

Research Article

Competition between Plasmid-Bearing and Plasmid-Free Organisms in a Chemostat with Pulsed Input and Washout

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We consider a model of competition between plasmid-bearing and plasmid-free organisms in the chemostat with pulsed input and washout. We investigate the subsystem with nutrient and plasmid-free organism and study the stability of the boundary periodic solutions, which are the boundary periodic solutions of the system. The stability analysis of the boundary periodic solution yields the invasion threshold of the plasmid-bearing organism. By using the standard techniques of bifurcation theory, we prove that above this threshold there are periodic oscillations in substrate, plasmid-free, and plasmid-bearing organisms. Numerical simulations are carried out to illustrate our results.

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1. Introduction

The chemostat, a laboratory apparatus used for the continuous culture of microorganisms, has played an important role in microbiology and population biology. It is the most simple idealization of a biological system where the parameters are measurable, the experiments are reasonable, and the mathematics is tractable [1]. Experimental verification of the match between theory and experiment in the chemostat can be found in [2]. For a general discussion of competition, see [3, 4] while a detailed mathematical description of competition in the chemostat may be found in [1].

The ability to manufacture desired products through genetically altered organisms represents one of the major developments in biotechnology. The genetic alteration commonly takes place through the insertion of a recombinant DNA into the cell in the form of a plasmid to code for the production of the desired protein. The load imposed by production can result in the genetically altered (plasmid-bearing) organism being a less able competitor than the plasmid-free (or “wild-type”) organism. Unfortunately, the plasmid can be lost

in the reproductive process. Since commercial production can take place on a scale of many generations, it is possible for the plasmid-free organism to take over the culture. In pharmaceuticals, changes in the plasmid could cause changes in the amino acid sequence of a protein product or changes in the background from which it must be purified. It is vital to produce a uniform product if it is a drug intended for human use. Since commercial production of products manufactured by genetically altered organisms is a reality, understanding the competition between plasmid-bearing and plasmid-free organisms in a mathematically rigorous fashion seems important. The study of mathematical models for the competition between plasmid-free and plasmid-bearing populations has recently been a problem of considerable interest. We refer the readers to Ryder and BiBiasio [5], Stephanopoulos and Lapudis [6], Hsu et al. [7–12], Luo and Hsu [13], Lu and Haderler [14], Ai [15], Yuan et al. [16–18] as well as Xiang and Song [19], Wu et al. [20], and the references therein for recent studies on this respect.

To simulate the effect of perturbations such as seasonal or other variation in the chemostat, the chemostat models described in impulsive differential equations have been studied by many authors, see, for example, Funasaki and Kot [21], Xiang and Song [19], Wang et al. [22], Smith and Wolkowicz [23, 24], Fan and Wolkowicz [25], and the references therein for recent studies on this respect. Recently impulsive differential equations have been introduced in almost every domain of applied sciences. Numerous examples are given in Bařnov et al. work [26, 27]. In this paper, we focus on a model of competition between plasmid-bearing and plasmid-free organisms in the chemostat with periodically pulsed nutrient input and washout. Assuming that the specific growth rates of the organisms take the form of Holling II type, we want to explore if some new dynamical behaviors could occur in comparison with the model with constant input and washout and under what conditions can both the plasmid-bearing and plasmid-free organisms coexist in the chemostat.

The organization of this paper is as follows. In Section 2, we present the model under periodic pulsed chemostat conditions. In Section 3, we investigate the existence and stability of the periodic solutions of the impulsive subsystem with nutrient and plasmid-free organism. In Section 4, we study the local stability of the boundary periodic solution of the system and obtain the threshold of the invasion of the plasmid-bearing organism. By use of standard techniques of bifurcation theory, we prove that above this threshold there are periodic oscillations in substrate, plasmid-bearing, and plasmid-free organisms. Finally, numerical simulations and a brief discussion are presented in Section 5.

2. The Model

Let $S(t)$ be the concentration of nutrient at time t , let $x_1(t)$ be the concentration of the plasmid-free organisms at time t , and let $x_2(t)$ be the concentration of the plasmid-bearing organisms at time t . The model of competition between plasmid-bearing and plasmid-free organisms in the chemostat with pulsed input and washout can be described by the following impulsive differential equations:

$$\begin{aligned} \frac{dS(t)}{dt} &= -\frac{m_1 S(t)x_1(t)}{\delta_1 a_1 + S(t)} - \frac{m_2 S(t)x_2(t)}{\delta_2 a_2 + S(t)}, \\ \frac{dx_1(t)}{dt} &= \frac{m_1 S(t)x_1(t)}{a_1 + S(t)} + q \frac{m_2 S(t)x_2(t)}{a_2 + S(t)}, \quad t \neq n\tau, \\ \frac{dx_2(t)}{dt} &= (1 - q) \frac{m_2 S(t)x_2(t)}{a_2 + S(t)}, \end{aligned} \quad (2.1)$$

$$\begin{aligned}
\Delta S(t) &= D(S^0 - S(t)), \\
\Delta x_1(t) &= -Dx_1(t), \quad t = n\tau, \\
\Delta x_2(t) &= -Dx_2(t), \\
S(0^+) &= S_0 > 0, \quad x_1(0^+) = x_{10} > 0, \quad x_2(0^+) = x_{20} > 0,
\end{aligned} \tag{2.2}$$

where $n \in N$, N is the set of positive integers. All parameters are positive constants. However, q , where $0 < q < 1$, is the fraction constant of plasmid-bearing population converting into plasmid-free population during the replication; $m_i, a_i, i = 1, 2$ are the maximal growth rates of plasmid-free and plasmid-bearing organisms and the Michaelis-Menten (or half saturation) constants, respectively; $\delta_i, i = 1, 2$ are the yield constants, biologically one may assume $\delta_1 = \delta_2 = \delta$. The operating parameters are $S^{(0)}, D$ and τ , where $S^{(0)}$ is the input concentration of the nutrient, D is the input and washout flow of the chemostat, and τ is the period of the impulsive effects.

It is convenient to perform scaling for chemostat-type problems. To avoid even more complicated parameter dependence than what we will see below, we assume that the yield constants are equal, that is, $\delta_1 = \delta_2 = \delta$. Without this assumption, one has an additional parameter, the ratio of the yield constants, in the system. Specifically, let

$$\begin{aligned}
\bar{S} &= \frac{S}{S^0}, \quad \bar{x}_1 = \frac{x_1}{\delta S^0}, \quad \bar{x}_2 = \frac{x_2}{\delta S^0}, \\
\bar{m}_i &= \frac{m_i S^0}{a_i}, \quad b_i = \frac{S^0}{a_i}.
\end{aligned} \tag{2.3}$$

After dropping the bars, (2.2) becomes

$$\begin{aligned}
\frac{dS(t)}{dt} &= -\frac{m_1 S(t)x_1(t)}{1 + b_1 S(t)} - \frac{m_2 S(t)x_2(t)}{1 + b_2 S(t)}, \\
\frac{dx_1(t)}{dt} &= \frac{m_1 S(t)x_1(t)}{1 + b_1 S(t)} + q \frac{m_2 S(t)x_2(t)}{1 + b_2 S(t)}, \quad t \neq n\tau, \\
\frac{dx_2(t)}{dt} &= (1 - q) \frac{m_2 S(t)x_2(t)}{1 + b_2 S(t)}, \\
\Delta S(t) &= D(1 - S(t)), \\
\Delta x_1(t) &= -Dx_1(t), \quad t = n\tau, \\
\Delta x_2(t) &= -Dx_2(t), \\
S(0^+) &= S_0 > 0, \quad x_1(0^+) = x_{10} > 0, \quad x_2(0^+) = x_{20} > 0.
\end{aligned} \tag{2.4}$$

From the point of biology, we need only to consider (2.4) in the biological meaning region $R_+^3 = \{(S, x_1, x_2) \mid S, x_1, x_2 \geq 0\}$. The form of the equations in (2.4) implies the global existence and uniqueness of its solutions.

3. Dynamical Behaviors of the Nutrient and Plasmid-Free Organism Subsystem

In the absence of the plasmid-bearing organism, (2.4) reduces to

$$\begin{aligned}
 \frac{dS(t)}{dt} &= -\frac{m_1 S(t)x_1(t)}{1 + b_1 S(t)}, & t \neq n\tau, \\
 \frac{dx_1(t)}{dt} &= \frac{m_1 S(t)x_1(t)}{1 + b_1 S(t)}, \\
 \Delta S(t) &= D(1 - S(t)), \\
 \Delta x_1(t) &= -Dx_1(t), & t = n\tau, \\
 S(0^+) &= S_0 > 0, & x_1(0^+) = x_{10} > 0.
 \end{aligned} \tag{3.1}$$

This nonlinear system has simple periodic solutions. For our purpose, we present these solutions in this section.

If we add the first and second equations in system (3.1), we have $d(S(t) + x_1(t))/dt = 0$. Let $\Sigma(t) = S(t) + x_1(t)$, then (3.1) can be written as

$$\begin{aligned}
 \frac{d\Sigma(t)}{dt} &= 0, & t \neq n\tau, \\
 \Sigma(n\tau^+) &= D + (1 - D)\Sigma(n\tau), & t = n\tau, \\
 \Sigma(0^+) &= \Sigma_0 > 0.
 \end{aligned} \tag{3.2}$$

For system (3.2), we have the following lemma.

Lemma 3.1. *However, (3.2) has a positive solution $\tilde{\Sigma}(t) = 1$ and for every solution $\Sigma(t)$ of (3.2), we have $|\Sigma(t) - 1| \rightarrow 0$ as $t \rightarrow \infty$, where $\tilde{\Sigma}(t) = 1, t \in (n\tau, (n+1)\tau], n \in \mathbb{N}$.*

By Lemma 3.1, the following lemma is obvious.

Lemma 3.2. *Let $(S(t), x_1(t))$ be any solution of system (3.1) with initial condition $S(0) > 0, x_1(0) > 0$, then $\lim_{t \rightarrow \infty} |S(t) + x_1(t) - 1| = 0$.*

Lemma 3.2 says that the periodic solution $\tilde{\Sigma}(t) = 1$ is a unique invariant manifold of the system (3.1). Denote

$$m_1^* = \frac{-(1 + b_1) \ln(1 - D)}{\tau}. \tag{3.3}$$

Theorem 3.3. *For system (3.1), one has the following.*

- (1) *If $m_1 < m_1^*$, then system (3.1) has a unique globally asymptotically stable boundary τ -periodic solution $(S_e(t), x_{1e}(t))$, where $S_e(t) = 1, x_{1e}(t) = 0$.*

(2) If $m_1 > m_1^*$, then system (3.1) has a unique globally asymptotically stable positive τ -periodic solution $(S_s(t), x_{1s}(t))$ and the τ -periodic solution $(S_e(t), x_{1e}(t))$ is unstable. The τ -periodic solution $x_{1s}(t)$ satisfies

$$\frac{1}{1-D} = \exp\left(\int_0^\tau \frac{m_1(1-x_1(l))}{1+b_1(1-x_1(l))} dl\right). \quad (3.4)$$

Proof. By Lemma 3.2, we can consider (3.1) in its stable invariant manifold $\tilde{\Sigma}(t) = 1$. That is,

$$\begin{aligned} \frac{dx_1}{dt} &= \frac{m_1(1-x_1)x_1}{1+b_1(1-x_1)}, \quad t \neq n\tau, \\ \Delta x_1 &= -Dx_1, \quad t = n\tau, \\ 0 &\leq x_{10} \leq 1. \end{aligned} \quad (3.5)$$

Suppose $x_1(t, x_{10})$ is a solution of (3.5), with initial condition $x_{10} \in [0, 1]$, we have

$$\begin{aligned} x_1(t, x_{10}) &= x_1(n\tau^+) \exp\left(\int_{n\tau}^t \frac{m_1(1-x_1(l, x_{10}))}{1+b_1(1-x_1(l, x_{10}))} dl\right), \quad t \in (n\tau, (n+1)\tau], \\ x_1(n\tau^+) &= (1-D)x_1(n\tau), \quad x_1(0^+) = x_{10}, \quad t = n\tau. \end{aligned} \quad (3.6)$$

For (3.6), we have the following properties:

- (i) for $x_{10} \in (0, 1]$, $0 < x_1(t, x_{10}) \leq 1$, $t \in (0, \infty)$ is a piecewise continuous function;
- (ii) the function $F(x_{10}) = x_1(t, x_{10})$, $x_{10} \in (0, 1]$ is a increasing function;
- (iii) $x_1(t, 0) = 0$, $t \in (0, \infty)$ is a solution.

The periodic solutions of (3.5) satisfies the following equation:

$$x_{10} = (1-D)x_{10} \exp\left(\int_0^\tau \frac{m_1(1-x_1(l, x_{10}))}{1+b_1(1-x_1(l, x_{10}))} dl\right). \quad (3.7)$$

By (i) and (ii), we know that if $1 < 1/(1-D) < \exp(m_1\tau/(1+b_1))$, that is, $m_1 > m_1^*$, then (3.7) has a unique solution $x_{10}^* \in (0, 1]$; otherwise, it has no solution in $(0, 1]$.

If $m_1 < m_1^*$, then (3.5) has a periodic solution $x_{1e}(t) = 0$. By Lemma 3.2, we have $\lim_{t \rightarrow \infty} |S(t) - \tilde{\Sigma}(t)| = 0$. We have proved (1).

If $m_1 > m_1^*$, then (3.5) has a unique positive periodic solution $x_{1s}(t) = x_1(t, x_{10}^*)$. The multiplier μ_1 of $x_{1s}(t)$ is

$$\mu_1 = (1-D) \exp\left(\int_0^\tau \frac{m_1(S_s - x_{1s} + b_1 S_s^2)}{(1+b_1 S_s)^2} dl\right) = \exp\left(\int_0^\tau \frac{-m_1 x_{1s}}{(1+b_1 S_s)^2} dl\right) < 1, \quad (3.8)$$

where $S_s(t) = 1 - x_{1s}(t)$ and (3.7) has been used. Thus the periodic solution $x_{1s}(t)$ of (3.5) is local stable.

To prove the global attractivity of the periodic solution $x_{1s}(t)$, we define a function $G(x_{10}) : x_{10} \in (0, 1)$ as follows:

$$G(x_{10}) = (1 - D) \exp\left(\int_0^\tau \frac{m_1(1 - x_1(l, x_{10}))}{1 + b_1(1 - x_1(l, x_{10}))} dl\right). \quad (3.9)$$

Noticing (3.6), we have

$$G(x_{10}) = \frac{x_1(\tau, x_{10})}{x_{10}}, \quad x_{10} \in (0, 1). \quad (3.10)$$

It is obvious that $G(x_{10}^*) = 1$.

Furthermore, $\partial x_1(t, x_{10}) / \partial x_{10} \geq 0$, $t \in (0, \tau)$ (otherwise, there exist $t_0 > 0$, $0 < x_{10}^{(1)} < x_{10}^{(2)} < 1$ such that $x_1(t_0, x_{10}^{(1)}) = x_1(t_0, x_{10}^{(2)})$, a contradiction, since different flows of (3.5) do not intersect). Thus, the function $G(x_{10})$ has the following properties:

$$\begin{aligned} G(x_{10}) &< 1, & \text{if } x_{10}^* < x_{10} < 1, \\ G(x_{10}) &= 1, & \text{if } x_{10} = x_{10}^*, \\ G(x_{10}) &> 1, & \text{if } 0 < x_{10} < x_{10}^*. \end{aligned} \quad (3.11)$$

Furthermore, we obtain the following inequalities:

$$\begin{aligned} x_{10} &> x_1(\tau, x_{10}) > \cdots > x_1(n\tau, x_{10}) > \cdots > x_{10}^*, & \text{if } x_{10}^* < x_{10} \leq 1, \\ x_{10} &< x_1(\tau, x_{10}) < \cdots < x_1(n\tau, x_{10}) < \cdots < x_{10}^*, & \text{if } 0 < x_{10} < x_{10}^*. \end{aligned} \quad (3.12)$$

Let $x_{10} \in (0, 1)$. According to (3.12), we suppose that

$$\lim_{n \rightarrow \infty} x_1(n\tau, x_{10}) = \alpha. \quad (3.13)$$

We will prove that the solution $x_1(t, \alpha)$ is τ -periodic. We note that the functions $x_{1n}(t) = x_1(t + n\tau, x_{10})$, due to the τ -periodicity of (3.5), are also its solutions and $x_{1n}(\tau) \rightarrow \alpha$, as $n \rightarrow \infty$. By the continuous dependence of the solutions on the initial values, we have $x_1(\tau, \alpha) = \lim_{n \rightarrow \infty} x_{1n}(\tau) = \alpha$. Hence the solution $x_1(t, \alpha)$ is τ -periodic. Since the periodic solution $x_1(t, x_{10}^*)$ is unique, thus we have $\alpha = x_{10}^*$.

Let $\epsilon > 0$ be given. By [27, Theorem 2.9] on the continuous dependence of the solutions on the initial values, there exist a $\delta > 0$ such that if $|x_{10} - x_{10}^*| < \delta$ and $0 \leq t \leq \tau$, then

$$|x_1(t, x_{10}) - x_1(t, x_{10}^*)| < \epsilon. \quad (3.14)$$

Choose $n_1 > 0$ such that $|x_1(n\tau, x_{10}) - x_{10}^*| < \delta$ for $n > n_1$. Then $|x_1(t, x_{10}) - x_1(t, x_{10}^*)| < \epsilon$ for $t > n\tau$, which implies that

$$\lim_{t \rightarrow \infty} |x_1(t, x_{10}) - x_1(t, x_{10}^*)| = 0. \quad (3.15)$$

By Lemma 3.2, for any solution $(S(t), x_1(t))$ of system (3.1) with initial condition $S(0) > 0$, $x_1(0) > 0$, we have

$$\lim_{t \rightarrow \infty} |x_1(t) - x_{1s}(t)| = 0, \quad \lim_{t \rightarrow \infty} |S(t) - S_s(t)| = 0. \quad (3.16)$$

The proof of Theorem 3.3(2) is thus completed. \square

4. Existence of the Positive τ -Periodic Solution

In this section, we investigate the invasion of the plasmid-bearing organism of system (2.4). Denote $\Sigma(t) = S(t) + x_1(t) + x_2(t)$, it follows from (2.4) that

$$\begin{aligned} \frac{d\Sigma(t)}{dt} &= 0, \quad t \neq n\tau, \\ \Sigma(n\tau^+) &= D + (1 - D)\Sigma(n\tau), \quad t = n\tau, \\ \Sigma(0^+) &> 0. \end{aligned} \quad (4.1)$$

By Lemma 3.1, the following lemma is obvious.

Lemma 4.1. *Let $(S(t), x_1(t), x_2(t))$ be any solution of system (2.4) with initial value $S(0) > 0$, $x_i(0) > 0$, $i = 1, 2$, then*

$$\lim_{t \rightarrow \infty} |S(t) + x_1(t) + x_2(t) - 1| = 0. \quad (4.2)$$

Lemma 4.1 says that the periodic solution $\tilde{\Sigma}(t) = 1$ of (4.1) is an invariant manifold of (2.4).

By Theorem 3.3, we know that (2.4) has two nonnegative boundary τ -periodic solutions:

$$(S_e(t), x_{1e}(t), x_{2e}(t)) = (1, 0, 0), \quad (S_s(t), x_{1s}(t), 0) \quad (\text{if } m_1 > m_1^*). \quad (4.3)$$

4.1. Stability of the Boundary Periodic Solutions

For convenience, in the following discussion, if $m_1 > m_1^*$, we denote

$$m_2^* = \frac{-\ln(1 - D)}{\int_0^\tau ((1 - q)S_s(l)/(1 + b_2S_s(l))) dl}. \quad (4.4)$$

Theorem 4.2. *For (2.4), one has the following.*

- (1) *If $m_1 < m_1^*$, then (2.4) has a unique globally asymptotically stable boundary τ -periodic solution $(1, 0, 0)$.*
- (2) *If $m_1 > m_1^*$ and $m_2 < m_2^*$, then (2.4) has a unique globally asymptotically stable boundary τ -periodic solution $(S_s(t), x_{1s}(t), 0)$.*

(3) If $m_1 > m_1^*$ and $m_2 > m_2^*$, then the periodic boundary solution $(S_s(t), x_{1s}(t), 0)$ of system (2.4) is unstable.

Proof. The proof of (1) is easy, we want to prove (2) and (3). The local stability of periodic solution $(S_s(t), x_{1s}(t), 0)$ may be determined by considering the behavior of small amplitude perturbations of the solution. Define

$$S(t) = u(t) + S_s(t), \quad x_1(t) = v(t) + x_{1s}(t), \quad x_2(t) = w(t), \quad (4.5)$$

then we have

$$\begin{pmatrix} u(t) \\ v(t) \\ w(t) \end{pmatrix} = \Phi(t) \begin{pmatrix} u(0) \\ v(0) \\ w(0) \end{pmatrix}, \quad 0 \leq t < \tau, \quad (4.6)$$

where $\Phi(t)$ satisfies

$$\frac{d\Phi(t)}{dt} = \begin{pmatrix} -\frac{m_1 x_{1s}}{(1+b_1 S_s)^2} & -\frac{m_1 S_s}{1+b_1 S_s} & -\frac{m_2 S_s}{1+b_2 S_s} \\ \frac{m_1 x_{1s}}{(1+b_1 S_s)^2} & \frac{m_1 S_s}{1+b_1 S_s} & q \frac{m_2 S_s}{1+b_2 S_s} \\ 0 & 0 & (1-q) \frac{m_2 S_s}{1+b_2 S_s} \end{pmatrix} \Phi(t), \quad (4.7)$$

and $\Phi(0) = I$, the identity matrix. Hence, the fundamental solution matrix is

$$\Phi(\tau) = \begin{pmatrix} \phi_{11}(\tau) & \phi_{12}(\tau) & * \\ \phi_{21}(\tau) & \phi_{22}(\tau) & ** \\ 0 & 0 & \exp\left(\int_0^\tau \frac{(1-q)m_2 S_s}{1+b_2 S_s} dl\right) \end{pmatrix}. \quad (4.8)$$

The linearization of impulsive subsystem (2.4) is written as

$$\begin{pmatrix} u(n\tau^+) \\ v(n\tau^+) \\ w(n\tau^+) \end{pmatrix} = \begin{pmatrix} 1-D & 0 & 0 \\ 0 & 1-D & 0 \\ 0 & 0 & 1-D \end{pmatrix} \begin{pmatrix} u(n\tau) \\ v(n\tau) \\ w(n\tau) \end{pmatrix}. \quad (4.9)$$

The stability of the periodic solution $(S_s(t), x_{1s}(t), 0)$ is determined by the eigenvalues of

$$M = \begin{pmatrix} 1-D & 0 & 0 \\ 0 & 1-D & 0 \\ 0 & 0 & 1-D \end{pmatrix} \Phi(\tau), \quad (4.10)$$

which are $\mu_3 = (1 - D) \exp(\int_0^\tau ((1 - q)m_2 S_s / (1 + b_2 S_s)) dl)$ and the eigenvalues μ_1, μ_2 of the following matrix:

$$(1 - D) \begin{pmatrix} \phi_{11}(\tau) & \phi_{12}(\tau) \\ \phi_{21}(\tau) & \phi_{22}(\tau) \end{pmatrix}. \quad (4.11)$$

The μ_1, μ_2 are also the multipliers of the locally linearization system of (3.1) provided with $D \in (0, D_0)$ at the asymptotically stable periodic solution $(S_s(t), x_{1s}(t))$, where $D_0 = 1 - \exp((1 + b_1)/m_1^* \tau)$. According to Theorem 3.3, we have that $\mu_1 < 1, \mu_2 < 1$.

If $m_2 < m_2^*$, then $\mu_3 = (1 - D) \exp(\int_0^\tau ((1 - q)m_2 S_s / (1 + b_2 S_s)) dl) < 1$, the boundary periodic solution $(S_s(t), x_{1s}(t), 0)$ of system (2.4) is locally stable. We obtain that

$$x_2(t) = x_2(0)(1 - D)^n \exp\left(\int_0^t \frac{(1 - q)m_2 S_s(l)}{1 + b_2 S_s(l)} dl\right), \quad t \in (n\tau, (n + 1)\tau]. \quad (4.12)$$

Hence, we obtain that for any solution $(S(t), x_1(t), x_2(t))$ with initial value $S(0) > 0, x_i(0) > 0, i = 1, 2, x_2(t) \rightarrow 0$ as $t \rightarrow \infty$. By Lemma 4.1, we have $\lim_{t \rightarrow \infty} |S(t) + x_1(t) - 1| = 0$. Now using Theorem 3.3, we have $\lim_{t \rightarrow \infty} |S(t) - S_s(t)| = 0$ and $\lim_{t \rightarrow \infty} |x_1(t) - x_{1s}(t)| = 0$.

If $m_2 > m_2^*$, then $\mu_3 > 1$, the boundary periodic solution $(S_s(t), x_{1s}(t), 0)$ of (2.4) is unstable. The proof of Theorem 4.2 is completed. \square

4.2. Bifurcation Analysis of the Boundary Periodic Solution $(S_s(t), x_{1s}(t), 0)$

Let \mathcal{B} denote the Banach space of piecewise continuous, τ -periodic function $\mathcal{N} : [0, \tau] \rightarrow \mathbb{R}^2$, and have points of discontinuity τ , where they continuous from the left. In the set \mathcal{B} introduce the norm $\|\mathcal{N}\|_0 = \sup_{0 \leq t \leq \tau} \|\mathcal{N}(t)\|$ with which \mathcal{B} becomes a Banach space with the uniform convergence topology.

For convenience, we introduce Lemmas 4.3 and 4.5 from Cushing [28] with small modifications.

Lemma 4.3. Suppose $a_{ij} \in \mathcal{B}$ and $0 \leq d_i < 1$ ($i = 1, 2$).

(a) If $(1 - d_2) \exp(\int_0^\tau a_{22}(s) ds) \neq 1, (1 - d_1) \exp(\int_0^\tau a_{11}(s) ds) \neq 1$, then the linear impulsive homogenous system

$$\begin{aligned} \frac{dy_1}{dt} &= a_{11}y_1 + a_{12}y_2, \\ \frac{dy_2}{dt} &= a_{22}y_2, \end{aligned} \quad t \neq n\tau, \quad (4.13)$$

$$\begin{aligned} \Delta y_1 &= -d_1 y_1, \\ \Delta y_2 &= -d_2 y_2, \end{aligned} \quad t = n\tau,$$

has no nontrivial solution in $\mathcal{B} \times \mathcal{B}$. In this case, the nonhomogeneous system

$$\begin{aligned} \frac{dx_1}{dt} &= a_{11}x_1 + a_{12}x_2 + f_1, & t \neq n\tau, \\ \frac{dx_2}{dt} &= a_{22}x_2 + f_2, \\ \Delta x_1 &= -d_1x_1, & t = n\tau, \\ \Delta x_2 &= -d_2x_2, \end{aligned} \quad (4.14)$$

has for every $(f_1, f_2) \in \mathcal{B} \times \mathcal{B}$, a unique solution $(x_1, x_2) \in \mathcal{B} \times \mathcal{B}$ and the operator $L : \mathcal{B} \times \mathcal{B} \rightarrow \mathcal{B} \times \mathcal{B}$ defined by $(x_1, x_2) = L(f_1, f_2)$ is linear and compact.

(b) If $(1 - d_2) \exp(\int_0^\tau a_{22}(s)ds) = 1$, $(1 - d_1) \exp(\int_0^\tau a_{11}(s)ds) \neq 1$, then (4.13) has exactly one independent solution in $\mathcal{B} \times \mathcal{B}$.

Remark 4.4. In fact, under the conditions of Lemma 4.1(a),

$$\begin{aligned} \frac{dx_2}{dt} &= a_{22}x_2 + f_2, & t \neq n\tau, \\ \Delta x_2 &= -d_2x_2, & t = n\tau, \end{aligned} \quad (4.15)$$

has a unique solution $x_2 \in \mathcal{B}$ and the operator $L_2 : \mathcal{B} \rightarrow \mathcal{B}$ defined by $x_2 = L_2f_2$ is linear and compact. Furthermore,

$$\begin{aligned} \frac{dx_1}{dt} &= a_{11}x_1 + f_3, & t \neq n\tau, \\ \Delta x_1 &= -d_1x_1, & t = n\tau, \end{aligned} \quad (4.16)$$

for $f_3 \in \mathcal{B}$ has a unique solution (since $(1 - d_1) \exp(\int_0^\tau a_{11}(s)ds) \neq 1$) in \mathcal{B} , and $x_1 = L_1f_3$ defines a linear, compact operator $L_1 : \mathcal{B} \rightarrow \mathcal{B}$. Then, we have

$$L(f_1, f_2) = (L_1(a_{12}L_2f_2 + f_1), L_2f_2). \quad (4.17)$$

Lemma 4.5. Suppose that $a \in \mathcal{B}$, $0 \leq d < 1$, $(1 - d) \exp(\int_0^\tau a(s)ds) = 1$ and $f \in \mathcal{B}$. Then, the impulsive equation

$$\begin{aligned} \frac{dx}{dt} &= ax + f, & t \neq n\tau, \\ \Delta x &= -dx, & t = n\tau, \end{aligned} \quad (4.18)$$

has a solution $x \in \mathcal{B}$ if and only if $\int_0^\tau f(l) \exp(-\int_0^l a(s)ds)dl = 0$.

By Lemma 4.1, in its invariant manifold $\tilde{\Sigma}(t) = S(t) + x_1(t) + x_2(t) = 1$, (2.4) reduces to an equivalently nonautonomous system as follows:

$$\begin{aligned} \frac{dx_1}{dt} &= \frac{m_1 x_1 (1 - x_1 - x_2)}{1 + b_1 (1 - x_1 - x_2)} + q \frac{m_2 x_2 (1 - x_1 - x_2)}{1 + b_2 (1 - x_1 - x_2)}, \\ \frac{dx_2}{dt} &= (1 - q) \frac{m_2 x_2 (1 - x_1 - x_2)}{1 + b_2 (1 - x_1 - x_2)}, \\ \Delta x_1 &= -Dx_1, \\ \Delta x_2 &= -Dx_2, \\ x_{10} &> 0, \quad x_{20} > 0, \quad x_{10} + x_{20} \leq 1. \end{aligned} \quad \begin{array}{l} t \neq n\tau, \\ \\ \\ t = n\tau, \\ \\ \end{array} \quad (4.19)$$

If $m_1 > m_1^*$, for (4.19), by Theorem 4.2, the boundary periodic solution $(x_{1s}(t), 0)$ is locally asymptotically stable provided with $m_2 < m_2^*$, hence the value m_2^* plays an important role as a bifurcation threshold.

For system (4.19), we have the following results.

Theorem 4.6. *For system (4.19), assume $m_1 > m_1^*$ holds, then there exists a constant $\lambda_0 > 0$, such that for each $m_2 \in (m_2^*, m_2^* + \lambda_0)$, there exists a solution $(x_1, x_2) \in \mathcal{B} \times \mathcal{B}$ of (4.19) satisfying $0 < x_1 < x_{1s}$, $x_2 > 0$ and $S = 1 - x_1 - x_2 > 0$ for all $t > 0$. Hence, (2.4) has a positive τ -periodic solution (S, x_1, x_2) .*

Proof. Let $y_1 = x_1 - x_{1s}$, $y_2 = x_2$ in (4.19), then

$$\begin{aligned} \frac{dy_1}{dt} &= F_{11}(S_s, x_{1s})y_1 + F_{12}(m_2, S_s, x_{1s})y_2 + g_1(y_1, y_2), \\ \frac{dy_2}{dt} &= F_{22}(m_2, S_s)y_2 + g_2(y_1, y_2), \\ \Delta y_1 &= -Dy_1, \\ \Delta y_2 &= -Dy_2, \\ x_{10} &> 0, \quad x_{20} > 0, \quad x_{10} + x_{20} \leq 1, \end{aligned} \quad \begin{array}{l} t \neq n\tau, \\ \\ \\ t = n\tau, \\ \\ \end{array} \quad (4.20)$$

where

$$\begin{aligned} F_{11}(S_s, x_{1s}) &= \frac{m_1 S_s}{1 + b_1 S_s} - \frac{m_1 x_{1s}}{(1 + b_1 S_s)^2}, \\ F_{12}(m_2, S_s, x_{1s}) &= -\frac{m_1 x_{1s}}{(1 + b_1 S_s)^2} + \frac{q m_2 S_s}{1 + b_2 S_s}, \\ F_{22}(m_2, S_s) &= \frac{(1 - q) m_2 S_s}{1 + b_2 S_s}. \end{aligned} \quad (4.21)$$

Since $(1 - D) \exp(\int_0^t ((1 - q)m_2 S_s(l)/(1 + b_2 S_s(l))) dl) \neq 1$, by Lemma 4.3, using L , we can equivalently write (4.20) as the operator equation:

$$(y_1, y_2) = L^*(y_1, y_2) + G(y_1, y_2), \quad (4.22)$$

where

$$G(y_1, y_2) = (L_1(F_{12}(m_2, S_s, x_{1s})L_2 g_2(y_1, y_2) + g_1(y_1, y_2)), L_2 g_2(y_1, y_2)). \quad (4.23)$$

Here $L^* : \mathcal{B} \times \mathcal{B} \rightarrow \mathcal{B} \times \mathcal{B}$ is linear and compact (since L_1 and L_2 are compact) and satisfies $G = o(\|(y_1, y_2)\|_0)$ near $(0, 0)$. A nontrivial solution $(y_1, y_2) \neq (0, 0)$ for some $m_2 > m_2^*$ yields a solution $(x_1, x_2) = (x_{1s} + y_1, y_2)$ of (4.19). The solution $(x_1, x_2) \neq (x_{1s}, 0)$ is called a nontrivial solution of (4.19).

We apply the well-known local bifurcation techniques to (4.22). As is well known, bifurcation can occur only at the nontrivial solution of the linearized problem:

$$(y_1, y_2) = L^*(y_1, y_2). \quad (4.24)$$

If $(y_1, y_2) \in \mathcal{B} \times \mathcal{B}$ is a solution of (4.24) for some $m_2 > 0$, then by the very manner in which L^* was defined, (y_1, y_2) solves the system

$$\begin{aligned} \frac{dy_1}{dt} &= F_{11}(S_s, x_{1s})y_1 + F_{12}(m_2, S_s, x_{1s})y_2, & t \neq n\tau, \\ \frac{dy_2}{dt} &= F_{22}(m_2, S_s)y_2, & \\ \Delta y_1 &= -Dy_1, & t = n\tau, \\ \Delta y_2 &= -Dy_2, & \end{aligned} \quad (4.25)$$

and conversely. Using Lemma 4.3(b), we see that (4.25) and hence (4.24) has one nontrivial solution in $\mathcal{B} \times \mathcal{B}$ if and only if $m_2 = m_2^*$. Hence, there exists a continuum $C = (m_2; y_1, y_2) \subseteq (0, \infty) \times \mathcal{B} \times \mathcal{B}$ nontrivial solutions of (4.24) such that the closure \bar{C} contains $(m_2^*; 0, 0)$. This continuum gives rise to a continuum $C_1 = (m_2; x_1, x_2) \subseteq (0, \infty) \times \mathcal{B} \times \mathcal{B}$ of the solutions of (4.19) whose closure \bar{C}_1 contains the bifurcation point $(m_2^*; x_{1s}, 0)$.

To see that solutions in C_1 correspond to solutions (x_1, x_2) of (4.19), we investigate the nature of the continuum C near the bifurcation point $(m_2^*; 0, 0)$ by expanding m_2 and (y_1, y_2) in Lyapunov-Schmidt series:

$$\begin{aligned} m_2 &= m_2^* + \lambda\epsilon + \cdots, \\ y_1 &= y_{11}\epsilon + y_{12}\epsilon^2 + \cdots, \\ y_2 &= y_{21}\epsilon + y_{22}\epsilon^2 + \cdots, \end{aligned} \quad (4.26)$$

for $y_{ij} \in \mathcal{B}$ where ϵ is a small parameter. If we substitute these series into the differential system (4.19) and equate coefficients of ϵ and ϵ^2 , we find that

$$\begin{aligned} \frac{dy_{11}}{dt} &= F_{11}(S_s, x_{1s})y_{11} + F_{12}(m_2^*, S_s, x_{1s})y_{21}, & t \neq n\tau, \\ \frac{dy_{21}}{dt} &= F_{22}(m_2^*, S_s)y_{21}, & \\ \Delta y_{11} &= -Dy_{11}, & t = n\tau, \\ \Delta y_{21} &= -Dy_{21}, & \end{aligned} \quad (4.27)$$

$$\begin{aligned} \frac{dy_{12}}{dt} &= F_{11}(S_s, x_{1s})y_{12} + F_{12}(m_2^*, S_s, x_{1s})y_{22} + G_{12}(y_{11}, y_{12}, \lambda), & t \neq n\tau, \\ \frac{dy_{22}}{dt} &= F_{22}(m_2^*, S_s)y_{22} + \frac{(1-q)y_{21}}{1+b_2S_s} \left(\lambda S_s - \frac{m_2^*(y_{11} + y_{21})}{1+b_2S_s} \right), & \\ \Delta y_{21} &= -Dy_{21}, & t = n\tau, \\ \Delta y_{22} &= -Dy_{22}, & \end{aligned} \quad (4.28)$$

respectively. Thus, $(y_{11}, y_{21}) \in \mathcal{B} \times \mathcal{B}$ must be a solution of (4.22). We choose the specific solution satisfying the initial conditions $y_{21}(0) = 1$. Then

$$\begin{aligned} y_{21} &= \exp\left(\int_{n\tau}^t \frac{(1-q)m_2^*S_s}{1+b_2S_s} dl\right) > 0, & n\tau < t \leq (n+1)\tau, \\ y_{21}(0) &= 1. \end{aligned} \quad (4.29)$$

Moreover, $y_{11} < 0$ for all t (since $m_1 > m_1^*$ and (3.8), hence $-\int_0^\tau (m_1 x_{1s}(l)/(1+b_1S_s(l))^2) dl < 0$, which implies that the Green's function for first equation in (4.24) is positive). Using Lemma 4.5, we find that

$$\lambda = \frac{\int_0^\tau \left((1-q)y_{21}m_2^*(y_{11} + y_{21})/(1+b_2S_s)^2 \right) \exp\left(-\int_0^l ((1-q)m_2^*S_s/(1+b_2S_s)) dl\right) dt}{\int_0^\tau \left((1-q)y_{21}S_s/(1+b_2S_s) \right) \exp\left(-\int_0^l ((1-q)m_2^*S_s/(1+b_2S_s)) dl\right) dt} > 0. \quad (4.30)$$

Thus we see that near the bifurcation point $(m_2^*, 0, 0)$ the continuum C has two branches corresponding to $\epsilon < 0$, $\epsilon > 0$, respectively,

$$\begin{aligned} C^+ &= (m_2; x_1, x_2) : m_2^* < m_2 < m_2^* + \lambda_0, & x_1 < 0, & x_2 > 0, \\ C^- &= (m_2; x_1, x_2) : m_2^* - \lambda_0 < m_2 < m_2^*, & x_1 > 0, & x_2 < 0. \end{aligned} \quad (4.31)$$

The solution is on C^+ which prove the theorem, since $\lambda > 0$ is equivalent to $m_2 > m_2^*$. We have left only to show that $x_1 = y_1 + x_{1s}$ for all t . This is easy, for if λ_0 is small, then x_1 is near x_{1s}

in the sup norm of B ; thus since x_{1s} is bounded away from zero, so is x_1 . At the same time, by Theorem 4.2, for (2.4), x_2 is near x_{2s} means that x_1 is near x_{1s} ; thus $S = 1 - x_1 - x_2 > 0$. We notice that the periodic solution (x_1, x_2) is τ -periodic. So $S = 1 - x_1 - x_2$ is piecewise continuous and τ -periodic. The proof is thus completed. \square

5. Simulations and Discussion

The ability to manufacture desired products through genetically altered organisms represents one of the major developments in biotechnology. Competition between plasmid-bearing and plasmid-free organisms is a subject of considerable interest [29]. In this paper, we have considered a model for competition between plasmid-bearing and plasmid-free organisms in the chemostat with pulsed nutrient input and washout. Our research shows that the dynamical behaviors of model (2.4) are completely determined by two thresholds: m_1^* , the invasion threshold of the plasmid-free organism and m_2^* , the invasion threshold of the plasmid-bearing organism. If $m_1 < m_1^*$, the periodic solution $(1, 0, 0)$ is globally asymptotically stable, both the plasmid-bearing and the plasmid-free organisms are eradicated from the chemostat except the nutrient; if $m_1 > m_1^*$ and $m_2 < m_2^*$, the periodic solution $(S_s(t), x_{1s}(t), 0)$ is globally asymptotically stable, then the nutrient, plasmid-free organisms coexist periodically in the chemostat and the plasmid-bearing organism tends to extinction; if $m_1 > m_1^*$ and $m_2 > m_2^*$, (2.4) has a positive periodic solution $(S(t), x_1(t), x_2(t))$ and therefore, both the plasmid-bearing and the plasmid-free organisms coexist periodically in the chemostat.

To justify the theoretic results, we obtained in Section 4, we give two examples which concern the results in Theorems 4.2 and 4.6, respectively.

Example 5.1. In (2.4), set $m_2 = 1.2$, $a_1 = 0.3$, $a_2 = 0.25$, $D = 0.7$, $q = 0.0015$, we can compute $m_1^* \doteq 1.4448$. By Theorem 4.2, we know that if $m_1 < m_1^*$, the periodic solution $(1, 0, 0)$ is globally asymptotically stable; if $m_1 > m_1^*$, the plasmid-free organism begins to invade the system and the periodic solution $(S_s(t), x_{1s}(t), 0)$ is globally asymptotically stable. Our simulations support these results (see Figures 1 and 2, where $m_1 = 1.2$ and $m_1 = 1.8$, resp.).

Example 5.2. In (2.4), set $m_1 = 1.8 (> m_1^*)$ and a_1, a_2, D, q have similar values as in Example 5.1. We can estimate numerically that $m_2^* \doteq 1.74$ (since we cannot compute the exact value from the expression of m_2^* in (4.4)). By Theorem 4.6, we know that if $m_2 > m_2^*$, the plasmid-bearing organism begins to invade the system and, in this case, (2.4) has a positive periodic solution $(S(t), x_1(t), x_2(t))$. Our simulations support this result (see Figure 3, where $m_2 = 1.745$).

From the chemical engineering standpoint, the consumption of nutrient by the plasmid-free organism represents a loss of production in the bioreactor. Moreover, if it is a sufficiently better competitor, the plasmid-bearing organism (the production) may be eliminated from the chemostat (in this situation, the periodic solution $(S_s(t), x_{1s}(t), 0)$ exists and is globally stable). Then no product is manufactured (and nutrient is consumed). This is an undesirable situation. Note also that the plasmid-bearing organism can always lose the plasmid. Thus, if the plasmid-bearing organism does not go to extinction, then neither does the plasmid-free organism. This can also be seen from the form of the equations in system (2.4) (as a consequence, there is no nonnegative periodic solution $(S_s(t), 0, x_{2s}(t))$ in the space $x_1 = 0$). Thus, the best situation for the manufacture by genetically altered organism is that

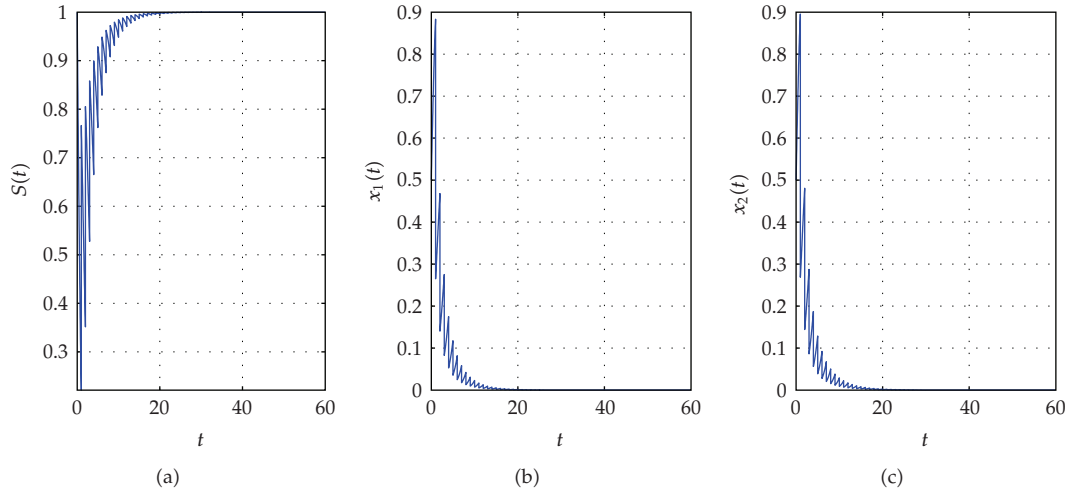


Figure 1: Time-series of (2.4) with periodically input and washout with initial value $S_0 = 1$, $x_{10} = 0.5$, $x_{20} = 0.5$: $m_1 = 1.2$, $m_2 = 1.2$, $a_1 = 0.3$, $a_2 = 0.25$, $D = 0.7$, $q = 0.0015$, $\tau = 1$.

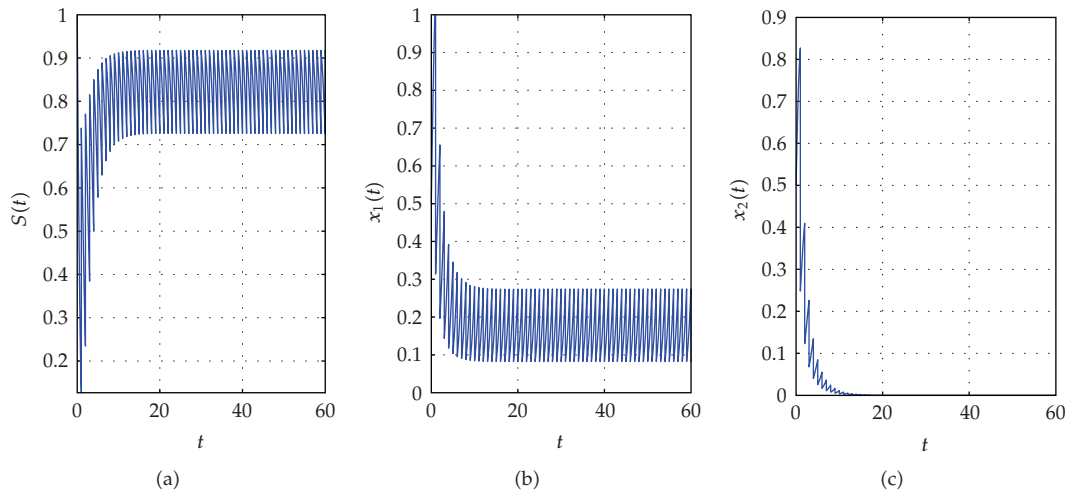


Figure 2: Time-series of system (2.4) with periodically input and washout with initial value $S_0 = 1$, $x_{10} = 0.5$, $x_{20} = 0.5$: $m_1 = 1.8$, m_2 , a_1 , a_2 , D , q , and τ have similar values as in Figure 1.

both the plasmid-free and the plasmid-bearing organisms coexist in the chemostat. Therefore, the study of the existence of the positive periodic solution $(S(t), x_1(t), x_2(t))$ of the system is paramount. By Theorem 4.6 we can see from the expressions of m_1^* , m_2^* given, respectively, by (3.3) and (4.4) and the scaling formulations in (2.3) that the controllers of the bioreactor can do this by only control the parameters S^0, D and τ such that the conditions $m_1 > m_1^*$ and $m_2 > m_2^*$ are satisfied.

For the situation when both the plasmid-free and the plasmid-bearing organisms coexist in the culture, we further want to know the optimum values of S^0, D , and τ under which the product manufacturer can obtain the maximum production by genetically altered organism. This is a challenging question to answer. We leave this for future consideration.

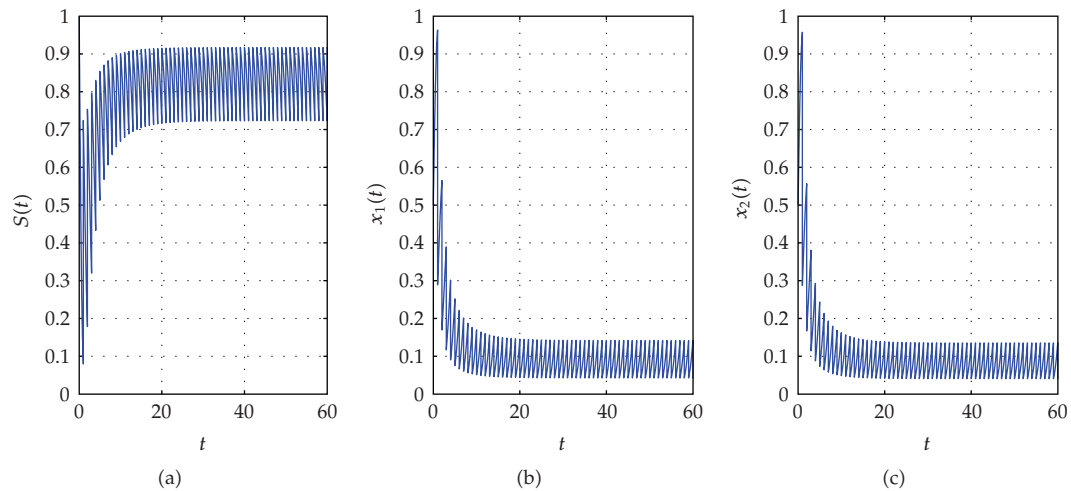


Figure 3: Time-series of (2.4) with periodically input and washout with initial value $S_0 = 1$, $x_{10} = 0.5$, $x_{20} = 0.5$: $m_1 = 1.8 (> m_1^*)$, $m_2 = 1.745$, a_1, a_2, D, q, τ have similar values as in Figures 1 and 2.

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