mathematical model of antibiotic resistant bacteria in a river. Their model takes the following form

$$
\begin{cases}
\dfrac{dR_s}{dt} = -\alpha R_s(R_I + L_I) + \dfrac{\beta R_I}{L+1} + r\left(1 - \dfrac{B}{K}\right)R_s, \\[2mm]
\dfrac{dR_I}{dt} = \alpha R_s(R_I + L_I) - \dfrac{\beta R_I}{L+1} + r\left(1 - \dfrac{B}{K}\right)R_I, \\[2mm]
\dfrac{dL_s}{dt} = F_s(t) - \gamma L_s - \alpha L_s(R_I + L_I) + \dfrac{\beta L_I}{L+1} + r\left(1 - \dfrac{B}{K}\right)L_s, \\[2mm]
\dfrac{dL_I}{dt} = F_I(t) - \gamma L_I + \alpha L_s(R_I + L_I) - \dfrac{\beta L_I}{L+1} + r\left(1 - \dfrac{B}{K}\right)L_I, \\[2mm]
B = R_s + R_I + L_s + L_I, \quad L = L_s + L_I.
\end{cases}
\tag{1}
$$

---

where α, β, γ, r and K are positive constants. In the model (1), the authors consider two distinct classes of bacteria in the river: those that are river bacteria, R, and those that are land bacteria, L. Both the river and land bacteria are further subdivided into those that have the antibiotic resistant gene, called resistant, R_I, L_I, and those that do not, called non-resistant or susceptible, R_s, L_s. The subscripts are drawn from infectious disease modelling where S denotes susceptible and I infected; here the bacteria are considered to be "infected" with an antibiotic resistance gene. Many antibiotic resistance genes are contained on plasmids. These are genetic elements that can be replicated and transferred between bacteria upon contact between two cells. This is captured above with the rate parameter α representing this transmission rate of an antibiotic resistant gene. Conversely, plasmids can be spontaneously lost from the cell at rate β. r is the specific growth rate of all types of cells (here it is assumed that all subsets of bacteria grow at the same rate), that are subject to a shared carrying capacity, K (meaning that the river can only sustain a limited number of bacteria in total). To represent the fact that land bacteria are not in their natural environment in the rivers, an additional death rate γ is imposed where $\gamma > r$.

Finally, $F_s(t)$ and $F_I(t)$ are the rates of bacteria entering the river from the shore. These functions have been assumed to be positive and continuous in $\mathbb{R}_+$. In [10], some numerical simulations are shown in order to illustrate the dynamics of the model (1), although no mathematical analysis has been presented for general parameters. However, in the reference [11], the author has done a qualitative study of this model by first looking at its associated autonomous system, then reviewing the non autonomous system where $F_s(t)$ and $F_I(t)$ are periodic functions. In the autonomous case, the study showed the existence of three boundary equilibria $E_0(0, 0, 0, 0)$ and $E_1(K, 0, 0, 0)$, and a third one $E_2\left(\dfrac{\beta}{\alpha}, K - \dfrac{\beta}{\alpha}, 0, 0\right)$ if $\beta < \alpha K$. Moreover, the existence of a positive periodic solution was proven when $F_s(t)$ et $F_I(t)$ are periodic functions under the condition

$$\frac{1}{T} \int_0^T (F_s(t) + F_I(t))dt < \alpha K, \tag{2}$$

for additional details, readers are requested to consult the paper [11].

The most common approach to modelling resistance transfer, is to adopt mass action kinetics as above (the term $\alpha S I$ where α is transmission rate and S and I denote the non-resistant and resistant bacteria, respectively) [12,13,14,15]. However, this means that if the number of non-resistant bacteria increases, the number of bacteria that become resistant per unit of time increases even for very small numbers of resistant bacteria, which is not necessarily realistic. Instead, a good illustration in the context of epidemiological models has been given by Keeling and Rohani in [16], where the contact between susceptible S and infected I is modelled by $\dfrac{S I}{S + I}$. This has been used to represent the transfer of an antibiotic resistance gene between bacteria in the following works [17,18,19,20].

The term $-\dfrac{rB}{K} R_s$ (and the corresponding terms in the other equations) gathers intra and inter species competition pressure in a single term. However, as land bacteria enter the river from the shore and we assume they are not adaptable to the river. Therefore, the inter and intra species competitive pressure should not be considered to be the same (see [21]). More specifically, the term $-\dfrac{rB}{K} R_S$ should be replaced by

$$-r\left(\frac{R_S}{K_{R_S}} + \frac{R_I}{K_{R_I}} + \frac{L_S}{K_{L_S}} + \frac{L_I}{K_{L_I}}\right) R_s.$$

On the other hand, in [22] it is shown that *E. coli* bacteria isolated from highly contaminated river water are more likely to contain resistance genes than those from cleaner water. The authors of [10] have captured this through the assumption that contamination correlates with the presence of land bacteria and hence the loss rate of the resistance gene should be a decreasing function of L (the total number of polluting bacteria), $g(L)$. This is not an unreasonable assumption: if the contamination is coming from, for example, fecal bacteria in a nearby sewage plant, the presence of antibiotic resistant genes in those bacteria would suggest also the possible presence of the relevant antibiotic. Resistance-loss is much less likely to occur in the presence of this stressor. The specific function chosen in [10] is $g(L) = \beta/(L + 1)$. However, several functions are existing and similar to the above specific function. Moreover, in our proposed model we consider the terms of $g_R(L)$ and $g_L(L)$ for the river and land bacteria loss rates

respectively. Here, we propose an extension of model (1) that captures the four changes above as follows

$$
\begin{cases}
\dfrac{dR_s}{dt} = -\alpha \dfrac{R_s(R_I + L_I)}{B} + g_R(L)R_I + r\left(1 - \dfrac{R_S}{K_{R_S}} - \dfrac{R_I}{K_{R_I}} - \dfrac{L_S}{K_{L_S}} - \dfrac{L_I}{K_{L_I}}\right)R_s, \\[2mm]
\dfrac{dR_I}{dt} = \alpha \dfrac{R_s(R_I + L_I)}{B} - g_R(L)R_I + r\left(1 - \dfrac{R_S}{K_{R_S}} - \dfrac{R_I}{K_{R_I}} - \dfrac{L_S}{K_{L_S}} - \dfrac{L_I}{K_{L_I}}\right)R_I, \\[2mm]
\dfrac{dL_s}{dt} = F_s(t) - \gamma L_s - \alpha \dfrac{L_s(R_I + L_I)}{B} + g_L(L)L_I + r\left(1 - \dfrac{R_S}{K_{R_S}} - \dfrac{R_I}{K_{R_I}} - \dfrac{L_S}{K_{L_S}} - \dfrac{L_I}{K_{L_I}}\right)L_s, \\[2mm]
\dfrac{dL_I}{dt} = F_I(t) - \gamma L_I + \alpha \dfrac{L_s(R_I + L_I)}{B} - g_L(L)L_I + r\left(1 - \dfrac{R_S}{K_{R_S}} - \dfrac{R_I}{K_{R_I}} - \dfrac{L_S}{K_{L_S}} - \dfrac{L_I}{K_{L_I}}\right)L_I, \\[2mm]
B = R_s + R_I + L_s + L_I, \quad R = R_s + R_I, \quad L = L_s + L_I,
\end{cases}
\tag{3}
$$

Nevertheless, mathematical study needs some simplifications, in this paper we consider the following model

$$
\begin{cases}
\dfrac{dR_s}{dt} = -\alpha \dfrac{R_s(R_I + L_I)}{B} + g(L)R_I + r\left(1 - \dfrac{B}{K}\right)R_s, \\[2mm]
\dfrac{dR_I}{dt} = \alpha \dfrac{R_s(R_I + L_I)}{B} - g(L)R_I + r\left(1 - \dfrac{B}{K}\right)R_I, \\[2mm]
\dfrac{dL_s}{dt} = F_s(t) - \gamma L_s - \alpha \dfrac{L_s(R_I + L_I)}{B} + g(L)L_I + r\left(1 - \dfrac{B}{K}\right)L_s, \\[2mm]
\dfrac{dL_I}{dt} = F_I(t) - \gamma L_I + \alpha \dfrac{L_s(R_I + L_I)}{B} - g(L)L_I + r\left(1 - \dfrac{B}{K}\right)L_I, \\[2mm]
B = R_s + R_I + L_s + L_I, \quad R = R_s + R_I, \quad L = L_s + L_I,
\end{cases}
\tag{4}
$$

where F_s and F_I are continuous T-periodic functions such that

$$
0 \le F_s(t) \le a_s = \max_{t \in \mathbb{R}_+} F_s(t)
\tag{5}
$$

and

$$
0 \le F_I(t) \le a_I = \max_{t \in \mathbb{R}_+} F_I(t).
\tag{6}
$$

These functions represent regular release of land bacteria into the river water, for example as might happen at set times of the day downstream of a sewage treatment plant. It is assumed that all the parameters α, γ, r and K are positive constants with $\gamma > r$. In addition, we suppose that g is a C^1-function satisfying the following conditions:

(H1) $g(L) > 0$ for all $L > 0$,

(H2) $g'(L) \le 0$ for all $L > 0$,

(H3) $\displaystyle \lim_{L \to +\infty} g(L) = 0$.

We denote by

$$
\mathbb{R}_+^4 = \left\{(R_s, R_I, L_s, L_I) \in \mathbb{R}^4, \ R_s \ge 0, \ R_I \ge 0, \ L_s \ge 0, \ L_I \ge 0\right\}
$$

and

$$
\mathrm{Int}(\mathbb{R}_+^4) = \left\{(R_s, R_I, L_s, L_I) \in \mathbb{R}^4, \ R_s > 0, \ R_I > 0, \ L_s > 0, \ L_I > 0\right\}.
$$

In this paper, we realize a qualitative study of the model (4) by first analyzing its associated autonomous system (i.e. $F_s = F_I = 0$), then investigating the non autonomous system. Specifically we show the existence of a positive periodic solution.

In [11], only sufficient conditions for global stability of equilibria have been given, whereas, in the present paper we have obtained sufficient and necessary conditions for global stability by using suitable Lyapunov functions. In addition, the paper [11] has proven the existence of a positive periodic solution for $g(L) = \beta/(L+1)$, under the condition

$$\frac{1}{T} \int_0^T (F_s(t) + F_I(t)) dt < \alpha K,$$

this theoretical result has not been validated numerically. In this work, we establish the existence of a positive periodic solution for every function g satisfying (H1)-(H3), no further conditions are necessary for that, this by an homotopy conveniently chosen; moreover, here we have obtained a numerical solution which is periodic.

Obtaining reliable parameter estimates in this field is a huge challenge (even more so in models of this kind where each variable captures a spread of bacterial strains and resistance mechanisms), and so any progress that can be made for general parameter sets is an important step. The rest of this paper is organized as follows, in Section 2 we show boundedness of solutions and existence of a positively invariant attracting set. In Section 3, a mathematical analysis of the associated autonomous system is provided by establishing the local and global stability of equilibria. Section 4 is devoted to study the existence of a periodic positive solution of the non-autonomous system. In addition, we carry out numerical simulations to verify our theoretical results. Some conclusions are given in the end and put into the context of the biology.

2 | BOUNDEDNESS OF THE MODEL AND EXISTENCE OF A POSITIVELY INVARIANT ATTRACTING SET

Let us denote by $F = (F_1, F_2, F_3, F_4)$ the right-hand side of system (4). Obviously, $F \in C^1(\text{Int}(\mathbb{R}^4_+), \mathbb{R}^4_+)$, then from the Cauchy-Lipschitz theorem the system admits a unique maximal solution in $[0, T_{\max})$, where $T_{\max} > 0$, for any associated Cauchy problem [23]. In the literature of biological models, the solutions are typically bounded in $\text{Int}(\mathbb{R}^4_+)$. Hereafter, the existence of a positively invariant attracting set is regarded.

To prove the positivity of solutions we use the following proposition [24].

Proposition 1. Consider a system of differential equations in $\mathbb{R}^n$,

$$x' = F(t, x),$$

$x(t) = (x_1(t), x_2(t), \dots, x_n(t))$, $F(t, x) = (F_1(t, x), F_2(t, x), \dots, F_n(t, x))$, where $F(t, x)$ is defined for all $t \geq 0$, $x \in \mathbb{R}^n$. Assume that F has the property that solutions of the initial value problems $x(t_0) = x_0$ are unique for $x_0 \in [0, +\infty)^n$, $t_0 \geq 0$. Furthermore, assume that, for all $j = 1, \dots, n$, $t \geq 0$, we have

$$F_j(t, x) \geq 0 \text{ whenever } x \in [0, +\infty)^n, \quad x_j = 0, \quad t \geq 0.$$

Then $x(t) \in [0, +\infty)^n$ for all $t \geq t_0 \geq 0$ for which it is defined, whenever $x(t_0) \in [0, +\infty)^n$.

Theorem 1. Let $\mathcal{A}$ be the set defined by

$$\mathcal{A} = \left\{ (R_s, R_I, L_s, L_I) \in \text{Int}(\mathbb{R}^4_+), \ R_s + R_I \leq K, \ L_s + L_I \leq \frac{a_s + a_I}{\gamma - r} \right\}.$$

Then,

  (a) $\mathcal{A}$ is positively invariant,

  (b) for all $(R_s(0), R_I(0), L_s(0), L_I(0)) \in \text{Int}(\mathbb{R}^4_+)$,

$$(R_s(t), R_I(t), L_s(t), L_I(t)) \to \mathcal{A} \quad \text{as} \quad t \to +\infty.$$

Proof. Let $(R_s(0), R_I(0), L_s(0), L_I(0)) \in \mathcal{A}$. The positivity of the solution can be obtained directly from Proposition 1. It remains to show that $R_s + R_I \leq K$ and $L_s + L_I \leq \frac{a_s + a_I}{\gamma - r}$. In fact, summing the first and second equations of (4), we get

$$R'(t) = r \left(1 - \frac{B}{K}\right) R.$$

Since, $R_s > 0$, $R_I > 0$, $L_s > 0$ and $L_I > 0$, then

$$\frac{dR}{dt} = r\left(1 - \frac{B}{K}\right)R \le r\left(1 - \frac{R}{K}\right)R.$$

Thereupon $R(t) \le x(t)$, where $x(t)$ is the solution of

$$\frac{dx}{dt} = r\left(1 - \frac{x}{K}\right)x, \quad x(0) = R_s(0) + R_I(0),$$

as $x(0) \le K$, then $x(t) \le K$, which implies that $R(t) \le K$. In the same manner we can see that $L(t) \le \dfrac{a_s + a_I}{\gamma - r}$.

We proceed to demonstrate the second part of Theorem 1. Let the initial condition $(R_s(0),\ R_I(0),\ L_s(0),\ L_I(0)) \in \text{Int}(\mathbb{R}_+^4)$. As before,

$$\frac{dR}{dt} \le r\left(1 - \frac{R}{K}\right)R, \quad R(0) = R_s(0) + R_I(0)$$

then from a standard comparison theorem

$$R(t) \le \frac{Ke^{rt}}{e^{rt} + \frac{K - R(0)}{R(0)}}.$$

Hence,

$$\limsup_{t \to +\infty} R(t) \le K. \tag{7}$$

Likewise, $L(t)$ satisfies

$$\frac{dL}{dt} = F_s(t) + F_I(t) - \gamma L + r\left(1 - \frac{B}{K}\right)L, \quad L(0) = L_s(0) + L_I(0)$$

which yields

$$L(t) \le \left(L(0) - \frac{a_s + a_I}{\gamma - r}\right)e^{-(\gamma - r)} + \frac{a_s + a_I}{\gamma - r}.$$

Since $\gamma > r$, we have

$$\limsup_{t \to +\infty} L(t) \le \frac{a_s + a_I}{\gamma - r}, \tag{8}$$

and the proof is complete. $\qquad\square$

3 | QUALITATIVE STUDY OF THE AUTONOMOUS SYSTEM

One important question is whether the bacterial resistance persists in the river once pollution stops. Mathematically, the qualitative study of the associated autonomous system ($F_s(t) = F_I(t) = 0$) is an answer to this question:

$$\begin{cases} \dfrac{dR_s}{dt} = -\dfrac{\alpha R_s(R_I + L_I)}{B} + g(L)R_I + r\left(1 - \dfrac{B}{K}\right)R_s, \\[2mm] \dfrac{dR_I}{dt} = \alpha\dfrac{R_s(R_I + L_I)}{B} - g(L)R_I + r\left(1 - \dfrac{B}{K}\right)R_I, \\[2mm] \dfrac{dL_s}{dt} = -\gamma L_s - \alpha\dfrac{L_s(R_I + L_I)}{B} + g(L)L_I + r\left(1 - \dfrac{B}{K}\right)L_s, \\[2mm] \dfrac{dL_I}{dt} = -\gamma L_I + \alpha\dfrac{L_s(R_I + L_I)}{B} - g(L)L_I + r\left(1 - \dfrac{B}{K}\right)L_I, \\[2mm] B = R_s + R_I + L_s + L_I, \quad R = R_s + R_I, \quad L = L_s + L_I. \end{cases} \tag{9}$$

In this section, we discuss mainly the global stability of positive equilibria of system (9).

3.1 | Steady states and their existence

System (9) possesses the following three equilibria:

(i) The trivial equilibrium $E_0(0, 0, 0, 0)$.

(ii) The resistant free steady state $E_1(K, 0, 0, 0)$.

(iii) The resistant steady state $E_2 \left(\dfrac{g(0)K}{\alpha}, K - \dfrac{g(0)K}{\alpha}, 0, 0 \right)$ which exists for $\alpha > g(0)$.

Biologically, $E_0(0, 0, 0, 0)$ means that all bacteria are eliminated from the river. Furthermore, the stability of E_1 means the disappearance of resistant bacteria. However, the stability of E_2 signifies that resistant bacteria persist. In all cases, the land bacteria are eliminated from the river when unreplenished in this autonomous system.

Rivers, like everything else on earth are full of bacteria. Mathematically, this corresponds to the instability of E_0: positive perturbations away from this equilibrium will result in bacterial regrowth.

Proposition 2. The equilibrium E_0 is unstable.

Proof. Firstly, from (8) one sees immediately that

$$\lim_{t \to +\infty} L(t) = 0.$$

Accordingly, for an arbitrary $\varepsilon > 0$, there corresponds a $\tilde{t} > 0$ such that for each $t \geq \tilde{t}$, we have $L(t) \leq \varepsilon$. Hence, for all $t \geq \tilde{t}$ the function $R = R_s + R_I$ satisfies

$$R'(t) = r \left(1 - \frac{R + L}{K} \right) R$$

$$\geq r \left(1 - \frac{R + \varepsilon}{K} \right) R$$

$$\geq r \left(1 - \frac{\varepsilon}{K} \right) \left(1 - \frac{R}{K \left(1 - \frac{\varepsilon}{K} \right)} \right) R.$$

In this way, for all $t \geq \tilde{t}$ we have $R(t) \geq \bar{R}(t)$ where $\bar{R}$ is the solution of

$$\bar{R}'(t) = r \left(1 - \frac{\varepsilon}{K} \right) \left(1 - \frac{\bar{R}}{K \left(1 - \frac{\varepsilon}{K} \right)} \right) \bar{R}, \quad \bar{R}(\tilde{t}) = R(\tilde{t}).$$

This yields

$$\liminf_{t \to +\infty} R(t) \geq K - \varepsilon.$$

Since ε had been set arbitrarily, we obtain $\liminf_{t \to +\infty} R(t) \geq K$. The instability of E_0 corresponds to the permanence of river bacteria. $\square$

3.2 | Dynamical behavior: global stability

In this part, we establish the global stability of the equilibrium points E_1 and E_2. To this end, we use the Lyapunov function method.

Theorem 2. The equilibrium E_1 is globally asymptotically stable iff $\alpha < g(0)$.

Proof. Let us show the global stability of E_1. To do this consider

$$V_1(R_s, R_I, L_s, L_I) = R_s - K - K \ln \left(\frac{R_s}{K} \right) + R_I + L_s + L_I. \tag{10}$$

This function is defined and continuous on $\text{Int}(\mathbb{R}_+^4)$. Moreover, $V_1(K, 0, 0, 0) = 0$ and for any $(R_s, R_I, L_s, L_I) \neq (K, 0, 0, 0)$, $V_1(R_s, R_I, L_s, L_I) > 0$. The derivative of V_1 along solutions of the system (9) is

$$\frac{dV_1}{dt} = -\frac{\alpha(R_s - K)(R_I + L_I)}{B} + \frac{R_s - K}{R_s}g(L)R_I - \frac{r}{K}(R_s - K)^2 - \frac{r}{K}(R_s - K)R_I - \frac{r}{K}(R_s - K)L + \alpha\frac{R_s(R_I + L_I)}{B}$$

$$-g(L)R_I - \frac{r}{K}(R_s - K)R_I - \frac{r}{K}R_I^2 - \frac{r}{K}LR_I - \gamma L - \frac{r}{K}(R_s - K)L - \frac{r}{K}LR_I - \frac{r}{K}L^2$$

$$= -\frac{r}{K}(R_s - K + R_I + L)^2 - \gamma L + \frac{\alpha K(R_I + L_I)}{B} - \frac{Kg(L)R_I}{R_s}.$$

From the proof of Proposition 2, for an arbitrary $\varepsilon > 0$, there exists a $\tilde{t} > 0$ such that for each $t \geq \tilde{t}$, we have $L(t) \leq \varepsilon$.

Since $g(0) > \alpha$ and g is decreasing, it follow that for ε sufficiently small

$$\alpha < g(L) \leq g(\varepsilon) \leq g(0)$$

and

$$\frac{dV_1}{dt}(R_s, R_I, L_s, L_I) \leq -\frac{r}{K}(R_s - K + R_I + L)^2 - \gamma L - \frac{KR_I}{R_s}(g(0) - \alpha).$$

Consequently, $\dfrac{dV_1}{dt}(R_s, R_I, L_s, L_I) = 0$ if and only if $(R_s, R_I, L_s, L_I) = (K, 0, 0, 0)$. Thus, $V_1(R_s, R_I, L_s, L_I)$ satisfies Lyapunov's asymptotic stability theorem[25], which is our claim. □

Theorem 3. The equilibrium E_2 is globally asymptotically stable iff $\alpha > g(0)$.

Proof. Let us show the global stability of E_2 by using the following Lyapunov function

$$V_2(R_s, R_I, L_s, L_I) = R_s - R_s^* - R_s^* \ln\left(\frac{R_s}{R_s^*}\right) + R_I - R_I^* - R_I^* \ln\left(\frac{R_I}{R_I^*}\right) + L_s + L_I, \tag{11}$$

where $R_s^* = \dfrac{g(0)K}{\alpha}$ and $R_I^* = K - \dfrac{g(0)K}{\alpha}$. We have $V_2(R_s^*, R_I^*, 0, 0) = 0$. Moreover, an easy computation shows that

$$\frac{dV_2}{dt} = -\frac{r}{K}(R_s + R_I + L - K)^2 - \gamma L + \frac{g(0)K(R_I + L_I)}{B} - \frac{g(0)g(L)R_I K}{\alpha R_s}$$

$$- \frac{\alpha K R_s(R_I + L_I)}{BR_I} + \frac{g(0)K R_s(R_I + L_I)}{R_I B} + Kg(L) - \frac{Kg(0)g(L)}{\alpha}$$

$$\leq -\frac{r}{K}(R_s + R_I + L - K)^2 - \gamma L + \frac{g(0)K}{\alpha}(\alpha - g(L)) + \frac{KR_s}{B}(g(0) - \alpha) + \frac{Kg(L)}{\alpha}\left(\alpha - \frac{g(0)R_s}{B}\right).$$

Analysis similar to that in the proof of Theorem 2 gives

$$\frac{dV_2}{dt} \leq -\frac{r}{K}(R_s + R_I + L - K)^2 - \gamma L - \frac{K}{\alpha R_s B}(\alpha R_s - g(0)B)^2 \leq 0.$$

Therefore, $\dfrac{dV_2}{dt}(R_s, R_I, L_s, L_I) = 0$ if and only if $B = K$, $L = 0$ and

$$R_s = \frac{g(0)B}{\alpha} = \frac{g(0)K}{\alpha},$$

that means $(R_s, R_I, L_s, L_I) = (R_s^*, R_I^*, 0, 0)$. According to the Lyapunov's asymptotic stability theorem[25], we obtain the desired conclusion. □

Figures 1 and 2 show the dynamics of resistant and susceptible bacteria in the river. Fig. 1 represents the global asymptotic stability of E_1 once $\alpha < g(0)$; this case occurs when the maximum loss rate of the antibiotic resistance gene is larger than the transmission rate. On the other hand, Figs. 2–4 show that E_2 is globally asymptotically stable when $\alpha > g(0)$, this case appears when the transmission rate of the antibiotic-resistant gene is strong compared to the loss rate of this gene. It can be seen that whether resistant or susceptible bacteria dominate in E_2 depends on the value of $2g(0) - \alpha$: positive values (i.e. where the loss rate is significantly higher than transmission) yield higher levels of susceptible bacteria, negative values of resistant bacteria
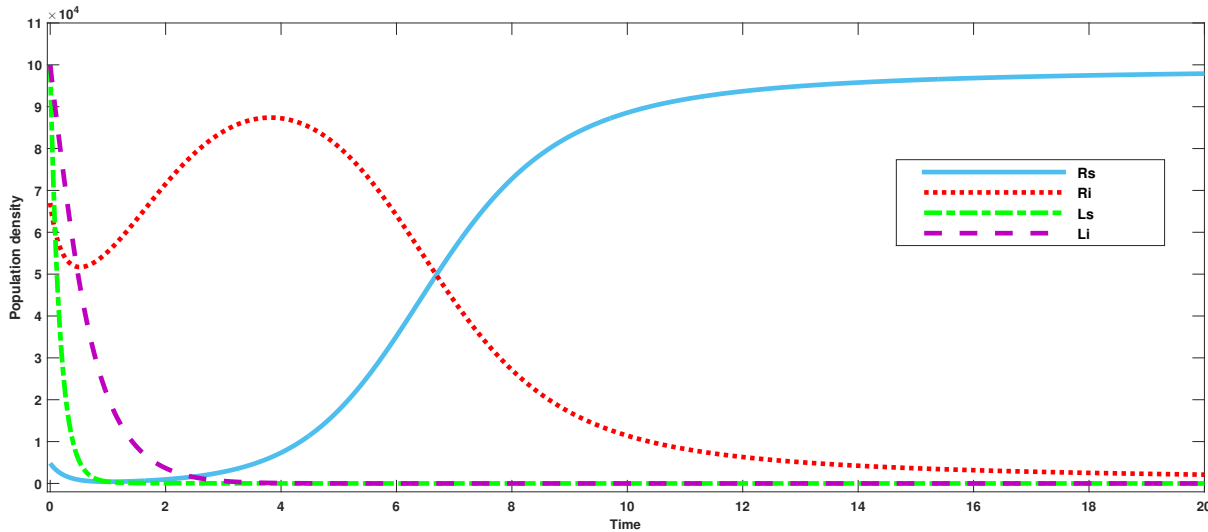
FIGURE 1 Choosing $\alpha = 3$, $\gamma = 2$, $r = 1$, $K = 100000$ and $g(L) = \frac{4}{\sqrt{L+1}}$, we have convergence to E_1.
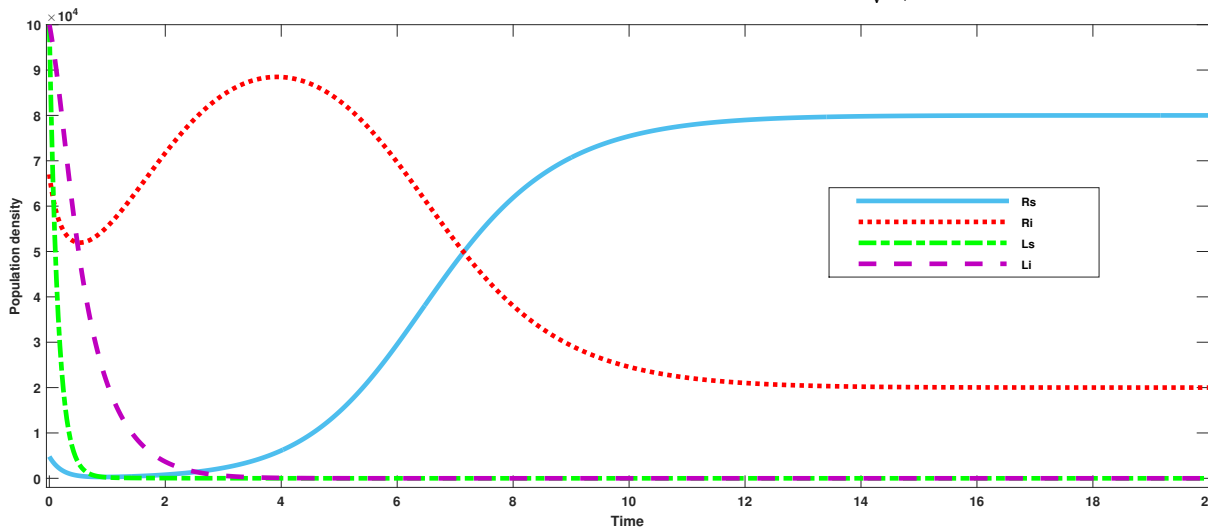
FIGURE 2 Choosing $\alpha = 5$, $\gamma = 2$, $r = 1$, $K = 100000$ and $g(L) = \frac{4}{\sqrt{L+1}}$, we have convergence to E_2.

and when equal to zero the two types of bacteria are equal in number. Each of these scenarios is depicted in Figs. 2 –4 . The parameters and the form of $g(L)$ are chosen for illustrative purposes only.

Another important issue related to the non-existence of nontrivial periodic solutions of the autonomous system. It is a simple matter to prove the non-existence using the Dulac's criteria. This follows by the same method as in [11].

4 | EXISTENCE OF PERIODIC SOLUTIONS OF NON-AUTONOMOUS SYSTEM

A positive periodic solution in the non-autonomous system plays a similar role to a stable equilibrium in the autonomous system. In this section, we are concerned with the existence of positive periodic solutions of the non-autonomous system (4). To achieve this, we use the coincidence degree theory; specifically the continuation theorem [26]; readers are encouraged to review the methodology in [11,27,28].

Let X and Y be two Banach spaces, $L : Dom L \subset X \rightarrow Y$ be a linear mapping and $N : X \rightarrow Y$ be a continuous mapping. If L is Fredholm mapping of index zero, then there exist two continuous projectors $P : X \rightarrow X$ and $Q : Y \rightarrow Y$ such that $\text{Im} P = \ker L$, $\ker Q = \text{Im} L = \text{Im}(I - Q)$ and $X = \ker L \oplus \ker P$, $Y = \text{Im} L \oplus \text{Im} Q$. As a result, the restriction of L on

FIGURE 3 Choosing $\alpha = 8$, $\gamma = 2$, $r = 1$, $K = 100000$ and $g(L) = \frac{4}{\sqrt{L+1}}$, we have convergence to E_2.
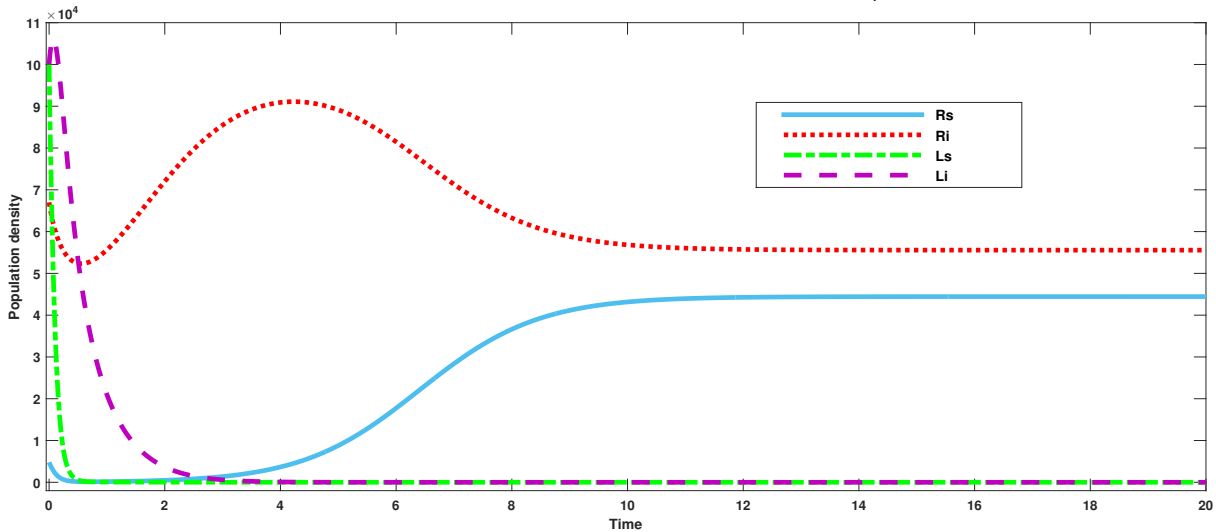
FIGURE 4 Choosing $\alpha = 9$, $\gamma = 2$, $r = 1$, $K = 100000$ and $g(L) = \frac{4}{\sqrt{L+1}}$, we have convergence to E_2.
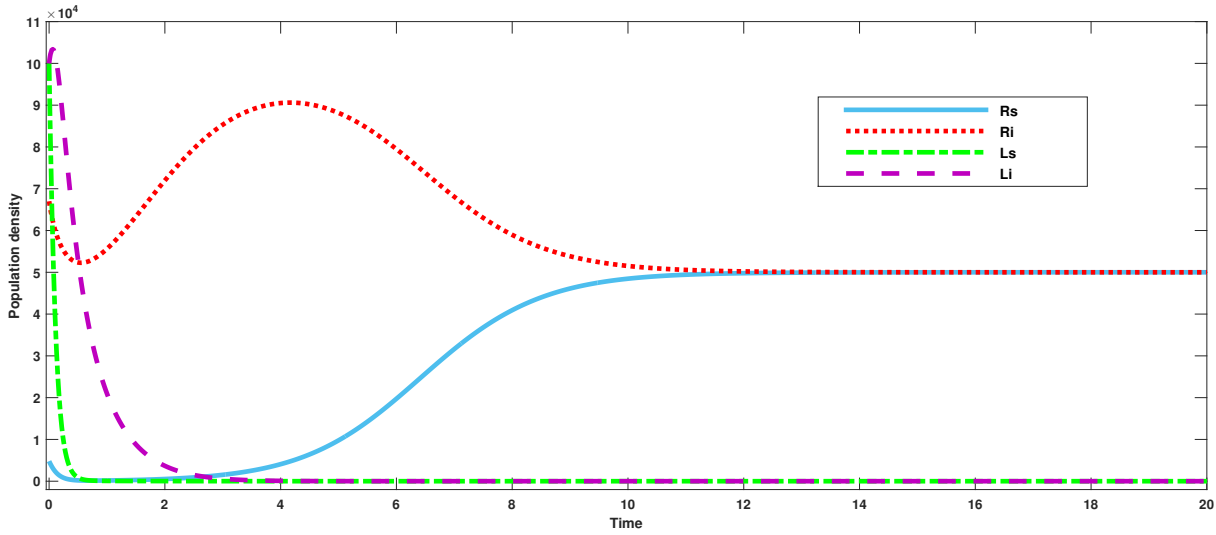
$DomL \cap \ker P$ defined as $L|_{DomL \cap \ker P} : (I - P)X \rightarrow \text{Im } L$ is invertible and its inverse is noted by K_P. If Ω is an open subset of X, then N is called **L-compact** on $\overline{\Omega}$ if $QN(\overline{\Omega})$ is bounded and $K_P(I - Q)N : \overline{\Omega} \rightarrow X$ is compact. As $\text{Im } Q$ is isomorphic to $\ker L$ there exists an isomorphism $J : \text{Im } Q \rightarrow \ker L$.

Theorem 4. (Mawhin's continuation theorem[26]) Let $\Omega \subset X$ be an open bounded set. Let L be a Fredholm mapping of index zero and N is L-compact on X. If the following conditions hold

1. for all $\lambda \in (0, 1)$, $x \in \partial\Omega \cap DomL$, $Lx \neq \lambda Nx$,

2. for all $x \in \partial\Omega \cap \ker L$, $QNx \neq 0$,

3. $\deg\{JQN, \Omega \cap \ker L, 0\} \neq 0$,

then the equation $Lx = Nx$ has at least one solution in $DomL \cap \overline{\Omega}$.

Our main aim is to write the system (4) in the form $Lx = Nx$, with L a Fredholm mapping of index zero and N being L-compact and select a suitable open set Ω such that the three conditions of the continuation theorem are satisfied.

First of all, since we look for positive solutions, the following change of variables is considered

$$R_s(t) = e^{x_1(t)}, \quad R_I(t) = e^{x_2(t)}, \quad L_s(t) = e^{x_3(t)}, \quad L_I(t) = e^{x_4(t)}. \tag{12}$$

Hence, the system (4) can be written as follows

$$
\begin{cases}
x_1'(t) = -\dfrac{\alpha(e^{x_2} + e^{x_4})}{\omega} + e^{x_2 - x_1} g(e^{x_3} + e^{x_4}) + r\left(1 - \dfrac{\omega}{K}\right), \\[2mm]
x_2'(t) = \dfrac{\alpha e^{x_1 - x_2}(e^{x_2(t)} + e^{x_4})}{\omega} - g(e^{x_3} + e^{x_4}) + r\left(1 - \dfrac{\omega}{K}\right), \\[2mm]
x_3'(t) = e^{-x_3} F_s(t) - \gamma - \dfrac{\alpha(e^{x_2} + e^{x_4})}{\omega} + e^{x_4 - x_3} g(e^{x_3} + e^{x_4}) + r\left(1 - \dfrac{\omega}{K}\right), \\[2mm]
x_4'(t) = e^{-x_4} F_I(t) - \gamma + \dfrac{\alpha e^{x_3 - x_4}(e^{x_2} + e^{x_4})}{\omega} - g(e^{x_3} + e^{x_4}) + r\left(1 - \dfrac{\omega}{K}\right), \\[2mm]
\omega = e^{x_1} + e^{x_2} + e^{x_3} + e^{x_4}.
\end{cases}
\tag{13}
$$

Let us denote by X the set

$$X = Y = \{x(t) = (x_1(t), x_2(t), x_3(t), x_4(t))^T \in \mathcal{C}(\mathbb{R}_+, \mathbb{R}^4) : x(t + T) = x(t), t \geq 0\}$$

with the following norm

$$\|x\| = \|(x_1(t), x_2(t), x_3(t), x_4(t))^T\| = \sum_{i=1}^{4} \max_{t \in [0,T]} |x_i(t)|,$$

where $|\cdot|$ is the absolute value. Thereupon, $(X, \|\cdot\|)$ and $(Y, \|\cdot\|)$ are Banach spaces. We consider the mapping L defined as

$$L : DomL \to X, \quad L(x(t)) = x'(t) = (x_1'(t), x_2'(t), x_3'(t), x_4'(t))^T,$$

where $DomL = \{x(t) \in C^1(\mathbb{R}_+, \mathbb{R}^4) : x(t + T) = x(t), t \geq 0\} \subset X$. L is Fredholm mapping of index zero (see [27]). One can see that its inverse $K_p : \text{Im}\, L \to DomL \cap KerP$ is given by

$$K_p x(t) = \int_0^t x(s)ds - \frac{1}{T} \int_0^T \int_0^t x(s)ds\, dt.$$

Let $N : X \to X$ be the mapping given by

$$Nx(t) = (\delta_1(x(t), t), \delta_2(x(t), t), \delta_3(x(t), t), \delta_4(x(t), t))^T,$$

where

$$\delta_1(x(t), t) = -\frac{\alpha(e^{x_2} + e^{x_4})}{\omega} + e^{x_2 - x_1} g(e^{x_3} + e^{x_4}) + r\left(1 - \frac{\omega}{K}\right),$$

$$\delta_2(x(t), t) = \frac{\alpha e^{x_1 - x_2}(e^{x_2(t)} + e^{x_4})}{\omega} - g(e^{x_3} + e^{x_4}) + r\left(1 - \frac{\omega}{K}\right),$$

$$\delta_3(x(t), t) = e^{-x_3} F_s(t) - \gamma - \frac{\alpha(e^{x_2} + e^{x_4})}{\omega} + e^{x_4 - x_3} g(e^{x_3} + e^{x_4}) + r\left(1 - \frac{\omega}{K}\right),$$

$$\delta_4(x(t), t) = e^{-x_4} F_I(t) - \gamma + \frac{\alpha e^{x_3 - x_4}(e^{x_2} + e^{x_4})}{\omega} - g(e^{x_3} + e^{x_4}) + r\left(1 - \frac{\omega}{K}\right).$$

N is L-compact under $\overline{\Omega}$ for any open bounded set $\Omega \subset X$. On one side, $QN : X \to X$ is $QNx(t) = (q_1(t), q_2(t), q_3(t), q_4(t))^T$, where $q_i(t) = \int_0^T \delta_i(x(t), t)dt$, for $i = 1 \dots 4$. In addition, $K_p(I - Q)N : X \to X$ is written in the form

$$K_p(I - Q)Nx(t) = (\psi_1(x(t), t), \psi_2(x(t), t), \psi_3(x(t), t), \psi_4(x(t), t))^T,$$

with

$$\psi(x(t), t) = \int\limits_0^t \delta_i(x(s), s)ds - \frac{1}{T} \int\limits_0^T \int\limits_0^t \delta_i(x(s), s)ds\,dt - \left(\frac{t}{T} - \frac{1}{2}\right) \int\limits_0^T \delta_i(x(s), s)ds,$$

for $i = 1, \ldots, 4$. Since QN and $K_p(I - Q)N$ are compositions of continuous functions, then they are continuous on X. Furthermore, by using Arzela-Ascoli theorem[29], the mapping

$$K_p(I - Q)N : \overline{\Omega} \to X$$

is compact for any open bounded $\Omega \subset X$[28]. Finally, $QN(\overline{\Omega})$ is bounded and we conclude that N is L-compact under $\overline{\Omega}$ for any open bounded set $\Omega \subset X$.

We have successfully written our system in the form $Lx = Nx$ where L is a Fredholm mapping of index zero and N is L-compact in a Banach space $(X, \|\cdot\|)$. We are ready to prove the existence of a periodic solution using the continuation theorem.

Theorem 5. Let F_s and F_I be a T-periodic functions, then the system (9) has at least one positive T-periodic solution.

Proof. The proof is divided into several steps.

Step 1:

This part consists of the construction of an appropriate open $\Omega \subset X$ for which the equation $Lx = \lambda Nx$ does not have solutions on $\partial\Omega$, for each $\lambda \in (0, 1)$. $Lx = \lambda Nx$ is equivalent to the following system

$$\begin{cases}
x_1'(t) = \lambda \left[-\frac{\alpha(e^{x_2} + e^{x_4})}{\omega} + e^{x_2 - x_1} g(e^{x_3} + e^{x_4}) + r\left(1 - \frac{\omega}{K}\right) \right], \\[2mm]
x_2'(t) = \lambda \left[\frac{\alpha e^{x_1 - x_2}(e^{x_2(t)} + e^{x_4})}{\omega} - g(e^{x_3} + e^{x_4}) + r\left(1 - \frac{\omega}{K}\right) \right], \\[2mm]
x_3'(t) = \lambda \left[e^{-x_3} F_s(t) - \gamma - \frac{\alpha(e^{x_2} + e^{x_4})}{\omega} + e^{x_4 - x_3} g(e^{x_3} + e^{x_4}) + r\left(1 - \frac{\omega}{K}\right) \right], \\[2mm]
x_4'(t) = \lambda \left[e^{-x_4} F_I(t) - \gamma + \frac{\alpha e^{x_3 - x_4}(e^{x_2} + e^{x_4})}{\omega} - g(e^{x_3} + e^{x_4}) + r\left(1 - \frac{\omega}{K}\right) \right], \\[2mm]
\omega(t) = e^{x_1(t)} + e^{x_2(t)} + e^{x_3(t)} + e^{x_4(t)}.
\end{cases} \tag{14}$$

Moreover, we multiply the first equation of (14) by $e^{x_1(t)}$, the second by $e^{x_2(t)}$, the third by $e^{x_3(t)}$ and the fourth by $e^{x_4(t)}$. This leads to

$$\begin{cases}
e^{x_1} x_1'(t) = \lambda \left[-\frac{\alpha e^{x_1}(e^{x_2} + e^{x_4})}{\omega} + e^{x_2} g(e^{x_3} + e^{x_4}) + re^{x_1}\left(1 - \frac{\omega}{K}\right) \right], \\[2mm]
e^{x_2} x_2'(t) = \lambda \left[\frac{\alpha e^{x_1}(e^{x_2(t)} + e^{x_4})}{\omega} - e^{x_2} g(e^{x_3} + e^{x_4}) + re^{x_2}\left(1 - \frac{\omega}{K}\right) \right], \\[2mm]
e^{x_3} x_3'(t) = \lambda \left[F_s(t) - \gamma e^{x_3} - \frac{\alpha e^{x_3}(e^{x_2} + e^{x_4})}{\omega} + e^{x_4} g(e^{x_3} + e^{x_4}) + re^{x_3}\left(1 - \frac{\omega}{K}\right) \right], \\[2mm]
e^{x_4} x_4'(t) = \lambda \left[F_I(t) - \gamma e^{x_4} + \frac{\alpha e^{x_3}(e^{x_2} + e^{x_4})}{\omega} - e^{x_4} g(e^{x_3} + e^{x_4}) + re^{x_4}\left(1 - \frac{\omega}{K}\right) \right].
\end{cases}$$

Now, we integrate both sides of the above system from 0 to T with respect to t to get the equations

$$\int_0^T \left[-\frac{\alpha e^{x_1}(e^{x_2} + e^{x_4})}{\omega} + e^{x_2}g(e^{x_3} + e^{x_4}) + re^{x_1}\left(1 - \frac{\omega}{K}\right) \right] dt = 0, \tag{15}$$

$$\int_0^T \left[\frac{\alpha e^{x_1}(e^{x_2(t)} + e^{x_4})}{\omega} - e^{x_2}g(e^{x_3} + e^{x_4}) + re^{x_2}\left(1 - \frac{\omega}{K}\right) \right] dt = 0, \tag{16}$$

$$\int_0^T \left[F_s(t) - \gamma e^{x_3} - \frac{\alpha e^{x_3}(e^{x_2} + e^{x_4})}{\omega} + e^{x_4}g(e^{x_3} + e^{x_4}) + re^{x_3}\left(1 - \frac{\omega}{K}\right) \right] dt = 0, \tag{17}$$

$$\int_0^T \left[F_I(t) - \gamma e^{x_4} + \frac{\alpha e^{x_3}(e^{x_2} + e^{x_4})}{\omega} - e^{x_4}g(e^{x_3} + e^{x_4}) + re^{x_4}\left(1 - \frac{\omega}{K}\right) \right] dt = 0. \tag{18}$$

By summing (15) and (16), we obtain

$$r \int_0^T (e^{x_1(t)} + e^{x_2(t)})\left(1 - \frac{\omega(t)}{K}\right) dt = 0. \tag{19}$$

Consequently, by the mean value theorem[30], there exists $\mu \in (0, T)$ such that

$$r\left(1 - \frac{\omega(\mu)}{K}\right) \int_0^T (e^{x_1(t)} + e^{x_2(t)}) dt = 0,$$

which implies that $\omega(\mu) = K$, then $e^{x_i(\mu)} < K$, for $i = 1, \ldots, 4$, i.e. $x_i(\mu) < \ln K$. Hence, $\min_{t \in [0,T]} x_i(t) < \ln K$, for $i = 1, \ldots, 4$. On the other hand, the sum of (17) and (18) yields

$$\int_0^T (F_s(t) + F_I(t)) dt - \gamma \int_0^T (e^{x_3} + e^{x_4}) dt + r \int_0^T (e^{x_3} + e^{x_4})\left(1 - \frac{\omega}{K}\right) = 0. \tag{20}$$

Thus,

$$\int_0^T (F_s(t) + F_I(t)) dt - (\gamma - r) \int_0^T (e^{x_3} + e^{x_4}) dt = r \int_0^T (e^{x_3} + e^{x_4})\frac{\omega}{K} > 0.$$

As $\gamma > r$, we have

$$\int_0^T (e^{x_3(t)} + e^{x_4(t)}) dt < \frac{1}{\gamma - r} \int_0^T (F_s(t) + F_I(t)) dt. \tag{21}$$

From (19), it follows

$$K \int_0^T (e^{x_1} + e^{x_2}) dt = \int_0^T (e^{x_1} + e^{x_2})^2 dt + \int_0^T (e^{x_1} + e^{x_2})(e^{x_3} + e^{x_4}) dt,$$

thereupon

$$\int_0^T (e^{x_1} + e^{x_2})^2 dt < K \int_0^T (e^{x_1} + e^{x_2}) dt.$$

By applying the inequality of Cauchy-Swartz[31], we get

$$\left(\int_0^T (e^{x_1} + e^{x_2})^2 dt \right)^{\frac{1}{2}} < \sqrt{T}K. \tag{22}$$

Moreover, from (20)

$$\int_0^T (F_s(t) + F_I(t))dt = (\gamma - r)\int_0^T (e^{x_3} + e^{x_4})dt + \frac{r}{K}\int_0^T (e^{x_3} + e^{x_4})(e^{x_1} + e^{x_2})dt + \frac{r}{K}\int_0^T (e^{x_3} + e^{x_4})^2 dt,$$

then

$$\frac{r}{K}\int_0^T (e^{x_3} + e^{x_4})^2 dt < \int_0^T (F_s(t) + F_I(t))dt.$$

Therefore,

$$\left(\int_0^T (e^{x_3} + e^{x_4})^2 dt\right)^{\frac{1}{2}} < \sqrt{\frac{K}{r}}\left(\int_0^T (F_s(t) + F_I(t))dt\right)^{\frac{1}{2}}. \tag{23}$$

Now, we recall that

$$x_1'(t) = \lambda\left[-\frac{\alpha(e^{x_2} + e^{x_4})}{\omega} + e^{x_2 - x_1}g(e^{x_3} + e^{x_4}) + r\left(1 - \frac{\omega}{K}\right)\right].$$

Hence, from (21) and (22) we have

$$\int_0^T e^{x_2 - x_1}g(e^{x_3} + e^{x_4})dt = \int_0^T \frac{\alpha(e^{x_2} + e^{x_4})}{\omega}dt - r\int_0^T \left(1 - \frac{\omega}{K}\right)dt$$

$$\leq \alpha T + \frac{r}{K}\int_0^T (e^{x_1} + e^{x_2})dt + \frac{r}{K}\int_0^T (e^{x_3} + e^{x_4})dt$$

$$\leq \alpha T + \frac{r}{K}\sqrt{T}\left(\int_0^T (e^{x_1} + e^{x_2})^2 dt\right)^{\frac{1}{2}} + \frac{r}{K}\int_0^T (e^{x_3} + e^{x_4})dt$$

$$\leq \alpha T + rT + \frac{r}{K(\gamma - r)}\int_0^T (F_s(t) + F_I(t))dt = M_1.$$

Similarly,

$$\int_0^T e^{x_4 - x_3}g(e^{x_3} + e^{x_4})dt = -\int_0^T e^{x_3}F_s(t)dt + \gamma T + \int_0^T \frac{\alpha(e^{x_2} + e^{x_4})}{\omega}dt - r\int_0^T \left(1 - \frac{\omega}{K}\right)dt$$

$$\leq \gamma T + M_1 = M_2.$$

On the other hand, since g is a decreasing function on $\mathbb{R}_+$, we obtain

$$\int_0^T \frac{\alpha e^{x_1 - x_2}(e^{x_2} + e^{x_4})}{\omega}dt = \int_0^T g(e^{x_3} + e^{x_4})dt - r\int_0^T \left(1 - \frac{\omega}{K}\right)dt$$

$$\leq g(0)T + rT + \frac{r}{K(\gamma - r)}\int_0^T (F_s(t) + F_I(t))dt = M_3.$$

Likewise,

$$\int_0^T \frac{\alpha e^{x_3 - x_4}(e^{x_2} + e^{x_4})}{\omega}dt = -\int_0^T e^{-x_4}F_I(t)dt + \gamma T + \int_0^T g(e^{x_3} + e^{x_4})dt - r\int_0^T \left(1 - \frac{\omega}{K}\right)dt$$

$$\leq \gamma T + M_3 = M_4.$$

Hereafter, since $(x_1(t), x_2(t), x_3(t), x_4(t))^T \in X$, then the functions x_i are continuous bounded on $[0, T]$ and they have maximum and minimum values, we denote by $x_i(\eta_i) = \max_{t \in [0,T]} x_i(t)$ and $x_i(\xi_i) = \min_{t \in [0,T]} x_i(t)$. We see that

$$\int_0^T \left[F_s(t) + e^{x_4} g(e^{x_3} + e^{x_4})\right] dt = \int_0^T \gamma e^{x_3} dt + \int_0^T \frac{\alpha e^{x_3}(e^{x_2} + e^{x_4})}{\omega} dt - \int_0^T r e^{x_3} \left(1 - \frac{\omega}{K}\right) dt.$$

As a result,

$$\int_0^T F_s(t) dt \leq \gamma T e^{x_3(\eta_3)} + \alpha T e^{x_3(\eta_3)} + rT e^{x_3(\eta_3)} + \frac{r e^{x_3(\eta_3)}}{K(\gamma - r)} \int_0^T (F_s(t) + F_I(t)) dt.$$

Hence,

$$e^{x_3(\eta_3)} \geq \frac{\displaystyle\int_0^T F_s(t) dt}{(\gamma + \alpha + r)T + \dfrac{r}{K(\gamma - r)} \displaystyle\int_0^T (F_s(t) + F_I(t)) dt} = C_3.$$

Similar arguments apply to give

$$e^{x_4(\eta_4)} \geq \frac{\displaystyle\int_0^T F_I(t) dt}{(\gamma + g(0) + r)T + \dfrac{r}{K(\gamma - r)} \displaystyle\int_0^T (F_s(t) + F_I(t)) dt} = C_4.$$

Moreover, using a simple demonstration by reductio ad absurdum, we show the existence of $C_1 > 0$ and $C_2 > 0$ such that $e^{x_1(\eta_1)} > C_1$ and $e^{x_2(\eta_2)} > C_2$. Now the first equation of (14) gives

$$\int_0^T |x_1'(t)| dt \leq \lambda \left[\int_0^T \frac{\alpha(e^{x_2} + e^{x_4})}{\omega} + e^{x_2 - x_1} g(e^{x_3} + e^{x_4}) + r\left(1 + \frac{\omega}{K}\right) dt\right].$$

According to the above estimations, it follows that

$$\int_0^T |x_1'(t)| dt \leq 2M_1. \tag{24}$$

Similarly, $\int_0^T |x_2'(t)| dt \leq 2M_2$, $\int_0^T |x_3(t)| dt \leq 2M_3$ and $\int_0^T |x_4'(t)| dt \leq 2M_4$. Thus, for $t \in [0, T]$ we have

$$x_i(t) = x_i(\xi_i) + \int_{\xi_i}^t x_i'(s) ds \leq x_i(\xi_i) + \int_0^T |x_i'(s)| ds < \ln K + 2M_i,$$

for $i = 1, \ldots, 4$. Furthermore,

$$x_i(t) = x_i(\eta_i) + \int_{\eta_i}^t x_i'(s) ds \geq x_i(\eta_i) - \int_0^T |x_i'(s)| ds > \ln(C_i) - 2M_i,$$

for $i = 1, \ldots, 4$. It may be concluded that

$$\max_{t \in [0,T]} |x_i(t)| < \max\{|\ln K + 2M_i|, |\ln(C_i) - 2M_i|\} = R_i, \quad i = 1, \ldots, 4.$$

Step 2:

Let $(x_1, x_2, x_3, x_4)^T \in \ker L = \mathbb{R}^4$ be a solution of $QNx = 0$, this means that

$$
\begin{cases}
-\dfrac{\alpha e^{x_1}(e^{x_2} + e^{x_4})}{\omega} + e^{x_2}g(e^{x_3} + e^{x_4}) + re^{x_1}\left(1 - \dfrac{\omega}{K}\right) = 0, \\[2mm]
\dfrac{\alpha e^{x_1}(e^{x_2(t)} + e^{x_4})}{\omega} - e^{x_2}g(e^{x_3} + e^{x_4}) + re^{x_2}\left(1 - \dfrac{\omega}{K}\right) = 0, \\[2mm]
\displaystyle\int_0^T F_s(t)dt - T\gamma e^{x_3} - T\dfrac{\alpha e^{x_3}(e^{x_2} + e^{x_4})}{\omega} + Te^{x_4}g(e^{x_3} + e^{x_4}) + Tre^{x_3}\left(1 - \dfrac{\omega}{K}\right) = 0, \\[2mm]
\displaystyle\int_0^T F_I(t)dt - T\gamma e^{x_4} + T\dfrac{\alpha e^{x_3}(e^{x_2} + e^{x_4})}{\omega} - Te^{x_4}g(e^{x_3} + e^{x_4}) + Tre^{x_4}\left(1 - \dfrac{\omega}{K}\right) = 0.
\end{cases}
\tag{25}
$$

Now, we take $R_0 > 0$ large enough such that any solution $x^* = (x_1^*, x_2^*, x_3^*, x_4^*)$ of the algebraic system (25) satisfies $\|x^*\| < R_0$.

Step 3:

The task is now to find $\deg\{JQN, \Omega \cap \ker L, 0\}$ where J is the isomorphism $J : \operatorname{Im} Q \to \ker L$ such that $J(x) = x$. We solve the equation $JQNx = 0$, for $x \in \Omega \cap \ker L$, which is equivalent to the algebraic system:

$$
\begin{cases}
-\dfrac{\alpha e^{x_1}(e^{x_2} + e^{x_4})}{\omega} + e^{x_2}g(e^{x_3} + e^{x_4}) + re^{x_1}\left(1 - \dfrac{\omega}{K}\right) = 0, \\[2mm]
\dfrac{\alpha e^{x_1}(e^{x_2(t)} + e^{x_4})}{\omega} - e^{x_2}g(e^{x_3} + e^{x_4}) + re^{x_2}\left(1 - \dfrac{\omega}{K}\right) = 0, \\[2mm]
\displaystyle\int_0^T F_s(t)dt - T\gamma e^{x_3} - T\dfrac{\alpha e^{x_3}(e^{x_2} + e^{x_4})}{\omega} + Te^{x_4}g(e^{x_3} + e^{x_4}) + Tre^{x_3}\left(1 - \dfrac{\omega}{K}\right) = 0, \\[2mm]
\displaystyle\int_0^T F_I(t)dt - T\gamma e^{x_4} + T\dfrac{\alpha e^{x_3}(e^{x_2} + e^{x_4})}{\omega} - Te^{x_4}g(e^{x_3} + e^{x_4}) + Tre^{x_4}\left(1 - \dfrac{\omega}{K}\right) = 0.
\end{cases}
\tag{26}
$$

To this aim, we consider an homotopy $H : Dom L \times [0, 1] \to X$ defined by $H(x, \mu) =$

$$
\begin{pmatrix}
re^{x_1}\left(1 - \dfrac{e^{x_1}}{K}\right) \\[2mm]
re^{x_2}\left(1 - \dfrac{e^{x_2}}{K}\right) \\[2mm]
\displaystyle\int_0^T F_s(t)dt - T\gamma e^{x_3} + re^{x_3}\left(1 - \dfrac{e^{x_1}}{K}\right) \\[2mm]
\displaystyle\int_0^T F_I(t)dt - T\gamma e^{x_4} + re^{x_4}\left(1 - \dfrac{e^{x_2}}{K}\right)
\end{pmatrix}
+ \mu
\begin{pmatrix}
-\dfrac{\alpha e^{x_1}(e^{x_2} + e^{x_4})}{\omega} + e^{x_2}g(e^{x_3} + e^{x_4}) - \dfrac{re^{x_1}(e^{x_1} + e^{x_3} + e^{x_4})}{K} \\[2mm]
\dfrac{\alpha e^{x_1}(e^{x_2(t)} + e^{x_4})}{\omega} - e^{x_2}g(e^{x_3} + e^{x_4}) - \dfrac{re^{x_2}(e^{x_1} + e^{x_3} + e^{x_4})}{K} \\[2mm]
-T\dfrac{\alpha e^{x_3}(e^{x_2} + e^{x_4})}{\omega} + Te^{x_4}g(e^{x_3} + e^{x_4}) - \dfrac{rTe^{x_3}(e^{x_1} + e^{x_3} + e^{x_4})}{K} \\[2mm]
T\dfrac{\alpha e^{x_3}(e^{x_2} + e^{x_4})}{\omega} - Te^{x_4}g(e^{x_3} + e^{x_4}) - \dfrac{rTe^{x_3}(e^{x_1} + e^{x_3} + e^{x_4})}{K}
\end{pmatrix}.
$$

It is easily seen that the following algebraic system

$$
\begin{cases}
re^{x_1}\left(1 - \dfrac{e^{x_1}}{K}\right) = 0, \\[2mm]
re^{x_2}\left(1 - \dfrac{e^{x_2}}{K}\right) = 0, \\[2mm]
\displaystyle\int_0^T F_s(t)dt - T\gamma e^{x_3} + re^{x_3}\left(1 - \dfrac{e^{x_1}}{K}\right) = 0, \\[2mm]
\displaystyle\int_0^T F_I(t)dt - T\gamma e^{x_4} + re^{x_4}\left(1 - \dfrac{e^{x_2}}{K}\right) = 0,
\end{cases}
$$

has a unique positive solution given by

$$
e^{x_1} = K, \quad e^{x_2} = K, \quad e^{x_3} = \frac{1}{\gamma T}\int_0^T F_s(t)dt, \quad e^{x_4} = \frac{1}{\gamma T}\int_0^T F_I(t)dt. \tag{27}
$$

Let us denote

$$
R_5 = 2K + \frac{1}{\gamma T}\int_0^T (F_s(t) + F_I(t))dt
$$

and $R = \sum_{i=0}^5 R_i$. Therefore, by choosing Ω defined as

$$
\Omega = \left\{ x = (x_1, x_2, x_3, x_4)^T \in X \,:\, \|x\| < R \right\},
$$

then the first two conditions of the continuation theorem are fulfilled and the solution (27) belongs to Ω. Further, since the degree is invariant among homotopy, then

$$
\begin{aligned}
\deg\{JQN, \Omega \cap \ker L, 0\} &= \deg\{H(\cdot, 1), \Omega \cap \ker L, 0\} \\
&= \deg\{H(\cdot, 0), \Omega \cap \ker L, 0\} = 1 \neq 0,
\end{aligned}
$$

and the proof is complete. □

At the end of this section, we present some numerical simulations to illustrate the results. By choosing $F_s(t) = 5000 + 2500\cos(\pi t/10)\sin(\pi t/10)$, $F_I(t) = 5200 + 2600\cos(\pi t/10)\sin(\pi t/10)$ and $g(L) = \frac{100}{\sqrt{L+1}}$, we obtain the dynamics in Fig. 5 (again, parameters are chosen for illustrative purposes only).

5 | DISCUSSION

In the present paper, we investigate a model describing the dynamics of resistant and non-resistant bacteria in polluted rivers. Our model extends previous works realized by [10,11]. The main modification here is the nonlinear transmission rate of the antibiotic resistant gene, and the generalization of the rate of loss of this gene. Our model is defined by a non-autonomous system of four differential equations.

As with many models of this kind, certain aspects of the environment are naturally over-simplified. For example, there are of course many different strains of bacteria that would in reality have different growth, death, transmission and loss rates. Nevertheless, reducing the model to these four variables enables important headway to be made on understanding the general dynamics of river bacteria without the need for model parametrization from inevitably noisy data.

Firstly, we establish the existence of a positively invariant attracting set, which confirms that populations survive and there is a natural restriction to growth as a consequence of limited resources as captured in the logistic growth term.

Next, we study the associated autonomous system (i.e. $F_s = F_I = 0$) in order to understand bacterial resistance phenomena under non-polluted conditions. The global asymptotic stability of the resistant free equilibrium $E_1(K, 0, 0, 0)$ and the resistant equilibrium $E_2\left(R_s^*, R_I^*, 0, 0\right)$ is given by constructing Lyapunov functions. From a biological point of view, it can be noted that: (i) if the loss rate of the antibiotic-resistant gene is high compared to its transmission rate, then the resistant bacteria will be
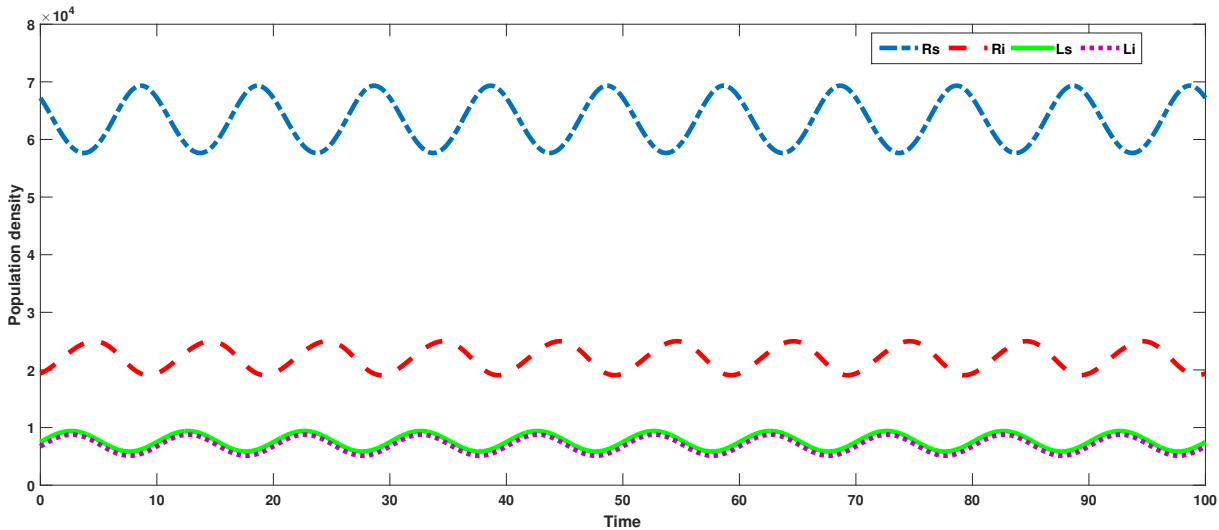
FIGURE 5 Choosing $\alpha = 1$, $\gamma = 7$, $r = 3$, $K = 100000$ and $R_s(0) = 67200$, $R_I(0) = 19400$, $L_s(0) = 7500$, $L_I(0) = 6700$, we have a periodic positive solution of (4).

eliminated in the long run, i.e., the resistant bacteria renew the population of non-resistant bacteria via loss of the gene. (ii) If the transmission rate of the antibiotic-resistant gene is strong as compared to the loss rate of this gene, then the resistant and non-resistant bacteria eventually persist alongside each other, and if this difference is sufficiently high ($\alpha > 2g(0)$), resistant bacteria could even outnumber susceptible bacteria (though this is a somewhat unrealistic outcome). In scenario (ii), even preventing new resistant bacteria from entering the river would be insufficient to eradicate the resistance gene from the environment. Whether the acquisition rate or loss rate of the antibiotic resistant gene is higher is likely to be determined by the environment in which the bacteria reside: maintenance of the antibiotic resistance gene typically requires energy and so the bacteria may shed this gene at a higher rate as an energy saving mechanism if they are not in the vicinity of antibiotic. Thus in areas immediately downstream of, say, a hospital (where antibiotic residue is more likely to enter the river) may be more likely to give rise to resistant bacteria persisting than elsewhere in the river.

Finally, the non-autonomous system is analyzed, in the case where $F_s(t)$ and $F_I(t)$ are periodic functions. In fact, the existence of at least one periodic solution is established. Biologically, this means that if the pollutants are being deposited into the river intensively and regularly, then pollutant bacteria remain in the river and promote antibiotic resistance. In our future work, we will try to show the stability of a unique periodic solution by constructing suitable Lyapunov functionals.

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