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Impulsive perturbation and bifurcation of solutions for a model of chemostat with variable yield *

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Abstract In this paper, we consider a variable yield model of a single-species growth in a well-stirred tank containing fresh medium, assuming the instances of time as triggering factors in which the nutrient refilling process and the removal of microorganisms by the uptake of lethal external antibiotic are initiated. It is also assumed that the periodic nutrient refilling and the periodic antibiotic injection occur with the same periodicity, but not simultaneously. The model is then formulated in terms of autonomous differential equations subject to impulsive perturbations. It is observed that either the population of microorganisms essentially washes out, or more favorably, the system is permanent. To describe this dichotomy, some biologically significant integral conditions are introduced. Further, it is shown that in a certain critical situation, a nontrivial periodic solution emerges via a bifurcation phenomenon. Finally, the dynamics of the model is illustrated with numerical experiments and computer simulations.

Key words chemostat, impulsive differential equation, permanence, extinction, fixed point approach, bifurcation

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Introduction

It is well-known that the chemostat plays an important role as a model in mathematical biology, being used to represent many kinds of microbiological ecosystems and having the advantage of being easily implementable in a laboratory. Consequently, various chemostat models have been studied by an increasing number of scholars[1-8]. One particular class of models includes deterministic models of microbial growth in continuous culture vessels. The equations of the basic model take the form

$$\begin{cases} S'(t) = \big(S_0 - S(t)\big)D - \dfrac{x(t)}{\gamma}P\big(S(t)\big), \\ x'(t) = \big(P(S(t)) - D\big)x(t), \end{cases} \tag{1}$$

where $S(t)$ and $x(t)$ denote the concentration of the nutrient in the culture vessel at the time t and the concentration of the population of microorganisms, respectively. Also, S_0 represents the concentration at which the nutrient is fed into the vessel, and D describes the volumetric dilution rate. The parameter γ denotes the ratio of the produced microbial biomass to the mass of the consumed nutrient. The function $P(S)$ is called the functional response and describes the microbial growth rate. Some forms for the functional response that have been used are the Monod (1942), Monod-Haldane (1968), Tessiet (1936), Tseng (1975), and Rosenzweig (1971) models (see Ref. [1]).

They are single functional responses trying to capture the essence of the microbial growth rate. However, in view of the accumulation of experimental data, it is evident that these simple models require some modifications. Specifically, in view of the experimental fact that the yield coefficient may depend on the substrate concentration, Pilyugin and Waltman[4] proposed the mathematical model of the chemostat with a variable yield, and then studied the existence of the multiple limit cycles. They emphasized that the novelty of their paper is that only supercritical bifurcations occur when the yield varies linearly with S. In 2005, Huang and Zhu[3] analyzed the relative positions of the limit cycles in a continuous culture vessel with a variable yield.

Recently, antibiotics have been used to treat serious infections because they may restore the balance among the internal microorganism populations without harming the patient. For example, pneumonia can be caused by bacteria such as Streptococcus and Pseudomonas. Also, Mycoplasma pneumoniae and other atypical pathogens, such as Chlamydia pneumoniae and Legionella spp., are important causes of the community-acquired pneumonia (CAP). To treat the CAP, some researchers discovered a synthetic fluoroquinolone antibiotic agent named moxifloxacin. Bayer then developed the drug initially called the BAY 12-8039 and marketed it worldwidely with the brand name Avelox®. Recently, Hoeffken et al.[9] presented the clinical results, which indicated that intravenous (IV)/oral (PO) moxifloxacin is an effective monotherapy for the patients with CAP caused by atypical pathogens. Obviously, the IV/PO treatment is not administered 24 hours a day, but in the periodic pulses. Actually, in the laboratory tests, each patient received the IV/PO moxifloxacin 400 mg per day.

It is noted that impulsive differential equations can be employed to faithfully describe the above-mentioned phenomena in the chemostat. The theory of impulsive differential equations is an important branch of differential equations, which has an extensive physical background. For a comprehensive overview, the reader may refer to Ref. [10]. This type of equations has been discussed recently by many authors[5-7,11-13]. However, only a few manuscripts[5-7,11] deal with the description of such equations in relation to the theory of the chemostat.

Motivated by these references, this paper aims to construct an impulsive differential model of substrate-microorganism interaction incorporating a variable yield, an impulsive nutrient perturbation consisting in the periodic refilling of the substrate concentration in a constant amount, and an impulsive microorganism perturbation consisting in periodic antibiotic injection. The dynamics of this system is investigated. The periodicity of the antibiotic injection is

similar to that of the substrate refilling. However, it avoids the simultaneous use of the controls. Thereby, we suggest an impulsive system, which includes two trophic levels, microorganism and substrate, to model the target microorganism and its nutrient fluid.

1 The model

On the basis of Ref. [7], we can formulate the model as follows:

$$\begin{cases} \left.\begin{aligned} S'(t) &= (S_0 - S)D - x\tfrac{P(S)}{\gamma(S)}, \\ x'(t) &= x\big(P(S) - D\big), \end{aligned}\right\} & t \neq (n + \widetilde{l} - 1)T,\ t \neq nT,\ n \in \mathbf{N}, \\ \left.\begin{aligned} \Delta S(t) &= 0, \\ \Delta x(t) &= -px(t), \end{aligned}\right\} & t = (n + \widetilde{l} - 1)T, \\ \left.\begin{aligned} \Delta S(t) &= TS_1, \\ \Delta x(t) &= 0, \end{aligned}\right\} & t = nT, \\ x(0) \geq 0, \quad S(0) \geq 0. \end{cases} \tag{2}$$

Here, $S(t)$ and $x(t)$ represent the nutrient concentration at the time t in a chemostat-grown culture and the concentration of the population of microorganisms, respectively. $0 < \widetilde{l} < 1$ is used to describe the intervals of time between the pulsed uses of controls of lengths $\widetilde{l}T$ and $(1 - \widetilde{l})T$. Also, $\Delta\varphi(t) = \varphi(t^+) - \varphi(t)$, and $\varphi \in \{x, S\}$. The following assumptions are made to derive the mathematical model.

(A_1) In the absence of the microorganism populations, the dynamics of the substrate follows the law of growth given as $g(S) = (S_0 - S)D$, where the parameters S_0 and D are the same as the ones given in the system (1).

(A_2) It is assumed that the substrate nutrient is added in an impulsive and periodic fashion with the periodicity T and a fixed amount TS_1 each time. On average, S_1 units of substrate are added per unit of time. It is also assumed that antibiotics are injected in an impulsive and periodic fashion with the same period as the action of adding nutrients, but at different moments. As a result of the antibiotics injecting, a fixed proportion p of the microorganism biomass is degraded each time.

(A_3) The function $P(S)$ describes the amount of the nutrient S consumed per microorganism unit of biomass per unit of time and is usually assumed to be of the Monod type; that is, $P(S) = \frac{\mu_m S}{K_m + S}$. Also, the variable yield $\gamma(S)$ is traditionally modeled by a general function $a + bS^l$ with $a, b, l > 0$.

Lemma 1.1 *The positive quadrant R^2_+ is an invariant region for the system* (2).

Lemma 1.2 *All solutions $(S(t), x(t))$ of* (2) *with the initial data $(S(\cdot), x(\cdot)) \in R^2_+$ are bounded and defined on R_+.*

2 Main results

With the recall of the treatment of the CAP mentioned in Introduction, our intention is to eradicate pathogenic bacteria. In the following, we shall investigate the dynamics of the pathogenic microorganism-free state.

2.1 Dynamics of the microorganism-free system

When the microorganism population x is eradicated, it is easy to see that the equations in (2) decouple, and we are led to consider the properties of the following subsystem:

$$\begin{cases} S'(t) = (S_0 - S)D, \quad t \neq (n + \widetilde{l} - 1)T, \quad t \neq nT, \\ \Delta S(t) = 0, \quad t = (n + \widetilde{l} - 1)T, \\ \Delta S(t) = TS_1, \quad t = nT, \\ S(0) \geq 0. \end{cases} \tag{3}$$

Lemma 2.1 *The system consisting of the first three equations of* (3) *has a positive periodic solution* $S^*(t)$ *with*

$$\int_0^T S^*(t)dt = \frac{TS_1}{D} + TS_0.$$

Moreover, for every solution $S(t)$ *of* (3), $|S(t) - S^*(t)| \to 0$ *as* $t \to \infty$.

Theorem 2.1 *The microorganism-eradication periodic solution* $(S^*(t), 0)$ *is globally asymptotically stable* (GAS) *provided that the condition*

$$\widetilde{\mathcal{L}}(S^*(t)) = \int_0^T P\big(S^*(t)\big)dt < DT + \ln\frac{1}{1-p} \tag{4}$$

holds.

Remark 2.1 Since

$$\widetilde{\mathcal{L}}(S^*(t)) = \mu_{\mathrm{m}}T - \frac{\mu_{\mathrm{m}}K_{\mathrm{m}}}{D(K_{\mathrm{m}} + S_0)} \ln\frac{(K_{\mathrm{m}} + S_0)(\mathrm{e}^{DT} - 1) + TS_1}{(K_{\mathrm{m}} + S_0)(1 - \mathrm{e}^{-DT}) + TS_1}, \tag{5}$$

the stability condition (4) can be stated explicitely as

$$\mu_{\mathrm{m}}T < \frac{\mu_{\mathrm{m}}K_{\mathrm{m}}}{D(K_{\mathrm{m}} + S_0)} \ln\frac{(K_{\mathrm{m}} + S_0)(\mathrm{e}^{DT} - 1) + TS_1}{(K_{\mathrm{m}} + S_0)(1 - \mathrm{e}^{-DT}) + TS_1} + DT + \ln\frac{1}{1-p}. \tag{6}$$

On the other hand, if

$$\mu_{\mathrm{m}}T > \frac{\mu_{\mathrm{m}}K_{\mathrm{m}}}{D(K_{\mathrm{m}} + S_0)} \ln\frac{(K_{\mathrm{m}} + S_0)(\mathrm{e}^{DT} - 1) + TS_1}{(K_{\mathrm{m}} + S_0)(1 - \mathrm{e}^{-DT}) + TS_1} + DT + \ln\frac{1}{1-p}, \tag{7}$$

$(S^*(t), 0)$ is unstable.

Remark 2.2 Here, the GAS of the microorganism-eradication periodic solution of (2) is independent of the variable yield $\gamma(S)$, while it depends on the effect of the functional response $P(S)$ of the microorganism population.

Remark 2.3 Theorem 2.1 extends Theorem 3.1 in Ref. [7].

The proofs of the above-mentioned results are obvious[14]. Consequently, from the above mathematical results, the pathogenic microorganism-free state will be stabilized by using the appropriate dose of antibiotic injection and the suitable time interval for injection. In other words, under appropriate circumstances, the bacterial clearance rate is equal to 100%. In 2006, Zhang et al.[15] also evaluated the clinical utility of moxifloxacin in the treatment of the patients with the moderate to severe CAP, and then found that in the case of 40 patients treated with moxifloxacin, 400 mg, q.i.d. for 7 to 14 days, the final bacterial clearance rate is 93.7%. This clinical result completely explains the necessity of studying the dynamics of the above-mentioned critical subsystem (3). In fact, after the clinical treatment, bacterial microorganisms may not be completely eradicated. Hence, in the following, we need to consider the case of the long-term survival of bacterial pathogens.

2.2 Permanence

Theorem 2.2 *Assume that*

$$\widetilde{\mathcal{L}}(S^*(t)) > DT + \ln\frac{1}{1-p}. \tag{8}$$

That is, the condition (7) *holds. Then, the system* (2) *is permanent.*

Remark 2.4 From Theorems 2.1 and 2.2, we can see that, if $T > \frac{\widetilde{\mathcal{L}}(S^*(t))+\ln(1-p)}{D}$, the microorganism-free periodic solution $(S^*, 0)$ is globally asymptotically stable; while, if $T < \frac{\widetilde{\mathcal{L}}(S^*(t))+\ln(1-p)}{D}$, the microorganism-free periodic solution $(S^*, 0)$ loses its stability, and the system becomes permanent.

Remark 2.5 Theorem 2.2 extends Theorem 3.3 in Ref. [7].

In the following, we shall observe the dynamical behavior of the critical case. That is,

$$T = \frac{\widetilde{\mathcal{L}}(S^*(t)) + \ln(1-p)}{D}.$$

2.3 Bifurcation

We modify the approach developed in Ref. [12] (see also Ref. [16]) and denote by $\Phi(t; X_0) = \big(\Phi_1(t, X_0), \Phi_2(t, X_0)\big)$ the solution of the pulse-free system corresponding to (2) with the initial data $X_0 = (x_0^1, x_0^2)$. We also define two operators $I_1, I_2 : R^2 \to R^2$ by

$$I_1(x_1, x_2) = (x_1, (1-p)x_2), \quad I_2(x_1, x_2) = (x_1 + TS_1, x_2),$$

two maps $F_1, F_2 : R^2 \to \mathbb{R}$ by

$$\begin{aligned} F_1(x_1, x_2) &= (S_0 - x_1)D - x_2\frac{P(x_1)}{\gamma(x_1)}, \\ F_2(x_1, x_2) &= x_2(P(x_1) - D), \end{aligned}$$

and $F : R^2 \to R^2$ by

$$F(x_1, x_2) = (F_1(x_1, x_2), F_2(x_1, x_2)).$$

In the following, we shall reduce the problem of finding a periodic solution of (2) to a certain fixed point problem. To this end, define the evolution operator $\Psi : [0, \infty) \times R^2 \to R^2$ by

$$\Psi(T, X_0) = I_2((1-\widetilde{l})T; I_1(\widetilde{l}T, X_0)),$$

also

$$\Psi(T, X_0) = (\Psi_1(T, X_0), \Psi_2(T, X_0)).$$

Then, X is a T-periodic solution of (2) if and only if X_0 is a fixed point for the operator $\Psi(T, \cdot)$, where $X(0) = X_0$.

We note that

$$D_X\Psi(T, X) = D_X\Phi((1-\widetilde{l})T; I_1(\Phi(\widetilde{l}T, X))) \begin{pmatrix} 1 & 0 \\ 0 & 1-p \end{pmatrix} D_X\Phi(\widetilde{l}T; X).$$

Let $X_0 = (x_0, 0)$ be the initial condition corresponding to the trivial periodic solution $(S^*(t), 0)$, where $x_0 = S^*(0)$. We can easily obtain that

$$D_X\Psi(T, X_0) = \begin{pmatrix} d_{11} & d_{12} \\ 0 & d_{22} \end{pmatrix},$$

where

$$\begin{aligned}
d_{11} &= \mathrm{e}^{-DT},\\
d_{12} &= -\mathrm{e}^{-DT}\bigg((1-p)\int_{\widetilde{l}T}^{T}\frac{P\big(S^*(s)\big)}{\gamma\big(S^*(s)\big)}\mathrm{e}^{\int_0^s\left[P\left(S^*(\xi)\right)-D\right]d\xi+Ds}ds\\
&\quad+\int_0^{\widetilde{l}T}\frac{P\big(S^*(s)\big)}{\gamma\big(S^*(s)\big)}\mathrm{e}^{\int_0^s\left[P\left(S^*(\xi)\right)-D\right]d\xi+Ds}ds\bigg),\\
d_{22} &= (1-p)\mathrm{e}^{\int_0^T\left[P(S^*(s))-D\right]ds}.
\end{aligned}$$

Denote

$$\tau = T+\overline{\tau},\quad X = X_0+\overline{X}.$$

To find a nontrivial periodic solution of the period τ with the initial data X, we need to solve the fixed point problem $X=\Psi(\tau,X)$. That is,

$$X_0+\overline{X} = \Psi(T+\overline{\tau},X_0+\overline{X}).$$

Let

$$\Theta(\overline{\tau},\overline{X}) = X_0+\overline{X}-\Psi(T+\overline{\tau},X_0+\overline{X}) \tag{9}$$

and

$$\Theta(\overline{\tau},\overline{X}) = (\Theta_1(\overline{\tau},\overline{X}),\Theta_2(\overline{\tau},\overline{X})).$$

We are then led to solve the equation $\Theta(\overline{\tau},\overline{X})=0$. We note that

$$D_X\Theta(0,(0,0)) = E_2-D_X\Psi(T,X_0) = \begin{pmatrix}1-d_{11} & -d_{12}\\ 0 & 1-d_{22}\end{pmatrix} = \begin{pmatrix}a_0' & b_0'\\ 0 & d_0'\end{pmatrix}. \tag{10}$$

A necessary condition for the bifurcation of the nontrivial periodic solutions near the trivial periodic solution $(S^*(t),0)$ is

$$\det\left[D_X\Theta(0,(0,0))\right]=0.$$

Since $a_0'\neq 0$, it follows that $d_0'=0$, i.e.,

$$(1-p)\mathrm{e}^{\int_0^T\left[P(S^*(s))-D\right]ds}=1 \Longleftrightarrow \widetilde{\mathcal{L}}(S^*(t)) = DT+\ln\frac{1}{1-p_1}. \tag{11}$$

It can be seen that

$$\dim\{\mathrm{Ker}[D_X\Theta(0,(0,0))]\}=1,$$

and a basis in $\mathrm{Ker}[D_X\Theta(0,(0,0))]$ is $(-b_0'/a_0',1)$. Then, $\Theta(\overline{\tau},\overline{X})=0$ is equivalent to

$$\begin{cases}\Theta_1(\overline{\tau},\alpha Y_0+zE_0)=0,\\ \Theta_2(\overline{\tau},\alpha Y_0+zE_0)=0,\end{cases}$$

where

$$E_0=(1,0),\quad Y_0=(-b_0'/a_0',1),$$

and $\overline{X}=\alpha Y_0+zE_0=(\alpha(-b_0'/a_0')+z,\alpha)$ represents the the direct sum decomposition of X using the projections onto $\mathrm{Ker}[D_X\Theta(0,(0,0))]$ and $\mathrm{Im}[D_X\Theta(0,(0,0))]$ (see Ref. [1]).

Let

$$f_1(\overline{\tau},\alpha,z)=\Theta_1(\overline{\tau},\alpha Y_0+zE_0), \tag{12}$$

$$f_2(\overline{\tau},\alpha,z)=\Theta_2(\overline{\tau},\alpha Y_0+zE_0). \tag{13}$$

We need solve the following system:

$$\begin{cases} f_1(\overline{\tau},\alpha,z)=0,\\ f_2(\overline{\tau},\alpha,z)=0. \end{cases}$$

Since

$$\frac{\partial f_1}{\partial z}(0,0,0)=\frac{\partial \Theta_1}{\partial x_1}(0,(0,0))=a_0'\neq 0,$$

by applying the implicit function theorem, we may locally solve the equation $f_1(\overline{\tau},\alpha,z)=0$ near $(0,0,0)$ with respect to z as a function of $\overline{\tau}$ and α, and find $z=z(\overline{\tau},\alpha)$ such that $z(0,0)=0$ and

$$f_1(\overline{\tau},\alpha,z(\overline{\tau},\alpha))=\Theta_1(\overline{\tau},\alpha Y_0+z(\overline{\tau},\alpha)E_0)=0.$$

By deriving the above implicit function with respect to α at $(0,0)$, we may then deduce that

$$\frac{\partial \Theta_1}{\partial x_1}(0,(0,0))\left(\frac{\partial x_1}{\partial \alpha}(0,0)+\frac{\partial x_1}{\partial z}\frac{\partial z}{\partial \alpha}(0,0)\right)+\frac{\partial \Theta_1}{\partial x_2}(0,(0,0))\frac{\partial x_2}{\partial \alpha}(0,0)=0.$$

It follows from (10) that

$$\frac{\partial z}{\partial \alpha}(0,0)=0. \tag{14}$$

It can be easily seen that

$$\begin{aligned}\frac{\partial z}{\partial \overline{\tau}}(0,0) &= \frac{1}{a_0'}\big[(-DS^*(T)+DS_0)(1-\widetilde{l})+\mathrm{e}^{-D(1-\widetilde{l})T}(-DS^*(\widetilde{l}T)+DS_0)\cdot\widetilde{l}\,\big]\\ &= -\frac{D}{a_0'}(S^*(T)-S_0).\end{aligned}$$

Now, we study the solvability of the equation

$$f_2(\overline{\tau},\alpha,z(\overline{\tau},\alpha))=\Theta_2(\overline{\tau},\alpha Y_0+z(\overline{\tau},\alpha)E_0)=0. \tag{15}$$

The equation (15) is called the determining equation, and the number of its solutions equals that of the periodic solutions of (2)[17]. In the following, we proceed to solve (15) by using the Taylor expansions. We denote

$$f(\overline{\tau},\alpha)=f_2(\overline{\tau},\alpha,z(\overline{\tau},\alpha)). \tag{16}$$

First, we observe that

$$f(0,0)=\Theta_2(0,(0,0))=0.$$

Second, it is easy to see that

$$\frac{\partial f}{\partial \alpha}(0,0)=1-\frac{\partial \Phi_2}{\partial x_2}\big((1-\widetilde{l})T;I_1(\Phi(\widetilde{l}T;X_0))\big)(1-p)\frac{\partial \Phi_2}{\partial x_2}(\widetilde{l}T;X_0)=d_0'=0. \tag{17}$$

It consequently follows that

$$\frac{\partial f}{\partial \overline{\tau}}(0,0)=0. \tag{18}$$

Third, according to the computations, we obtain that

$$\frac{\partial^2 f}{\partial \overline{\tau}^2}(0,0)=-\frac{\partial^2 \Phi_2}{\partial \overline{\tau}^2}\big((1-\widetilde{l})T;I_1(\Phi(\widetilde{l}T;X_0))\big)(1-\widetilde{l})^2=0, \tag{19}$$

$$\frac{\partial^2 f}{\partial \alpha^2}(0,0)>0, \tag{20}$$

and

$$\frac{\partial^2 f}{\partial \overline{\tau}^2}(0,0) = 0. \tag{21}$$

By constructing the second-order Taylor expansion of f near $(0,0)$, we obtain from (17)–(21) that

$$f(\overline{\tau},\alpha) = \frac{\partial^2 f}{\partial\alpha\partial\overline{\tau}}(0,0)\alpha\overline{\tau} + \frac{1}{2}\underbrace{\frac{\partial^2 f}{\partial\alpha^2}(0,0)}_{>0}\alpha^2 + o(\overline{\tau},\alpha)(\overline{\tau}^2+\alpha^2).$$

Next, we need to consider two cases:

Case I Assume that

$$\frac{\partial^2 f}{\partial\alpha\partial\overline{\tau}}(0,0) < 0. \tag{22}$$

Let $\alpha = k\overline{\tau}$ and $k = k(\overline{\tau})$. It follows from the above equation that

$$f(\overline{\tau}) = \overline{\tau}^2\left(\underbrace{\frac{\partial^2 f}{\partial\overline{\tau}\partial\alpha}(0,0)}_{<0}k + \frac{1}{2}\underbrace{\frac{\partial^2 f}{\partial\alpha^2}(0,0)}_{>0}k^2 + o(\overline{\tau},k\overline{\tau})(1+k^2)\right).$$

Obviously, the following equation

$$\underbrace{\frac{\partial^2 f}{\partial\overline{\tau}\partial\alpha}(0,0)}_{<0}k + \frac{1}{2}\underbrace{\frac{\partial^2 f}{\partial\alpha^2}(0,0)}_{>0}k^2 + o(\overline{\tau},k\overline{\tau})(1+k^2) = 0$$

has a nontrivial positive solution $k = k(\overline{\tau})$ if $\overline{\tau}$ is positive and small enough.

In conclusion, from the above analysis, we present the following theorem.

Theorem 2.3 *Assume that the conditions* (11) *and* (22) *are satisfied. Then, there is an* ϵ (>0) *such that, for all* $0<\overline{\tau}<\epsilon$, *there is a stable positive nontrivial periodic solution of* (2) *with the initial data* $X_0+\alpha(\overline{\tau})Y_0+z(\overline{\tau},\alpha(\overline{\tau}))E_0$ *and the period* $T+\overline{\tau}$.

Case II Assume that

$$\frac{\partial^2 f}{\partial\alpha\partial\overline{\tau}}(0,0) > 0. \tag{23}$$

Then, we can also get a result similar to Theorem 2.3.

Theorem 2.4 *Assume that the conditions* (11) *and* (23) *are satisfied. Then, there is an* ϵ (>0) *such that, with the initial data* $X_0-\alpha(\overline{\tau})Y_0+z(\overline{\tau},-\alpha(\overline{\tau}))E_0$ *and the period* $T+\overline{\tau}$, *for all* $0<\overline{\tau}<\epsilon$, *there is a subcritical bifurcation of a positive nontrivial periodic solution of* (2).

Remark 2.6 The final part of the existence argument can also be obtained with the use of the substitution $\overline{\tau} = k\alpha$ (or $\overline{\tau} = -k\alpha$) and $k = k(\alpha)$.

Remark 2.7 The condition (11), which is a sufficient condition for the bifurcation of a nontrivial periodic solution and indicates the separation of the phase space into two regions with different topological structures of the phase portraits, can be explicitely stated as

$$\mu_{\rm m}T = \frac{\mu_{\rm m}K_{\rm m}}{D(K_{\rm m}+S_0)}\ln\frac{(K_{\rm m}+S_0)(\mathrm{e}^{DT}-1)+TS_1}{(K_{\rm m}+S_0)(1-\mathrm{e}^{-DT})+TS_1} + DT + \ln\frac{1}{1-p}. \tag{24}$$

If p is chosen as a bifurcation parameter, the critical value, for which the bifurcation occurs, is denoted as

$$p^* = 1 - \frac{1}{\exp\left[\mu_{\rm m}T - \frac{\mu_{\rm m}K_{\rm m}}{D(K_{\rm m}+S_0)}\ln\frac{(K_{\rm m}+S_0)(\mathrm{e}^{DT}-1)+TS_1}{(K_{\rm m}+S_0)(1-\mathrm{e}^{-DT})+TS_1} - DT\right]}. \tag{25}$$

A similar critical value T^* can be found if T is chosen as a bifurcation parameter.

3 Numerical simulations

To facilitate the interpretation of our mathematical results, with the help of the mathematical software Maple 8, we proceed to a further investigation by employing numerical simulations. Consider the following concrete numerical system:

$$\begin{cases} \left.\begin{aligned} S'(t) &= (1-S) - x\tfrac{\frac{2S}{0.58+S}}{1+50S^2}, \\ x'(t) &= x\big(\tfrac{2S}{0.58+S} - 1\big), \end{aligned}\right\} & t \neq 2(n-\frac{1}{2}),\ t \neq 2n,\ n \in \mathbf{N}, \\ \left.\begin{aligned} \triangle S(t) &= 0, \\ \triangle x(t) &= -0.579\,2x(t), \end{aligned}\right\} & t = 2(n-\frac{1}{2}), \\ \left.\begin{aligned} \triangle S(t) &= S_1 T, \\ \triangle x(t) &= 0, \end{aligned}\right\} & t = 2n, \\ x(0) = 10, \quad S(0) = 5.8. \end{cases} \tag{26}$$

Straightforward computations show that, for the above system, the critical condition (11) is satisfied by choosing $S_1 = 0.5$, i.e., when $S_1 < 0.5$, the microorganism-eradication periodic solution $(S^*(t), 0)$ is globally asymptotically stable, while, for $S_1 > 0.5$, the system (26) is permanent.

The resulting bifurcation diagrams (Fig. 1) show that, with S_1 varying from 0 to 2.5 and increasing over $[1.2, 2]$, respectively, the microorganism population experiences complex dynamical process of zero→ cycles → quasi-periodic oscillating → cycles → quasi-periodic oscillating→ cycles→ periodic doubling cascade → chaos → cycles.

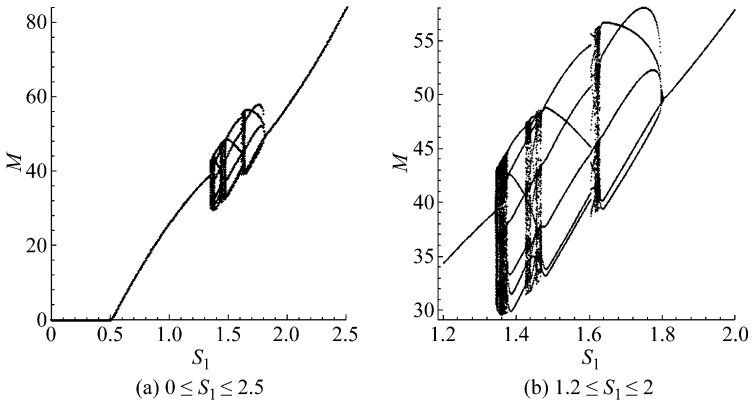

Fig. 1 Bifurcation diagrams of the microorganism population x with $S(0) = 5.8$ and $x(0) = 10$

When $S_1 = 0.2$ (< 0.5) and other coefficients are same as the ones given in (26), the microorganism-free periodic solution $(S^*, 0)$ is globally asymptotically stable (see Fig. 2(a)). With S_1 increasing and then crossing the threshold of $S_1 = 0.5$, the trivial periodic solution becomes unstable because of a supercritical branch $\big(\frac{\partial^2 f}{\partial\alpha\partial\overline{\tau}}(0,0) = -0.293\,792 < 0\big)$. A typical numerical example of a unique limit cycle is captured in Fig. 2(b) for $S_1 = 1.2$ and the same coefficients used in (26). With an increase of S_1, it is also observed that the solutions of (26) ultimately oscillate around the limit cycle (see Fig. 2(c)). Subsequently, the trajectory of the perturbed system tends to a periodic orbit of the period $7T$ (see Fig. 3(a)). A somewhat similar situation (a periodic orbit of the period $6T$) is captured in Fig. 3(b). From Fig. 1, a chaotic behavior (strange attractor) is captured in Fig. 4(c) ($S_1 = 1.626$). Also, the time series for S and x also indicates that the trajectory has a chaotic behavior (see Figs. 4(a) and 4(b)). A

slight increase in S_1 ($S_1 = 1.628$) "stabilizes" the behavior of the system, and the trajectory tends again to a periodic solution of the period $5T$ (see Fig. 3(c)).

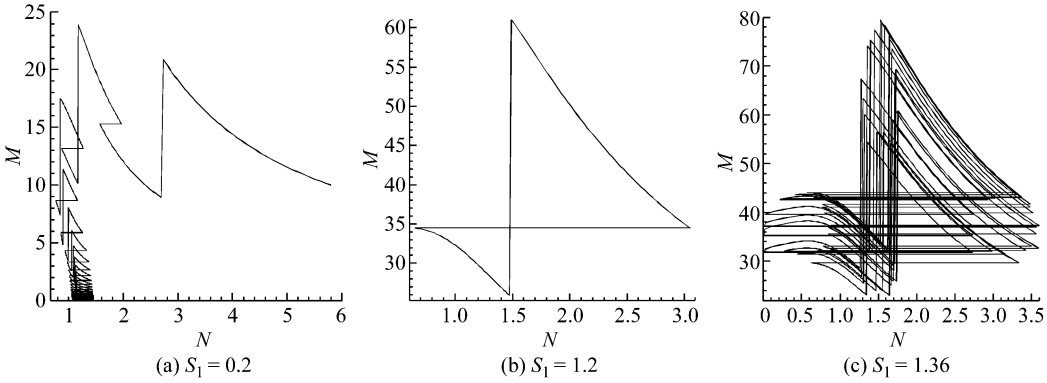

Fig. 2 Dynamical behavior of (26) with impulsive perturbations for S_1=0.2, 1.2, 1.36

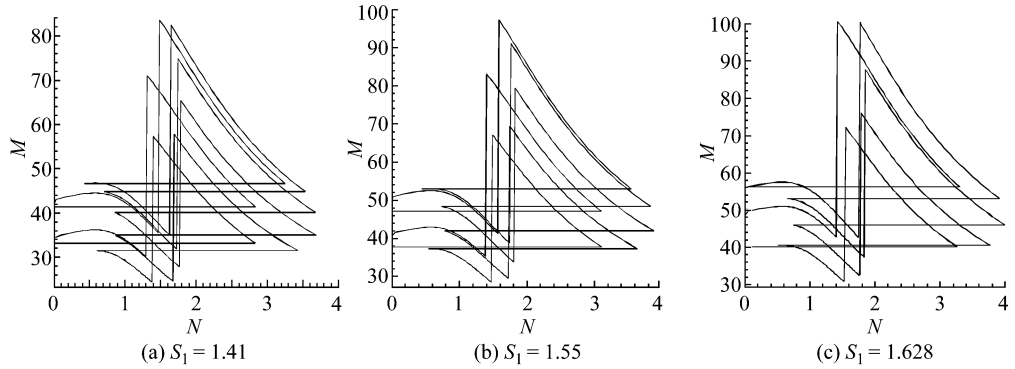

Fig. 3 Dynamical behavior of (26) with impulsive perturbations for S_1=1.41, 1.55, 1.628

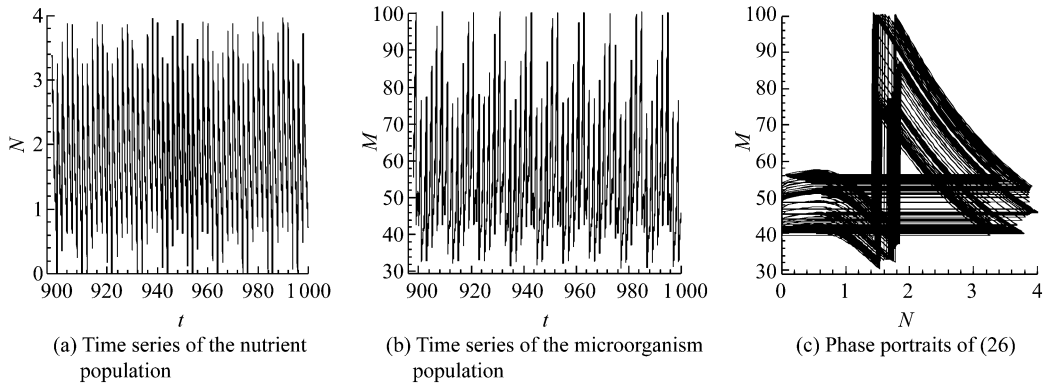

Fig. 4 Dynamical behavior of (26) with impulsive perturbations for $S_1 = 1.626$

4 Conclusions

(i) We construct a new model of a chemostat with a variable yield including a nutrient refilling control in the form of the periodic release of the substrate in a fixed amount and a microorganism control in the form of the periodic lethal external antibiotic injection. It is also assumed that the impulsive perturbations of the nutrient and population of microorganisms, respectively, have the same periodicity, but do not occur simultaneously.

(ii) We obtain a set of threshold-like conditions guaranteeing the global stability of the semi-trivial periodic solution and the permanence of (2). Then, a bifurcation of a nontrivial solution arises. Finally, the numerical analysis of some situations leading to a chaotic behavior of the system is given.

(iii) Our simulation results show that the nontrivial positive periodic solution of (2) may be stable. The larger the period is, the higher the concentration of the bacterial microorganism population becomes. Therefore, we can control the bacterial pathogens below some given levels by choosing an appropriate impulsive period T. This mathematical result explains why a patient should receive 400 mg moxifloxacin a day during the quadruple therapy of the CAP.

In our model, we assume that the drug acts instantaneously by removing a certain fraction of the treated microbial population. This facilitates the analysis of the dynamics of our model using the known methods of impulsive differential equations. From a biological viewpoint, a separate dynamic variable should be introduced to the current version of our model to represent the pharmacokinetics of the drug itself. This is left for the future work.

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