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Toxic action and antibiotic in the chemostat: permanence and extinction of a model with functional response

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A system of periodic coefficients functional differential equations is used to model the single microorganism in the chemostat environment with a periodic nutrient and antibiotic input. Furthermore, the total toxic action on the microorganism expressed by an integral term is considered in our system. Based on the technique of analysis, we obtain sufficient conditions which guarantee the permanence of the system and extinction of the microorganism.

KEY WORDS: antibiotic, functional differential equation, toxic action, permanence, extinction

AMS subject classifications: 34K12, 92D25

1. Introduction

As we all know that the nature of disease is to break the balance of the ecosystem (organism and its internal and external environment). And the over controlling of all factors, which have some influence on the organism, can lead to the imbalance. For the purpose of keeping this balance, there are many people are concerning the dynamic behavior of one or more populations of organisms.

The biosphere inside the organism are characterized as comparatively sealed, densely populated, short-generated, and naturally chemostated, etc. When the internal microorganism populations are in disproportion or disease appear.

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In order to cure such diseases, antibiotics are usually applied to restore the balance among the internal microorganism populations. Antibiotics have been used since the 1940s, and the first one is penicillin. According to experiments with electronic microscope and radioactive penicillin, It is confirmed that penicillin can destroy the organism synthesis on the wall of the sensitive bacteria's L-shaped cell, then result in the death of the cell. Also, in most populations of organisms, the accumulation of metabolic products may seriously inconvenience a population and one of the consequences can be a fall in the birth and an increase in the mortality rate. But how to measure the influence of antibiotics and the total toxic action on the amount of microorganism populations?

On the other hand, since biological and environmental parameters are naturally subject to fluctuation in time, the effects of a periodically varying environment are considered as important selective forces on systems in a fluctuating environment. Hence more realistic and interesting models should take into account the seasonality of the changing environment [1, 2].

With the idea of chemostat model [3–14] and ecotoxicology [15–17], when the nutrient and antibiotic are both input periodically, we establish a non-autonomous chemostat model with antibiotic and the total toxic action on birth and death rates of the single microorganism. By using the technique of analysis, we determine sufficient conditions which guarantee the permanence of the system and extinction of the microorganism. These results explain, to some degree, the phenomena – the disease in clinical therapy will exist for ever and go away.

This paper is organized as follows. In section 2, we describe our model and the preliminary results. In section 3, we obtain sufficient conditions for the permanence of the system and extinction of the microorganism. Finally, a brief discussion is given in last section.

2. Mathematical model and the preliminary results

In this paper, we consider the following periodic chemostat model

$$\begin{cases} S'(t) = \big(S^0(t) - S(t)\big)D(t) - p_1(t)\phi_1(t, S(t))S(t)x(t), \\ R'(t) = \big(R^0(t) - R(t)\big)D(t) - p_2(t)\phi_2(t, R(t))R(t)x(t), \\ x'(t) = x(t)\Big[- D(t) + h_1(t)\phi_1(t, S(t))S(t) - h_2(t)\phi_2(t, R(t))R(t) \\ \qquad\qquad -p(t)x(t) - q(t)\left(\int_{-\infty}^{0} k(s)x(t+s)\mathrm{d}s\right)^n\Big], \end{cases} \tag{1}$$

where $S(t)$ is the nutrient concentration, $R(t)$ the antibiotic concentration, $x(t)$ is the microorganism concentration. $S^0(t)$ and $R^0(t)$ denote the input concentration of nutrient S and, respectively, antibiotic R. $D(t)$ is the dilution(or washout) rate. $p_i(t)$ and $h_i(t) (i = 1, 2)$ give the coefficients that relate to the conversion rate of the nutrient and antibiotic. Also, $n \in (0, \infty)$. $S^0(t)$, $R^0(t)$, $D(t)$, $p(t)$, $p_i(t)(i = 1, 2)$, $\phi_1(t, S)$, $\phi_2(t, R)$, $h_i(t)(i = 1, 2)$, and $q(t)$ are all ω-periodic and continuous for $t \geqslant 0$, $S^0(t)$, $R^0(t)$, $D(t)$, $p(t)$, $p_i(t)(i = 1, 2)$, $h_i(t)(i{=}1, 2)$, and $q(t)$ are all positive, and $\phi_1(t, S)$ and $\phi_2(t, R)$ are non-negative. The terms $\phi_1(t, S)S$ and $\phi_2(t, R)R$ which called the functional response describe the number of the nutrient S and the antibiotic R consumed per microorganism in unit time, respectively. We assume that there exists a positive constant L such that

$$0 < \phi_1(t, S) < L, \; 0 < \phi_2(t, R) < L, \; \frac{\partial \phi_1(t, S)}{\partial S} \geqslant 0, \quad \frac{\partial \phi_2(t, R)}{\partial R} \geqslant 0 \quad \text{for } S, R > 0. \tag{2}$$

The last two conditions in (2) implies that, as the nutrient and antibiotic populations increase, the consumption rates of nutrient and antibiotic per microorganism increase, respectively. Some explicit forms [10] for the functional response that have been used are

$$X\phi(t, X) = \frac{\mu_m(t)X}{K_m(t) + X} \qquad Monod(1942),$$

$$X\phi(t, X) = \frac{\mu_m(t)X}{K_m(t) + X + \frac{X^2}{K_i(t)}} \qquad Monod\ Haldane(1968),$$

$$X\phi(t, X) = \frac{\mu_m(t)X \exp(-\frac{X}{K_i(t)})}{K_m(t) + X} \qquad Tessiet(1936),$$

$$X\phi(t, X) = \begin{cases} \dfrac{\mu_m(t)X}{K(t) + X}, & X < X_\theta, \\ \dfrac{\mu_m(t)X}{K(t) + X} - i(t)(X - X_\theta), & X > X_\theta \end{cases} \qquad Tseng(1975),$$

$$X\phi(t, X) = a(t)X^q (q < 1) \qquad Rosenzweig(1971).$$

The delay–kernel $k(s)$ is a non–negative bouned function defined on $\mathbf{R}_- = (-\infty, 0]$ and integrable, and describes the residual intensity of pollution. The present of the distributed time delay must not affect the equilibrium values, so we normalize the kernel such that

$$\int_{-\infty}^{0} k(s)\mathrm{d}s = 1. \tag{3}$$

Let $\mathbf{C}_+ = \Big\{\phi = (\psi_1, \psi_2, \psi_3) : \psi_i(t)$ is continuous and non-negative on $\mathbf{R}_-$ and $\psi_i(0) > 0,\ i = 1, 2, 3\Big\}$. In this paper, we always assume that solutions of (1) satisfy the following initial conditions

$$S(s) = \psi_1(s), \quad R(s) = \psi_2(s), \quad x(s) = \psi_3(s), \quad (\psi_1, \psi_2, \psi_3) \in \mathbf{C}_+, \quad s \in \mathbf{R}_-. \tag{4}$$

Before stating and proving our main results, we give the following definitions, notations and Lemmas which will be useful.

Let $f(t)$ be a continuous ω-periodic function defined on $[0, +\infty)$, we set

$$\mathcal{A}_\omega(f) = \omega^{-1} \int_0^\omega f(t)\mathrm{d}t, \quad f^U = \max_{t\in[0,\omega]} f(t), \quad f^L = \min_{t\in[0,\omega]} f(t).$$

Definition 2.1. System (1) is said to be permanent if there exists a compact region $D \subset int\Omega(\Omega \subset \mathbf{R}_+^3 \doteq \{(z_1, z_2, z_3) : z_i \geqslant 0, \ i = 1, 2, 3\})$ such that every solution of system (1) with initial conditions (4) will eventually enter and remain in region D.

Lemma 2.2. The system

$$\begin{cases} S'(t) = a(t)S^0(t) - b(t)S(t), \\ R'(t) = c(t)R^0(t) - d(t)R(t), \end{cases} \tag{5}$$

in which $a(t)$, $b(t)$, $c(t)$, $d(t)$ are all continuous positive ω–periodic for $t \geqslant 0$, has a positive ω-periodic solution $(\widetilde{S}(t), \widetilde{R}(t))$ which is globally asymptotically stable with respect to $\mathbf{R}_+^2$.

Proof. This Lemma is easy to be proved, then the process of proving is omitted. This completes the proof. □

Lemma 2.3. For the following non-autonomous differential equation

$$\dot{u} = u[a_1(t) - b_1(t)u - c_1(t)u^n], \tag{6}$$

where $a_1(t)$, $b_1(t)$, and $c_1(t)$ are $\omega-$periodic continuous functions, c_1^L, $b_1^L \geqslant 0$, $\mathcal{A}_\omega(b_1) > 0$ and $n \in (0, \infty)$, there is a constant $M^* > 0$ such that every positive solution $u(t)$ of (6) satisfies $\limsup_{t\to\infty} u(t) \leqslant M^*$.

Proof. The proof is obvious, in fact, $u' = u[a_1(t) - b_1(t)u - c_1(t)u^n] \leqslant u[a_1(t) - b_1(t)u]$. From [18], we note that there exists a constant M^* such that the solution $x(t)$ of the Logistic equation

$$\dot{x} = x[a_1(t) - b_1(t)x]$$

satisfies

$$\limsup_{t\to\infty} x(t) \leqslant M^*.$$

Using the comparison theorem of ordinary differential equations, this completes the proof. □

Lemma 2.4. There exist positive constants M_S, M_R, and M_x such that

$$\limsup_{t\to\infty} S(t) \leqslant M_S, \quad \limsup_{t\to\infty} R(t) \leqslant M_R, \quad \limsup_{t\to\infty} x(t) \leqslant M_x.$$

Proof. Obviously, R^3_+ is a positively invariant set of system (1). Given any positive solution $(S(t), R(t), x(t))$ of (1) with initial conditions (4), we have

$$\begin{cases} S' \leqslant \big(S^0(t) - S(t)\big)D(t), \\ R' \leqslant \big(R^0(t) - R(t)\big)D(t). \end{cases}$$

Next consider the following auxiliary equations

$$\begin{cases} u_1' = \big(S^0(t) - u_1(t)\big)D(t), \\ u_2' = \big(R^0(t) - u_2(t)\big)D(t). \end{cases} \tag{7}$$

According to lemma 2.2, it follows that (7) has a globally asymptotically stable positive ω-periodic solution $(S^*(t), R^*(t))$. Let $(u_1(t), u_2(t))$ be the solution of (7) with $u_1(0) = S(0)$, $u_2(0) = R(0)$. By the vector comparison theorem [19], we obtain

$$S(t) \leqslant u_1(t), \quad R(t) \leqslant u_2(t)$$

for all $t \geqslant 0$. From the global asymptotic stability of $(S^*(t), R^*(t))$, for any positive constant ε, there exists a $T_0 > 0$ such that for all $t \geqslant T_0$,

$$|u_1(t) - S^*(t)| < \varepsilon, \quad |u_2(t) - R^*(t)| < \varepsilon.$$

Hence, we derive

$$S(t) \leqslant S^*(t) + \varepsilon, \quad R(t) \leqslant R^*(t) + \varepsilon \quad \text{for all } t \geqslant T_0.$$

Let

$$M_S \doteq \max_{t\in[0,\omega]} \{S^*(t) + \varepsilon\},$$

$$M_R \doteq \max_{t\in[0,\omega]} \{R^*(t) + \varepsilon\}$$

we then get

$$S(t) \leqslant M_S, \quad R(t) \leqslant M_R. \tag{8}$$

Consequently,

$$\limsup_{t\to\infty} S(t) \leqslant M_S$$

and

$$\limsup_{t\to\infty} R(t) \leqslant M_R.$$

In addition, let $\alpha(t) = -D(t) + h_1(t)\phi_1(S^*(t)+\varepsilon)\big(S^*(t)+\varepsilon\big)$ and let the constant $\tau > 0$ be such that

$$\int_{-\tau}^{0} k(s)\exp(\alpha^U s)\mathrm{d}s > 0. \tag{9}$$

For $t \geqslant T_0$ it follows from (2) that

$$x'(t) \leqslant x(t)\Big[-D(t) + h_1(t)\phi_1(S^*(t)+\varepsilon)\big(S^*(t)+\varepsilon\big)\Big] = x\alpha(t).$$

Hence, for any $t \geqslant t+s \geqslant T_0+\tau (s \leqslant 0)$ we obtain

$$x(t+s) \geqslant x(t)\exp\int_t^{t+s}\alpha(\xi)\mathrm{d}\xi \geqslant x(t)\exp(\alpha^U s).$$

It follows from the above inequality that for any $t \geqslant T_0 + 2\tau$, we have

$$\begin{aligned} x' &\leqslant x\left[\alpha(t) - p(t)x(t) - q(t)\left(\int_{-\infty}^{0} k(s)x(t+s)\mathrm{d}s\right)^n\right] \\ &\leqslant x\left[\alpha(t) - p(t)x(t) - q(t)\left(\int_{-\tau}^{0} k(s)x(t+s)\mathrm{d}s\right)^n\right] \\ &\leqslant x\left[\alpha(t) - p(t)x(t) - q(t)\left(\int_{-\tau}^{0} k(s)\exp(\alpha^U s)\mathrm{d}s\right)^n x^n(t)\right]. \end{aligned}$$

Let $u(t)$ be the solution of the auxiliary equation

$$\dot{u} = u\left[\alpha(t) - p(t)u(t) - q(t)\left(\int_{-\tau}^{0} k(s)\exp(\alpha^U s)\mathrm{d}s\right)^n u^n(t)\right]$$

with the initial condition $u(T_0+2\tau) = x(T_0+2\tau)$, then we derive

$$x(t) \leqslant u(t) \quad \text{for all } t \geqslant T_0 + 2\tau. \tag{10}$$

From lemma 2.3, we know that there exists a constant $M_x > 0$ such that

$$\limsup_{t\to\infty} u(t) \leqslant M_x.$$

Consequently, by (10) we have

$$\limsup_{t\to\infty} x(t) \leqslant M_x. \tag{11}$$

This completes the proof. □

Lemma 2.5. There exist positive constants ρ_S and $\rho_R (\rho_S < M_S,\ \rho_R < M_R)$ such that

$$\liminf_{t\to\infty} S(t) \geqslant \rho_S$$

and

$$\liminf_{t\to\infty} R(t) \geqslant \rho_R.$$

Proof. By lemma 2.4, there exists a positive constant $T_1 > T_0 + 2\tau$ such that

$$0 < x(t) \leqslant M_x \ for \ t \geqslant T_1.$$

Then we derive that

$$\begin{cases} S'(t) \geqslant \big(S^0(t) - S(t)\big)D(t) - p_1(t)LS(t)M_x = -\big(D(t) + LM_x p_1(t)\big)S(t) + D(t)S^0(t), \\ R'(t) \geqslant \big(R^0(t) - R(t)\big)D(t) - p_2(t)LR(t)M_x = -\big(D(t) + LM_x p_2(t)\big)R(t) + D(t)R^0(t) \end{cases}$$

for $t \geqslant T_1$. By lemma 2.2, the auxiliary system

$$\begin{cases} u_1'(t) = -\big(D(t) + LM_x p_1(t)\big)u_1(t) + D(t)S^0(t), \\ u_2'(t) = -\big(D(t) + LM_x p_2(t)\big)u_2(t) + D(t)R^0(t) \end{cases}$$

has a positive ω–periodic solution $(u_1^*(t), u_2^*(t))$, which is globally asymptotically stable. Hence there exists a positive $T_2 > T_1$ such that

$$S(t) > \rho_S \doteq \min_{t\in[0,\omega]} \left\{ \frac{u_1^*(t)}{2} \right\}$$

and

$$R(t) > \rho_R \doteq \min_{t\in[0,\omega]} \left\{ \frac{u_2^*(t)}{2} \right\}.$$

This completes the proof. □

Lemma 2.6. Suppose that

$$\mathcal{A}_\omega\big(- D(t) + h_1(t)\phi_1(t, S^*(t))S^*(t) - h_2(t)\phi_2(t, R^*(t))R^*(t)\big) > 0, \tag{12}$$

in which $S^*(t)$ and $R^*(t)$ are defined in Lemma 2.4. Then there is a positive constant ϱ_x $(\varrho_x < M_x)$ such that

$$\limsup_{t\to\infty} x(t) \geqslant \varrho_x. \tag{13}$$

Proof. By (12), we can choose a positive constant $\varepsilon_0 \ll \frac{1}{2}\min_{t\in[0,\omega]}\{S^*(t), R^*(t)\}$, where $(S^*(t), R^*(t))$ is the unique positive solution of system (7) such that

$$A_\omega(\psi_{\varepsilon_0}(t)) > 0, \tag{14}$$

where

$$\begin{aligned}\psi_{\varepsilon_0}(t) = &-D(t) + h_1(t)\phi_1(t, S^*(t) - \varepsilon_0)(S^*(t) - \varepsilon_0)\\ &-h_2(t)\phi_2(t, (R^*(t) + \varepsilon_0))(R^*(t) + \varepsilon_0) - (2\varepsilon_0)^n q(t) - \varepsilon_0 p(t).\end{aligned}$$

Consider the following auxiliary system with a positive parameter μ

$$\begin{cases} u_1'(t) = -\big(D(t) + 2L\mu p_1(t)\big)u_1(t) + D(t)S^0(t),\\ u_2'(t) = -\big(D(t) + 2L\mu p_2(t)\big)u_2(t) + D(t)R^0(t). \end{cases} \tag{15}$$

By lemma 2.2, (15) has a positive ω–periodic solution $(u^*_{1\mu}(t), u^*_{2\mu}(t))$, which is globally asymptotically stable. Let $(u_{1\mu}(t), u_{2\mu}(t))$ be the solution of (15) with initial condition $u_{1\mu}(0) = S^*(0)$ and $u_{2\mu}(0) = R^*(0)$, where $(S^*(t), R^*(t))$ is the positive periodic solution of (7). Hence, for the above ε_0, there exists $T_3 > T_2$ such that

$$|u_{i\mu}(t) - u^*_{i\mu}(t)| < \varepsilon_0/4 \tag{16}$$

for $t \geqslant T_3$, $i = 1, 2$. According to the continuity of the solution in the parameter μ,

we then have $u_{1\mu}(t) \to S^*(t)$ and $u_{2\mu}(t) \to R^*(t)$ uniformly in $[T_3, T_3 + \omega]$ as $\mu \to 0$. Hence for $\varepsilon_0 > 0$, there exists $\mu_0 = \mu_0(\varepsilon_0)$ $(0 < \mu_0 < \varepsilon_0)$ such that

$$|u_{1\mu}(t) - S^*(t)| < \varepsilon_0/4, \quad |u_{2\mu}(t) - R^*(t)| < \varepsilon_0/4, \quad 0 \leqslant \mu \leqslant \mu_0 \tag{17}$$

$t \in [T_3, T_3 + \omega]$. Thus from (16) and (17), we get

$$|u^*_{1\mu}(t) - S^*(t)| < \varepsilon_0/2, \quad |u^*_{2\mu}(t) - R^*(t)| < \varepsilon_0/2, \quad 0 \leqslant \mu \leqslant \mu_0$$

$t \in [T_3, T_3 + \omega]$. Since $u^*_{i\mu}(t)$, $S^*(t)$, and $R^*(t)$ are all ω-periodic, we have

$$|u^*_{1\mu}(t) - S^*(t)| < \varepsilon_0/2, \quad |u^*_{2\mu}(t) - R^*(t)| < \varepsilon_0/2, \quad 0 \leqslant \mu \leqslant \mu_0 \tag{18}$$

$t \geqslant 0$.

Choose a constant $\mu_1 (0 < \mu_1 < \mu_0, \mu_1 < \varepsilon_0)$, from (18), we derive

$$\begin{aligned} &u^*_{1\mu_1}(t) \geqslant S^*(t) - \frac{\varepsilon_0}{2},\ u^*_{2\mu_1}(t) \geqslant R^*(t) - \tfrac{\varepsilon_0}{2},\\ &u^*_{1\mu_1}(t) \leqslant S^*(t) + \frac{\varepsilon_0}{2},\ u^*_{2\mu_1}(t) \leqslant R^*(t) + \tfrac{\varepsilon_0}{2} \end{aligned} \tag{19}$$

for $t \geqslant 0$.
Suppose that the conclusion (13) is false. Otherwise, for the above ε_0 there exists $\phi \in \mathbf{C}_+$ such that

$$\limsup_{t\to\infty} x(t,\phi) < \mu_1,$$

where $\big(S(t,\phi), R(t,\phi), x(t,\phi)\big)$ is the solution of (1) with the initial condition $\big(S(\widehat{\theta}), R(\widehat{\theta}), x(\widehat{\theta})\big) = \phi(\widehat{\theta})$. So there exists a constant $T_4(> T_3)$ such that

$$x(t,\phi) < 2\mu_1 \quad \text{for } t \geqslant T_4. \tag{20}$$

Then we get

$$\begin{cases} S'(t) \geqslant -\big(D(t) + 2L\mu_1 p_1(t)\big)u_1(t) + D(t)S^0(t), \\ R'(t) \geqslant -\big(D(t) + 2L\mu_1 p_2(t)\big)u_2(t) + D(t)R^0(t). \end{cases} \tag{21}$$

Also, from $\int_{-\infty}^{0} k(s)ds = 1$, we can choose a positive constant τ_0 such that

$$H_0 \int_{-\infty}^{-\tau_0} k(s)\mathrm{d}s < \mu_1 \tag{22}$$

in which

$$H_0 = \sup\{x(t+s) | t \geqslant 0,\ \ s \leqslant 0\}.$$

Let $(u_{1\mu_1}, u_{2\mu_1})$ be the solution of (15) with $\mu = \mu_1$ and $(u_{1\mu_1}(T_4), u_{2\mu_1}(T_4)) = (S(T_4), R(T_4))$, then by the vector comparison theorem, we obtain

$$S(t,\phi) \geqslant u_{1\mu_1}(t), \quad R(t,\phi) \geqslant u_{2\mu_1}(t) \tag{23}$$

$t \geqslant T_4$. By the global asymptotic stability of $(u^*_{1\mu_1}(t), u^*_{2\mu_1}(t))$, for the given $\varepsilon_0 > 0$ there exists $T_6 > T_5$ such that

$$u_{i\mu_1}(t) > u^*_{i\mu_1}(t) - \varepsilon_0/2, \quad t \geqslant T_6, \quad i = 1, 2$$

and hence , by (18), we derive

$$S(t,\phi) > S^*(t) - \varepsilon_0, \quad R(t,\phi) > R^*(t) - \varepsilon_0,\ \ t \geqslant T_6. \tag{24}$$

Therefore, for $t \geqslant T_6 + \tau_0$, we have

$$\begin{aligned}
x'(t,\phi) &= x(t,\phi)\bigg[- D(t) + h_1(t)\phi_1(t, S(t))S(t) - h_2(t)\phi_2(t, R(t))R(t) \\
&\quad - p(t)x(t,\phi) - q(t)\bigg(\int_{-\infty}^{0} k(s)x(t+s)\mathrm{d}s\bigg)^n\bigg] \\
&\geqslant x(t,\phi)\bigg[- D(t) + h_1(t)\phi_1(t, (S^*(t)-\varepsilon_0))(S^*(t)-\varepsilon_0) \\
&\quad - h_2(t)\phi_2(t, (R^*(t)+\varepsilon_0))(R^*(t)+\varepsilon_0) - p(t)u_1 \\
&\quad - q(t)\bigg(\int_{-\infty}^{-\tau_0} k(s)x(t+s)\mathrm{d}s + \int_{-\tau_0}^{0} k(s)x(t+s)\mathrm{d}s\bigg)^n\bigg] \\
&\geqslant x(t,\phi)\bigg[- D(t) + h_1(t)\phi_1(t, (S^*(t)-\varepsilon_0))(S^*(t)-\varepsilon_0) \\
&\quad - h_2(t)\phi_2(t, (R^*(t)+\varepsilon_0))(R^*(t)+\varepsilon_0) - p(t)u_1 \\
&\quad - q(t)\bigg(H_0\int_{-\infty}^{-\tau_0} k(s)\mathrm{d}s + \mu_1\int_{-\tau_0}^{0} k(s)\mathrm{d}s\bigg)^n\bigg] \\
&> x(t,\phi)\bigg[- D(t) + h_1(t)\phi_1(t, (S^*(t)-\varepsilon_0))(S^*(t)-\varepsilon_0) \\
&\quad - h_2(t)\phi_2(t, (R^*(t)+\varepsilon_0))(R^*(t)+\varepsilon_0) - p(t)\varepsilon_0 \\
&\quad - (2\varepsilon_0)^n q(t)\bigg] \\
&= y(t,\phi)\psi_{\varepsilon_0}(t).
\end{aligned}$$

Integrating the above inequality from $T_6 + \tau_0$ to t yields

$$x(t,\phi) \geqslant x(T_6+\tau_0)\exp\bigg(\int_{T_6+\tau_0}^{t} \psi_{\varepsilon_0}(s)\mathrm{d}s\bigg).$$

It follows from (14) that $x(t,\phi) \to \infty$ as $t \to \infty$, which is a contradiction. This completes the proof. □

Lemma 2.7. Assume that (12) holds. Then there exists a positive constant δ_x ($\delta_x < M_y$) such that any solution $(S(t), R(t), x(t))$ of system (1) with initial condition satisfies

$$\liminf_{t\to\infty} x(t) \geqslant \delta_x. \tag{25}$$

Proof. Suppose that (25) is not true, there must exist a sequence $\{\phi_k\} \subset \mathbf{C}_+$ such that

$$\liminf_{t\to\infty} x(t,\phi_k) < \frac{\varrho_x}{(k+1)^2}, \quad k = 1, 2, \ldots$$

and by lemma 2.6, we have $\limsup_{t\to\infty} x(t,\phi_k) > \varrho_x$, $k = 1, 2, \ldots$. Hence, for each k, we choose two time sequences $\{s_q^{(k)}\} and \{t_q^{(k)}\}$, satisfying $0 < s_1^{(k)} < t_1^{(k)} < s_2^{(k)} < t_2^{(k)} < \cdots < s_q^{(k)} < t_q^{(k)} < \cdots$ and $s_q^{(k)} \to \infty$ as $q \to \infty$, and

$$x(s_q^{(k)},\phi_k) = \frac{\varrho_x}{k+1}, \quad x(t_q^{(k)},\phi_k) = \frac{\varrho_x}{(k+1)^2}, \tag{26}$$

$$\frac{\varrho_x}{(k+1)^2} < x(t,\phi_k) < \frac{\varrho_x}{k+1}, \quad t \in (s_q^{(k)}, t_q^{(k)}). \tag{27}$$

By lemma 2.4, for a given positive integer k, there exists $\widetilde{T}^{(k)} > 0$ such that $S(t,\phi_k) \leqslant M_S$, $R(t,\phi_k) \leqslant M_R$, and $x(t,\phi_k) \leqslant M_x$ for all $t \geqslant \widetilde{T}^{(k)}$. Further, there is a constant $\sigma^{(k)} > 0$ such that

$$H_1^{(k)} \int_{-\infty}^{-\sigma^{(k)}} k(s)\,\mathrm{d}s < M_x,$$

where $H_1^{(k)} = \sup\{x(t+s,\phi_k) : t \geqslant 0, s \leqslant 0\}$. Because of $s_q^{(k)} \to \infty$ as $q \to \infty$, there is a positive integer $K_1^{(k)}$ such that $s_q^{(k)} > \widetilde{T}^{(k)} + \sigma^{(k)}$ as $q \geqslant K_1^{(k)}$. For any $t \geqslant \widetilde{T}^{(k)} + \sigma^{(k)}$, we have

$$\begin{aligned}
x'(t,\phi_k) &\geqslant x(t,\phi_k)\Big[-D(t) - h_2(t)LM_R - p(t)x(t,\phi_k) \\
&\qquad -q(t)\Big(\int_{-\infty}^{0} k(s)x(t+s,\phi_k)\mathrm{d}s\Big)^n\Big] \\
&\geqslant x(t,\phi_k)\Big[-D(t) - h_2(t)LM_R - p(t)M_x - q(t)\Big(\int_{-\infty}^{-\sigma^{(k)}} k(s)x(t+s,\phi_k)\mathrm{d}s \\
&\qquad + \int_{-\sigma^{(k)}}^{0} k(s)x(t+s,\phi_k)\mathrm{d}s\Big)^n\Big] \\
&\geqslant x(t,\phi_k)\big[-D(t) - h_2(t)LM_R - p(t)M_x - (2M_y)^n q(t)\big].
\end{aligned}$$

Integrating the above inequality from $s_q^{(k)}$ to $t_q^{(k)}$, for any $q \geqslant K_1^{(k)}$ we get

$$x(t_q^{(k)},\phi_k) \geqslant x(s_q^{(k)},\phi_k)\exp\Big(\int_{s_q^{(k)}}^{t_q^{(k)}} [-D(t) - h_2(t)LM_R - p(t)M_x - (2M_y)^n q(t)]\mathrm{d}t\Big).$$

Obviously, we derive

$$\int_{s_q^{(k)}}^{t_q^{(k)}} [D(t) + h_2(t)LM_R + p(t)M_x + (2M_y)^n q(t)]\mathrm{d}t \geqslant \ln(k+1) \quad \text{for } q \geqslant K_1^{(k)}.$$

Hence, in view of the periodicity of $D(t)$, $h_2(t)$, $p(t)$, and $q(t)$, we get

$$t_q^{(k)} - s_q^{(k)} \to \infty, \quad \textit{as } k \to \infty, \quad q \geqslant K_1^{(k)}. \tag{28}$$

By (14), (26), and (28), there are positive constants T and N_0 such that

$$x(s_q^{(k)}, \phi_k) = \frac{\varrho_x}{k+1} < \varepsilon_0, \tag{29}$$

$$t_q^{(k)} - s_q^{(k)} > 2T \tag{30}$$

and

$$\int_0^{\kappa} \psi_{\varepsilon_0}(t)\mathrm{d}t > 0 \tag{31}$$

for $k \geqslant N_0,\ q \geqslant K_1^{(k)},\ and\ \kappa > T$. (29) implies that

$$x(t, \phi_k) < \varepsilon_0,\ \ t \in [s_q^{(k)}, t_q^{(k)}] \tag{32}$$

for $k \geqslant N_0,\ q \geqslant K_1^{(k)}$. Noticing that $s_q^{(k)} \to \infty$ as $q \to \infty$ and $\int_{-\infty}^{0} k(s)\mathrm{d}s = 1$, for any k there exists $K_2^{(k)} > K_1^{(k)}$ such that for all $q > K_2^{(k)}$, we obtain

$$H_1^{(k)} \int_{-\infty}^{\widetilde{T}^{(k)} - s_q^{(k)} - \sigma^0} k(s)\mathrm{d}s < \frac{1}{2}\varepsilon_0 \tag{33}$$

and

$$M_x \int_{-\infty}^{-\sigma^0} k(s)\mathrm{d}s < \frac{1}{2}\varepsilon_0, \tag{34}$$

where $\sigma^0 > 0$. By (30), there exists a positive integer N_1 such that

$$t_q^{(k)} - s_q^{(k)} > \sigma^0 \quad \text{for } k > N_1,\ q \geqslant K_2^{(k)}.$$

For $k > N_1,\ q \geqslant K_2^{(k)}$, and $s_q^{(k)} + \sigma^0 \leqslant t \leqslant t_q^{(k)}$, it follows from (32) that

$$\begin{cases} S'(t, \phi_k) \geqslant -\big(D(t) + L\varepsilon_0 p_1(t)\big)S(t, \phi_k) + D(t)S^0(t), \\ R'(t, \phi_k) \geqslant -\big(D(t) + L\varepsilon_0 p_2(t)\big)R(t, \phi_k) + D(t)R^0(t). \end{cases} \tag{35}$$

Let $(u_{1\varepsilon_0}, u_{2\varepsilon_0})$ be the solution of (15) with $\mu = \frac{\varepsilon_0}{2}$ and $(u_{1\mu_1}(s_q^{(k)} + \tau^0), u_{2\mu_1}(s_q^{(k)} + \tau^0)) = (S(s_q^{(k)} + \tau^0), R(s_q^{(k)} + \tau^0))$, then by the vector comparison theorem, we obtain

$$S(t, \phi_k) \geqslant u_{1\varepsilon_0}(t), \quad R(t, \phi_k) \geqslant u_{2\varepsilon_0}(t), \quad t \in [s_q^{(k)} + \tau^0, t_q^{(k)}]. \tag{36}$$

From $\lim_{q\to\infty} s_q^{(k)} = \infty$ and Lemmas 2.4 and 2.5, we obtain that for any k there is a $K_3^{(k)} > K_2^{(k)}$ such that for any $q \geqslant K_3^{(k)}$,

$$\rho_S \leqslant S(s_q^{(k)} + \sigma^0, \phi_k) \leqslant M_S, \quad \rho_R \leqslant R(s_q^{(k)} + \sigma^0, \phi_k) \leqslant M_R.$$

For $\mu = \frac{\varepsilon_0}{2}$, equations (15) has a globally asymptotically stable positive ω-periodic solution $(u^*_{1\mu}(t), u^*_{2\mu}(t))$. From the periodicity of (15) we know that the periodic solution $(u^*_{1\mu}(t), u^*_{2\mu}(t))$ also is globally uniformly asymptotically stable. Hence, there is a $T_7 > T$, and T_7 is independent of any k and q, such that

$$u_{1\varepsilon_0}(t) > u^*_{1\mu}(t) - \frac{\varepsilon_0}{2}$$

for all $t \geqslant T_7 + s_q^{(k)} + \sigma^0$ and $q \geqslant K_3^{(k)}$. Consequently, by (19), we have

$$u_{1\varepsilon_0}(t) > S^*(t) - \varepsilon_0 \tag{37}$$

for all $t \geqslant T_7 + s_q^{(k)} + \sigma^0$ and $q \geqslant K_3^{(k)}$. By (28), there is a $N_2 \geqslant N_1$ such that $t_q^{(k)} - s_q^{(k)} \geqslant 2T$ for all $k \geqslant N_2$ and $q \geqslant K_3^{(k)}$, where $T \geqslant T_7 + \sigma^0$. Hence, from (36) and (37) we obtain

$$S(t, \phi_k) \geqslant S^*(t) - \varepsilon_0 \tag{38}$$

for all $t \in [T + s_q^{(k)}, t_q^{(k)}]$, $k \geqslant N_2$, and $q \geqslant K_3^{(k)}$.

Since, for any $t \in [T + s_q^{(k)} + \sigma_0, t_q^{(k)}]$, $k \geqslant N_2$ and $q \geqslant K_3^{(k)}$, by (1), (33), and (34), we have

$$\begin{aligned}
x'(t, \phi_k) = x(t, \phi_k)\Big[&- D(t) + h_1(t)\phi_1(t, S(t, \phi_k))S(t, \phi_k) \\
&- h_2(t)\phi_2(t, R(t, \phi_k))R(t, \phi_k) - p(t)x(t, \phi_k) - q(t) \\
&\times \Big(\int_{-\infty}^{\widetilde{T}^{(k)}} k(u - t)x(u, \phi_k)\mathrm{d}u + \int_{\widetilde{T}^{(k)}}^{s_q^{(k)}} k(u - t)x(u, \phi_k)\mathrm{d}u \\
&+ \int_{s_q^{(k)}}^{t} k(u - t)x(u, \phi_k)\mathrm{d}u \Big)^n \Big] \\
\geqslant x(t, \phi_k)\Big[&- D(t) + h_1(t)\phi_1(t, S(t, \phi_k))S(t, \phi_k) \\
&- h_2(t)\phi_2(t, R(t, \phi_k))R(t, \phi_k) - p(t)x(t, \phi_k) - q(t) \\
&\times \Big(H_1^{(k)} \int_{-\infty}^{\widetilde{T}^{(k)} - t} k(s)\,\mathrm{d}s + M_y \int_{-\infty}^{s_q^{(k)} - t} k(s)\,\mathrm{d}s \\
&+ \varepsilon_0 \int_{-\infty}^{0} k(s)\,\mathrm{d}s \Big)^n \Big] \\
\geqslant x(t, \phi_k)\big[&- D(t) + h_1(t)\phi_1(t, (S^*(t, \phi_k) - \varepsilon_0))(S(t, \phi_k) - \varepsilon_0) \\
&- h_2(t)\phi_2(t, (R^*(t, \phi_k) + \varepsilon_0))(R^*(t, \phi_k) + \varepsilon_0) - \varepsilon_0 p(t) - (2\varepsilon_0)^n q(t) \big] \\
= x(t, \phi_k)&\psi_{\varepsilon_0}(t).
\end{aligned}$$

Integrating from $T + s_q^{(k)} + \sigma^0$ to $t_q^{(k)}$ for any $k \geqslant N_2$ and $q \geqslant K_3^{(k)}$ we obtain

$$x(t_q^{(k)}, \phi_k) \geqslant x(T + s_q^{(k)} + \sigma^0, \phi_k) \exp \int_{T+s_q^{(k)}+\sigma^0}^{t_q^{(k)}} \psi_{\varepsilon_0}(t)\mathrm{d}t.$$

Hence, by (26) and (27), we finally have

$$\frac{\varrho_x}{(k+1)^2} \geqslant \frac{\varrho_x}{(k+1)^2} \exp \int_{T+s_q^{(k)}+\sigma^0}^{t_q^{(k)}} \psi_{\varepsilon_0}(t)\mathrm{d}t > \frac{\varrho_x}{(k+1)^2},$$

which leads to a contradiction. The proof is completed. □

3. Main results

Theorem 3.1. Suppose that (12) holds, in which $(S^*(t), R^*(t))$ is the positive ω–periodic solution of system (7). Then system (1) is permanent.

Proof. The proof is obvious, in fact, it follows from lemmas 2.4–2.7. This completes the proof. □

Let $\epsilon(\ll 1)$ be some positive constant and

$$\lambda(t) = -D(t) + h_1(t)\phi_1(t, (S^*(t) + \epsilon))(S^*(t) + \epsilon) \\ -h_2(t)\phi_1(t, (R^*(t) - \epsilon))(R^*(t) - \epsilon).$$

Theorem 3.2. Suppose that

$$\mathcal{A}_\omega\big(- D(t) + h_1(t)\phi_1(t, S^*(t))S^*(t) - h_2(t)\phi_2(t, R^*(t))R^*(t)\big) \leqslant 0 \tag{39}$$

and

$$l = \int_{-\infty}^{0} k(s) \exp\{\lambda^U s\}\mathrm{d}s < \infty, \tag{40}$$

where $(S^*(t), R^*(t))$ is the positive ω–periodic solution of system (7). Then for any solution $(S(t), R(t), x(t))$ of system (1), $x(t) \to 0$ as $t \to \infty$.

Proof. We shall prove that $\lim_{t\to\infty} x(t) = 0$. In fact, we know that for any given $0 < \varepsilon < 1(\varepsilon > \epsilon)$, there exists $\epsilon_0 > 0$ such that

$$\mathcal{A}_\omega\big(- D(t) + h_1(t)\phi_1(t, (S^*(t) + \epsilon))(S^*(t) + \epsilon) - h_2(t)\phi_1(t, (R^*(t) - \epsilon)) \\ (R^*(t) - \epsilon) - \frac{l\epsilon^n}{2}q(t)\big) \leqslant -\frac{1}{2}l\epsilon^n \int_0^\omega q(t)\mathrm{d}t < -\epsilon_0. \tag{41}$$

Choose a constant $\tau_1 > 0$ such that

$$\int_{-\tau_1}^{0} k(s)\exp(\lambda^U s)\,\mathrm{d}s > \sqrt[n]{\frac{l}{2}}. \tag{42}$$

For any $t \geqslant \overline{T} + \tau_1(\overline{T} > T_7)$, by (1) we have

$$\begin{aligned} x' &\leqslant x\big(-D(t) + h_1(t)\phi_1(t, S(t))S(t) - h_2(t)\phi_2(t, R(t))R(t)\big) \\ &\leqslant x\big(-D(t) + h_1(t)\phi_1(t, (S^*(t) + \epsilon))(S^*(t) + \epsilon) \\ &\quad -h_2(t)\phi_1(t, (R^*(t) - \epsilon))(R^*(t) - \epsilon)\big) \\ &= x\lambda(t). \end{aligned} \tag{43}$$

Hence, by (42), for any $t \geqslant t + s \geqslant \overline{T} + \tau_1$, we obtain

$$\begin{aligned} x' &\leqslant x\bigg[\lambda(t) - q(t)\bigg(\int_{-\tau_1}^{0} k(s)x(t+s)\,\mathrm{d}s\bigg)^n\bigg] \\ &\leqslant x\bigg[\lambda(t) - q(t)\bigg(\int_{-\tau_1}^{0} k(s)\exp(\lambda^U s)\,\mathrm{d}s\bigg)^n x^n\bigg] \\ &< x\Big[\lambda(t) - \frac{1}{2}lq(t)x^n\Big]. \end{aligned}$$

If $x(t) \geqslant \epsilon$ for all $t \geqslant \overline{T} + 2\tau_1$, then we have

$$x' < x\Big[\lambda(t) - \frac{1}{2}lq(t)\epsilon^n\Big]. \tag{44}$$

Consequently, by (41) we obtain

$$x(t) < x(\overline{T} + 2\tau_1)\exp\int_{\overline{T}+2\tau_1}^{t} [\lambda(s) - \frac{1}{2}lq(s)\epsilon^n]\mathrm{d}s \to 0$$

as $t \to \infty$, which leads to a contradiction. Hence, there is a $t_1 \geqslant \overline{T} + 2\tau_1$ such that $x(t_1) < \epsilon$.

Let $M(\epsilon) = \max_{t\geqslant 0}\{|\lambda(t)| + \frac{1}{2}lq(t)\epsilon^n\}$. We note that $M(\epsilon)$ is bounded for $\epsilon \in [0, 1]$. We then show that

$$x(t) \leqslant \epsilon\exp(M(\epsilon)\omega) \quad \text{for} \quad t \geqslant t_1. \tag{45}$$

Otherwise, there are $t_3 > t_2 > t_1$ such that $x(t_3) > \epsilon\exp(M(\epsilon)\omega)$, $x(t_2) = \epsilon$ and $x(t) > \epsilon$ for all $t \in (t_2, t_3]$. Let $\theta \geqslant 0$ be an integer such that $t_3 \in (t_2 + \theta\omega, t_2 +$

$(\theta + 1)\omega]$. Then from (45) we have

$$\begin{aligned}\epsilon \exp(M(\epsilon)\omega) &< x(t_3) \\ &\leqslant x(t_2)\exp\int_{t_2}^{t_3}[\lambda(t) - \frac{1}{2}lq(t)\epsilon^n]\mathrm{d}t \\ &= \epsilon \exp\left(\int_{t_2}^{t_2+\theta\omega} + \int_{t_2+\theta\omega}^{t_3}\right)[\lambda(t) - \frac{1}{2}lq(t)\epsilon^n]\mathrm{d}t \\ &< \epsilon \exp\left(\int_{t_2+\theta\omega}^{t_3}[\lambda(t) - \frac{1}{2}lq(t)\epsilon^n]\mathrm{d}t\right) \\ &< \epsilon \exp(M(\epsilon)\omega).\end{aligned}$$

This leads to a contradiction. Hence, inequality (45) holds. Further, in view of the arbitrariness of ϵ, we have $x(t) \to 0$ as $t \to \infty$. This completes the proof. □

4. Discussion

In this paper, we have considered a chemostat model with a periodic nutrient and antibiotic input. Further, we assume a periodic chemostat environment and the total toxic action on the microorganism in our model. Obviously, we note that

$$\mathcal{A}_\omega\big(-D(t) + h_1(t)\phi_1(t, S^*(t))S^*(t) - h_2(t)\phi_2(t, R^*(t))R^*(t)\big)$$

is a threshold parameter for the permanence of system (1). Here $(S^*(t), R^*(t))$ is the positive ω–periodic solution of system (7).

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