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Studies on the dynamics of a continuous bioprocess with impulsive state feedback control☆

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ABSTRACT

The oxygen demand in a bioreactor should be lower than the dissolved oxygen content. Biomass concentration is one of the most important factors which affect oxygen demand. Moreover, control of the medium substrate concentration is a result of the substrate inhibition phenomenon. Based on the design ideas of a continuous bioprocess which can regulate the biomass concentration, a mathematical model with the extended Monod growth kinetics and impulsive state feedback control is proposed in this paper. Through an analysis of the dynamic properties and a numerical simulation of the continuous bioprocess with impulsive state feedback control, the conditions are obtained for the existence and stability of the system's positive period-1 solution. It is also pointed out that the positive period-2 solution is nonexistent. The results simplify the choosing of suitable operating conditions for continuous bioprocess. It also presents the complete expression of the positive period-1 solution period, which provides the precise feeding time frame for a regularly continuous bioprocess to achieve an equivalent stable output as that of an impulsive bioprocess in the same production environment. The article also presents and discusses aspects of the bioprocess optimization.

1. Introduction

Microorganisms play an important role in nature and their activities have numerous industrial applications [1,2]. For that reason bioreactor engineering is an active research area of the cultivation of microorganisms [3]. In microbial as well as chemical processes, three different modes of operation, i.e., batch [4], fed-batch [5] and continuous [6] are applied. There are a lot of factors affecting the growth and reproduction of the microorganisms in the bioprocesses. For example, for some aerobic microbes, the dissolved oxygen concentration (DOC) in the bioreactor medium is a key factor in microbial growth. The performed bioprocesses demonstrate that it is possible to prevent decrease of the bioprocess DOC below a low level, by dosing the substrate in portions [7]. Moreover, by dosing the substrate in portions it is possible to maintain the dissolved oxygen concentration in an appropriate range, enabling easy monitoring of DOC changes, and reception of high biomass yield [7]. The DOC monitoring is necessary because the low level of DOC decreases the biomass yield and decreases the specific growth rate [8]. Additionally, during the growth of the microorganisms and increase of the biomass concentration, negative effects occur (e.g. the inhibition effect) when the biomass concentration reaches a critical level. Thereby in continuous bioprocesses it is necessary to keep the biomass concentration lower than the critical level and to prevent a significant decrease of DOC by e.g. dosing the substrate in portions.

Many biological phenomena involve thresholds, bursting rhythm models in e.g. medicine, biology, pharmacokinetics and frequency modulated systems, that exhibit impulsive effects. Thus impulsive differential equations appear as a natural description of observed evolution phenomena resulting from several real world problems [9]. Many papers have introduced impulsive differential equations in population dynamics and have obtained interesting results [10–13]. Research on the chemostat model with impulsive perturbations was undertaken by Sun and Chen [14]. Tang and Chen introduced a Lotka-Voterra model with state-dependent impulsion and analyzed the existence and stability of the positive period-1 solution [15]. Jiang et al. and Smith have studied the state-dependent models with impulsive state control, where the model has a first integral, and obtained the complete expression

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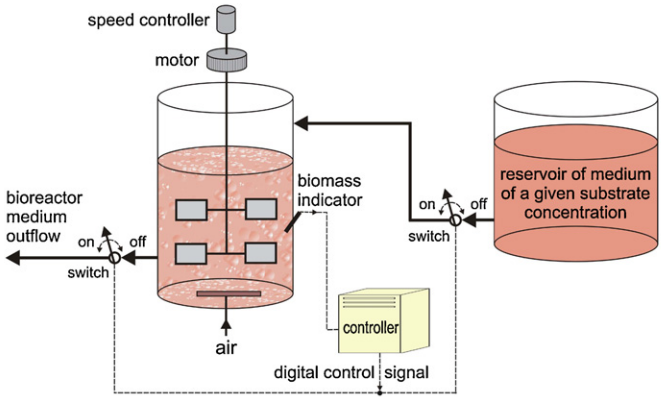

Fig. 1. Schematic diagram of the analyzed process.

of the periodic solution period [16,17]. Jiang et al. [18], Zeng et al. [19] and Guo and Chen [20,21] have also discussed some models which have no explicit solution, by applying the Poincare principle and Poincare-Bendixson of the impulsive differential equation.

In this paper, we consider a microorganism continuous culture system. The sketch map of the apparatus can be seen in Fig. 1. The apparatus includes an optical sensing device which continuously monitors the biomass concentration in the bioreactor medium and two switches controlled by a computer. When the biomass concentration is lower than the set level, the switches are closed. In this case the biomass increases by consuming the substrate. Once the biomass concentration reaches the set level, the two switches are opened, part of the medium containing biomass and substrate is discharged from the bioreactor, and the other part of the medium of the given substrate concentration is input. The rest of this paper is organized as follows. In Section 2 we introduce a continuous culture model with sigmoid biomass yield and impulsive state feedback control. In Section 3, we obtain the conditions for the existence of positive period-1 solution by using the analytical method. We also present the complete expression of the period-1 solution period. In addition, we show the non-existence of a positive period-2 solution. Following in Section 4, we analyze the stability of the positive period-1 solutions by analogue of the Poincare criterion. In Section 5, we provide numerical simulations to verify the theoretical results, such as the existence of period-1 solution and discuss the biochemical essence. Moreover, in Section 5 the bioprocess optimization is presented. Finally in Section 6 we present the conclusions.

2. Model formulation and preliminaries

In this research, an extended Monod kinetics model considering the existence of a critical inhibitor concentration above which cells cannot grow is assumed [22–24]. If the substrate is the inhibitor, the kinetics can be modelled as

$$\mu(S)=\frac{\mu_m S}{K_S+S}\left(1-\frac{S}{S_{\max}}\right)$$

which holds for all $0\le S\le S_{\max}$, where μ_m is the coefficient of the growth rate, $S_{\max}$ is the critical inhibitor concentration. If the substrate inhibition does not occur, the Monod's model is obtained with $\mu_m=\mu_{\max}$.

Denote $S^*=\sqrt{K_S^2+K_S S_{\max}}$. Since

$$\mu'(S)=-\frac{\mu_m}{S_{\max}}\,\frac{S^2+2K_S S-K_S S_{\max}}{(K_S+S)^2},$$

then $\mu'(S)>0$ for $0<S<S^*$ and $\mu'(S)<0$ for $S>S^*$. Therefore, $\mu(S)$ achieves its maximum $\mu_{\max}=\mu(S^*)=\mu_m S^*(S_{\max}-S^*)/(K_S S_{\max}+S^* S_{\max})$ at $S=S^*$.

On the other hand, Crooke et al. showed that the biomass yield expression plays an important role for the generation of oscillatory behavior in continuous bioprocess models [25]. So we assume that the biomass yield can be approximated by sufficiently flexible to fit reality the sigmoid function, i.e.,

$$Y_{X/S}=\frac{1}{a+e^{-bS}},\tag{1}$$

where $a=1/Y_{X/S_{\max}}$, b is the coefficient of the biomass yield, which determines of the sigmoid function slope. For the selected known point $(S, Y_{X/S})$, it can be calculated as: $b=-\ln(Y_{X/S}^{-1}-Y_{X/S_{\max}}^{-1})/S$. Then the following mathematical model works for a single species growing in a continuously stirred homogeneous bioreactor where the substrate and microorganisms are added before cultivation is started [26]:

$$\begin{cases}\dfrac{dX}{dt}=\dfrac{\mu_m S}{K_S+S}\left(1-\dfrac{S}{S_{\max}}\right)X\\ \dfrac{dS}{dt}=-(a+e^{-bS})\dfrac{\mu_m S}{K_S+S}\left(1-\dfrac{S}{S_{\max}}\right)X\\ X(0^+)=X_0,\quad S(0^+)=S_0\end{cases}\tag{2}$$

where $X=X(t)$ and $S=S(t)$ denote the biomass concentration and the substrate concentration in the bioreactor medium at time t; X_0 and S_0 denote the initial biomass concentration and substrate concentration in the bioreactor medium; $a>1$, $b>0$ are the coefficients of the sigmoid biomass yield. In particular, when substrate concentration (S) is high, $Y_{X/S}=1/a=Y_{X/S_{\max}}$, and the biomass yield is constant.

According to the design ideas of the bioreactor, the biomass concentration should be controlled to a certain level. When the biomass concentration $X(t)$ in the bioreactor reaches the set level X_1 (where $0<X_1\le X_{\text{critical}}$ and X_{critical} is the critical level of biomass concentration in the bioreactor medium), then part of the medium containing biomass and substrate is discharged from the bioreactor, and the next portion of medium of a given substrate concentration is input impulsively. Therefore, system (2) can be modified as follows by introducing the impulsive state feedback control:

$$\begin{cases}\left.\begin{aligned}&\dfrac{dX}{dt}=\dfrac{\mu_m S}{K_S+S}\left(1-\dfrac{S}{S_{\max}}\right)X\\ &\dfrac{dS}{dt}=-(a+e^{-bS})\dfrac{\mu_m S}{K_S+S}\left(1-\dfrac{S}{S_{\max}}\right)X\end{aligned}\right\}\quad X<X_1\\ \left.\begin{aligned}&\Delta X=-W_f X\\ &\Delta S=W_f(S_F-S)\end{aligned}\right\}\quad X=X_1\\ X(0^+)=X_0,\quad S(0^+)=S_0\end{cases}\tag{3}$$

where S_F is the concentration of the feed substrate which is input impulsively, $0<W_f<1$ is the part of biomass which is removed from the bioreactor in each biomass oscillation cycle.

In the following, we mainly discuss the existence and stability of periodic solution of system (3).

3. The existence of positive periodic solution of system (3)

In this section, we will discuss the existence of periodic solution of system (3) by the analytic method. Before discussing the periodic solution of system (3), we should consider the qualitative characteristics of system (2). By (2) we have

$$\frac{dX}{dS}=-\frac{1}{a+e^{-bS}}.\tag{4}$$

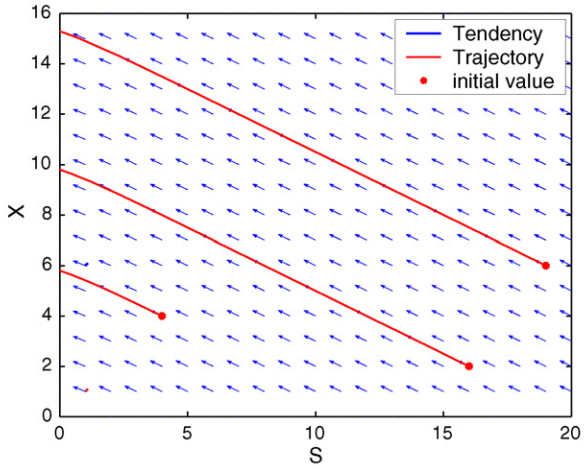

Fig. 2. Illustration of vector graph of system (2) when $Y_{X/S_{\max}} = 0.5[g/g]$ (i.e., $a = 2$), $b = 1$, $\mu_m = 0.3[1/h]$, $K_S = 2[g/l]$ and $S_{\max} = 100[g/l]$.

Hence we have

$$X(X_0, S_0, S) = \frac{\ln(ae^{bS_0}+1) - \ln(ae^{bS}+1)}{ab} + X_0. \tag{5}$$

The vector graph of system (2) can be seen in Fig. 2.

From Fig. 2 we know that in the bioprocess the substrate concentration S is decreasing and the biomass concentration X is increasing. If we do not adopt efficient control strategy, the microorganisms will finally consume the substrate and cause the whole bioprocess terminated. In order to not interrupt the culturing process and gain a stable output of the microorganism X, we need to discharge part of the bioreactor medium containing biomass and substrate, and add the medium of a given substrate concentration to the bioreactor when the biomass concentration reaches the set level X_1.

Before presenting the main results, we introduce the following notations which will be used throughout the content. Let $\lambda = abW_fX_1$, $B = e^{\lambda}$ and $C = aX_1/\lambda$. Then we define Γ_i, $i = 1, 2, 3$ as follows:

$$\Gamma_1(X_1) = C\ln\left(\frac{(a+1)B-1}{a}\right),$$
$$\Gamma_2(X_1) = C\ln\left(\frac{B}{1-W_f}\right),$$
$$\Gamma_3(X_1) = C\ln\left(\frac{1}{a}\left(\frac{B-1}{W_f}\right)^{W_f}\left(\frac{aB}{1-W_f}\right)^{1-W_f}\right).$$

Proposition 1.

(I) *If the set level X_1 and the feeding substrate concentration S_F satisfy the condition $S_F > \Gamma_1(X_1)$, then system* (3) *has a unique period-1 solution with initial condition $\frac{1}{ab}\ln(\frac{ae^{bS_0}+1}{a+1}) + X_0 \geq X_1$;*
(II) *If $\max\{\Gamma_2(X_1), \Gamma_3(X_1)\} < S_F \leq \Gamma_1(X_1)$, then system* (3) *has two period-1 solutions with initial condition $\frac{1}{ab}\ln(\frac{ae^{bS_0}+1}{a+1}) + X_0 \geq X_1$;*
(III) *If $\Gamma_3(X_1) > \Gamma_2(X_1)$ and the set level X_1 and the feeding substrate concentration S_F satisfy the condition $S_F = \Gamma_3(X_1)$, then system* (3) *has a unique period-1 solution with initial condition $\frac{1}{ab}\ln(\frac{ae^{bS_0}+1}{a+1}) + X_0 \geq X_1$,*
(IV) *For any X_1 and S_F, system* (3) *has no positive period-2 solution.*

Remark 1. From Proposition 1 it can be seen that the relation between X_1 and S_F determines the existence of the period-1 solution and the number of the period-1 solutions. For given set level X_1, the feeding substrate concentration S_F cannot be given too small, otherwise the substrate in the bioreactor will be consumed by microorganisms at some time, what causes the bioprocess interrupted. On the other hand, in order to obtain a stable output of the microorganisms and prevent negative effects occurring (e.g. the inhibition effect), the feeding substrate concentration S_F should not be given too high. Proposition 1 provides us a possibility to estimate a proper feeding substrate concentration, under which the system tends to a stable state.

Next we will give the complete expression of period of the positive period-1 solution. It follows from the first equation of the system (3) that

$$dt = \frac{S_{\max}(K_S + S(X))}{\mu_m S(X)(S_{\max} - S(X))X}dX \tag{6}$$

and $S(X)$ can be determined by the following equation:

$$S(X) = \frac{1}{b}\ln\left(\frac{1}{a}\left(\frac{Ae^{(1-W_f)\ln\bar{u}}+1}{Be^{ab(X-X_1)}} - 1\right)\right), \tag{7}$$

where $A = ae^{bW_fS_F}$, $B = e^{\lambda}$ and $\bar{u} > 1$ is the root of Eq. (A.5).

Then travelling along $S(X)$ from the point $P_0((1-W_f)X_1, \eta_0)$, with $t = t_{P_0}$ to the point $P_1(X_1, \eta_1)$, with $t = t_{P_1}$ in the counterclockwise direction yields the period T.

Proposition 2. *The period of the positive period-1 solution can be calculated by the following equation:*

$$T = \int_{(1-W_f)X_1}^{X_1} \frac{S_{\max}[K_S + S(X)]}{\mu_m X[S_{\max} - S(X)]S(X)}dX, \tag{8}$$

where $S(X)$ is determined in accordance with Eq. (7).

Remark 2. Let

$$\Phi(S) = \frac{S_{\max}(K_S + S)}{\mu_m(S_{\max} - S)S}.$$

Then we have

$$\Phi'(S) = \frac{S_{\max}}{\mu_m}\frac{S^2 + 2K_SS - K_SS_{\max}}{(S_{\max} - S)^2S^2}.$$

Denote $S^* = \sqrt{K_S^2 + K_SS_{\max}}$. Then $\Phi'(S) < 0$ for $0 < S < S^*$ and $\Phi'(S) > 0$ for $S > S^*$. Therefore, $\Phi(S)$ achieves its minimum at $S = S^*$. From Eq. (8), for any fixed X_1, T depends on the feeding substrate concentration S_F. By properly estimating the value of S_F we can ensure S close to S^* as much as possible and make T achieve its minimum.

4. Asymptotic behavior of positive period-1 solution

According to the definitions of orbitally asymptotically stable and enjoys the property of asymptotic phase [27], the following Proposition hold true.

Proposition 3.

(I) *If $S_F > \Gamma_1(X_1)$, the unique positive period-1 of system* (3) *is orbitally asymptotically stable enjoys the property of asymptotic phase;*
(II) *If $\max\{\Gamma_2(X_1), \Gamma_3(X_1)\} < S_F \leq \Gamma_1(X_1)$, then one positive period-1 solution of system* (3) *is orbitally asymptotically stable and enjoys the property of asymptotic phase, while the other one is not stable;*
(III) *If $S_F = \Gamma_3(X_1) > \Gamma_2(X_1)$, the stability of the positive period-1 solution of system* (3) *cannot be determined by* Lemma 1 (*see* Appendix A).

5. Numerical simulations and discussion

We have analyzed theoretically the feedback computer control of microorganism continuous culture process for pule dosage supply of substrates and removal of products. The results are new and significant, which not only provide the possibility of a check of system dynamic property including the existence and stability of period-1 solution for different microorganisms and several parameters, but also the possibility of a calculation of the period of the period-1 solution. Moreover, the results provide a possibility of making simulation of real process according to the mathematical models determined in the article. In order to verify the received results, we present the numerical simulations of systems (3). By changing one main parameter S_F and fixing all other parameters, we check the existence and stability of period-1 solution.

5.1. Numerical simulations

We assume in the following that $\mu_m = 0.3[1/h], K_S = 2[g/l], a = 2$ (i.e., $Y_{X/S_{\max}} = 1/2 = 0.5[g/g]$), $b = 1$ (i.e., for $S = 0.7[g/l]$, $Y_{X/S} = 1/(2+e^{-0.7}) \approx 0.4[g/g]$), $W_f = 0.1$, $S_0 = 2.62[g/l]$, $X_0 = 1.62[g/l]$ and $S_{\max} = 100[g/l]$. By computing we have

$$\frac{1}{ab}\ln\left(\frac{ae^{bS_0}+1}{a+1}\right) + X_0 \approx 2.74[g/l].$$

From Fig. 3 it can be easily seen that no impulse occurs when $X_1 = 3[g/l] > 2.74[g/l]$.

Next, we set $X_1 = 1.8[g/l]$. Then

$$\Gamma_1(1.8) \approx 5[g/l], \quad \Gamma_2(1.8) \approx 4.65[g/l], \quad \Gamma_3(1.8) \approx 4.96[g/l].$$

Firstly, according to point (I) of Proposition 1, we set $S_F = 6[g/l] > \Gamma_1$. In this case there exists a unique period-1 solution. The time series and phase diagram are presented in Fig. 4. From Fig. 4, it can be seen that the trajectory is the period-1 solution with $T \approx 0.64[h]$ and the oscillations of $S(t)$ in the range $[2.24[g/l], 2.62[g/l]]$.

If we select only one biomass oscillation cycle, for example the biomass oscillation cycle between $7.1[h]$ and $7.8[h]$, the changes of $S(t)$, $X(t)$, $\mu(t)$, $Y_{X/S}(t)$ and $\mu(t)X(t)$ are shown in Fig. 5. From Fig. 5 it can be seen that in the biomass oscillation cycle S decreases and X increases. Since $2.24\,[g/l] \le S(t) \le 2.63\,[g/l] < 10.2\,[g/l] = S^*$, then $\mu'(t) = \mu'(S)S'(t) < 0$, thus $\mu(t)$ decreases. $Y_{X/S}$ decreases too because $Y'_{X/S}(t) < 0$. As far as $P(t) = \mu(t)X(t)$, according to Fig. 5, $P(t)$ increases and reaches maximum at the end of biomass oscillation cycle.

Secondly, according to point (II) of Proposition 1, we set $S_F = \frac{\max\{\Gamma_2,\Gamma_3\}+\Gamma_1}{2} = 4.98\,[g/l]$. In this case there exist two period-1 solutions. The portrait phases with different initial points are presented in Fig. 6. From Fig. 6 (a), it can be seen that the trajectory tends to period-1 solution from the right side. Fig. 6 (b) illustrate the stable period-1 solution with $T \approx 1.33[h]$ calculated by Eq. (8) and the oscillations of $S(t)$ in the range $[0.51\,[g/l], 0.96\,[g/l]]$. Fig. 6 (c) illustrate the unstable period-1 solution with $T \approx 2.7[h]$ calculated by Eq. (8) and the oscillations of $S(t)$ in the range $[0.1\,[g/l], 0.6\,[g/l]]$.

Thirdly, we set $S_F = 4.6\,[g/l] < \Gamma_2$. In this case there does not exist period-1 solution. The dosaged substrate is used up after several biomass oscillation cycles what causes the bioprocess interruption, as shown in Fig. 7.

Till then, the numerical simulations are consistent with the theoretical results obtained and presented in the 3rd section. A potential application area of the proposed model with feedback control is the commercial and industrial biomass production. In such a production system the microorganisms always keep the suitable growth rate and the biomass concentration should be controlled to a given set level for which the dissolved oxygen concentration is considered as optimal. In this way, we can determine the rationality of the microorganism feedback concentration according to the conditions which stabilize the periodic solution. In other words, if we have the proper microorganism feedback concentration, we can achieve a stable output for a continuous culture system with feedback control in a determined production environment situation. Furthermore, we obtained the feeding period for a regularly continuous culture system, which can be useful in carrying out the bioprocesses and can also be

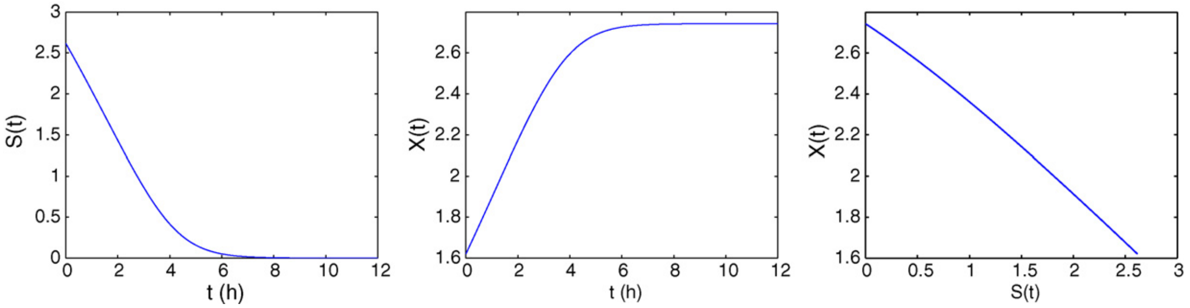

Fig. 3. Time series and portrait phase of system (3) when $X_0 = 1.62[g/l]$, $S_0 = 2.62[g/l]$ and $X_1 = 3[g/l]$.

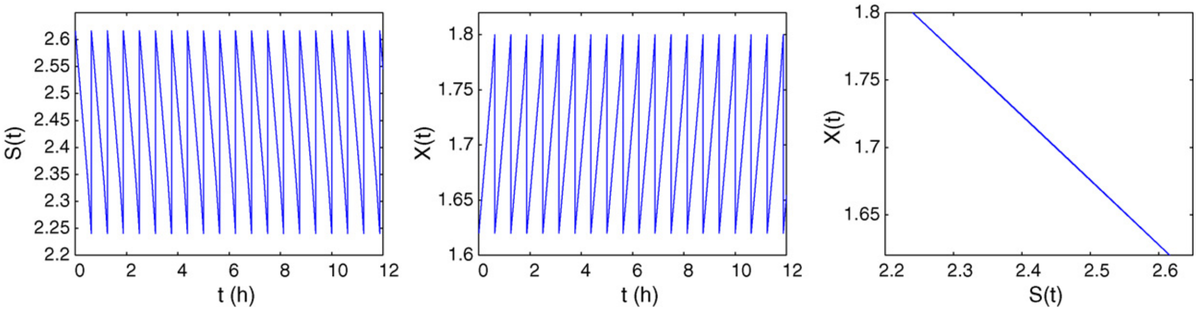

Fig. 4. Time series and portrait phase of system (3) when $X_0 = 1.62[g/l]$, $S_0 = 2.62[g/l]$ and $X_1 = 1.8[g/l]$ and $S_F = 6[g/l]$.

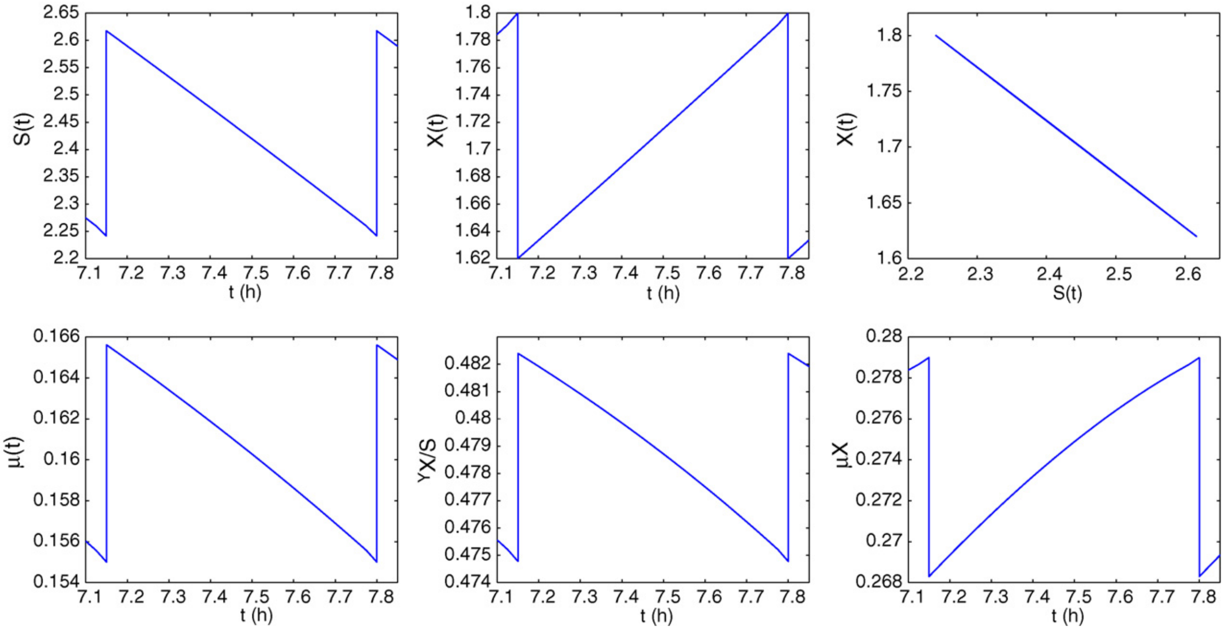

Fig. 5. The changes of $S(t)$, $X(t)$, $\mu(t)$, $Y_{X/S}(t)$ and $\mu(t)X(t)$ in one selected biomass oscillation cycle.

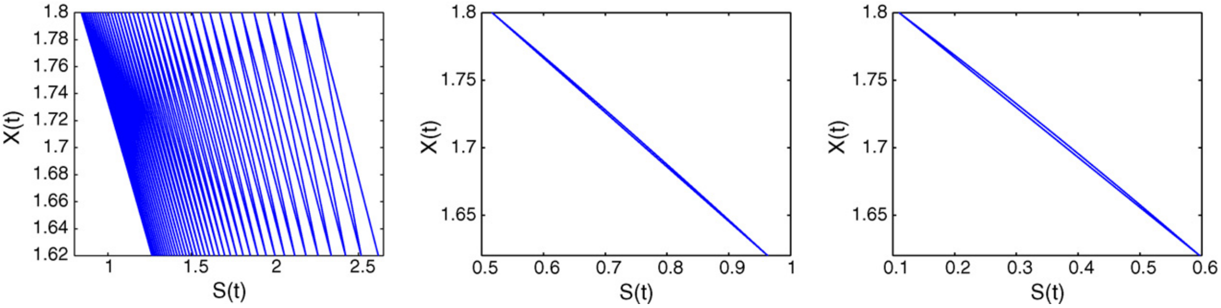

Fig. 6. The portrait phases of system (3) starting from different initial points when $X_1 = 1.8$ [g/l] and $S_F = 4.98$ [g/l]: (a) $X_0 = 1.62$ [g/l], $S_0 = 2.62$ [g/l]; (b) $X_0 = 1.62$ [g/l], $S_0 = 0.96$ [g/l]; (c) $X_0 = 1.62$ [g/l], $S_0 = 0.6$ [g/l].

utilized for example to check whether all measuring instruments (like the photoelectricity system or the annunciator) are working well.

5.2. Optimization of the bioprocess

In the 3rd section, it is shown that if the set level X_1 and the feeding substrate concentration S_F satisfy the constraint $S_F > \Gamma_1(X_1)$, then the system (3) has a unique period-1 solution, which is orbitally asymptotically stable enjoys the property of asymptotic phase. Next, we will discuss aspects of the bioprocess optimization.

5.2.1. The optimization criterion

The optimization consists in finding of the maximum of the proposed objective function (P_{out}) under the constraints (see Appendix (a)–(c)) in the steady state, i.e.,

$$P_{\text{out}} \to \max,$$

where

$$P_{\text{out}}(W_f, X_1, S_F) = \frac{W_f X_1}{T}. \tag{9}$$

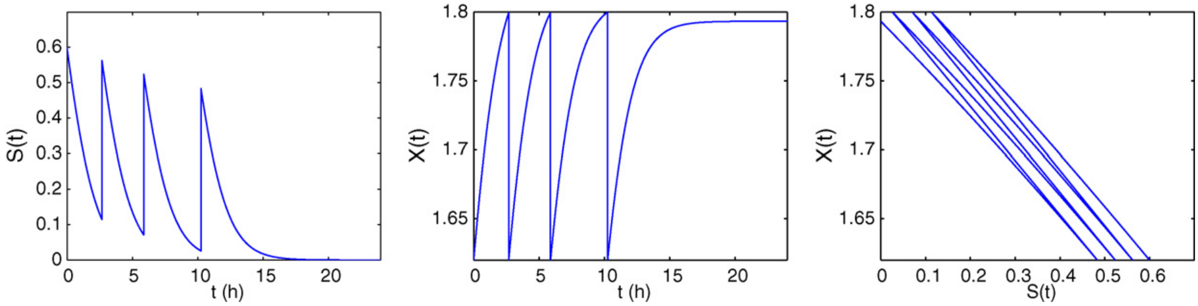

Fig. 7. Time series and portrait phase of system (3) when $X_0 = 1.62$ [g/l], $S_0 = 0.6$ [g/l], $X_1 = 1.8$ [g/l] and $S_F = 4.6$ [g/l].

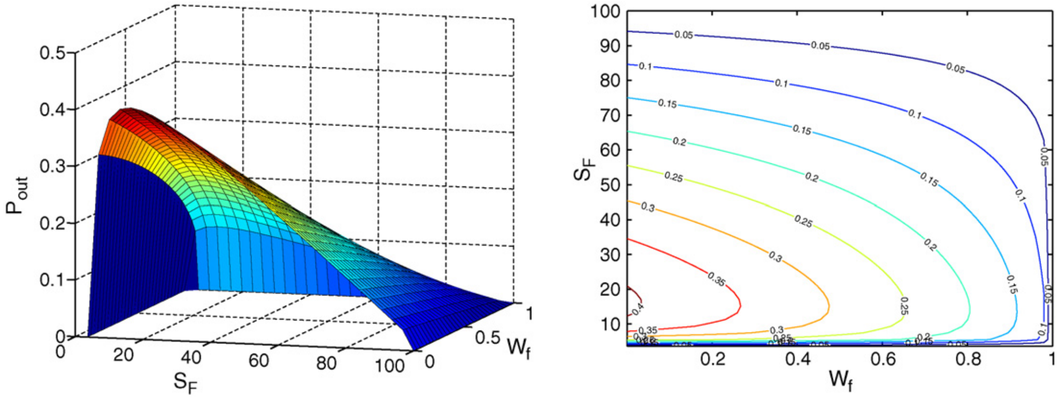

Fig. 8. The dependence of P_{out} on W_f and S_F for $Y_{x/S_{\max}} = 0.5[g/g]$ (i.e., $a = 2$), $\mu_m = 0.3[1/h]$, $S_{\max} = 100\,[g/l]$ and $X_1 = 1.8\,[g/l]$.

P_{out}—the biomass productivity (i.e., the productivity of the received biomass), and the unit of it is $[\frac{g/l}{h}] = [\frac{g}{lh}]$;
T-the period of the biomass oscillation.

5.2.2. Determination of the optimal result

As indicated at the beginning of the Section 2, if the growth kinetics is in accordance with the extended Monod's model, then the maximum growth rate is reached for $S = \sqrt{K_S^2 + K_S S_{\max}}$. For such range of the substrate concentration the biomass yield is practically constant, i.e., $Y_{x/S} = Y_{x/S_{\max}} = 1/a$. Then according to Eq. (8), the biomass oscillation period in the steady state is

$$T(W_f, X_1, S_F) = \frac{S_{\max}}{\mu_m}\left[\frac{K_S}{S_{\max} S_F}\ln\left(\frac{S_F - a(1-W_f)X_1}{S_F - aX_1}\right) + \frac{S_{\max} + K_S}{S_{\max}(S_F - S_{\max})}\ln\left(\frac{S_{\max} - S_F + aX_1}{S_{\max} - S_F + a(1-W_f)X_1}\right) - \frac{S_F + K_S}{S_F(S_{\max} - S_F)}\ln(1 - W_f)\right].$$

It is obvious that $T(0, X_1, S_F) = 0$. The objective function can be formulated as

$$P_{\text{out}}(W_f, X_1, S_F) = \frac{W_f X_1}{T(W_f, X_1, S_F)}. \quad (10)$$

The dependence of P_{out} on W_f and S_F for given X_1 is shown in Fig. 8.

To optimize the bioprocess we should find the maximum of the objective function (10) under the constraints $0 < W_f \le W_{f\max} < 1$, $0 < X_1 \le X_{\text{critical}}$ and $2aX_1 \le S_F \le S_{F_{\text{critical}}}$.

Let $\Psi(W_f, X_1, S_F) = T(W_f, X_1, S_F)/W_f$. Take the first partial derivative of $\Psi(W_f, X_1, S_F)$ with respect to W_f, we have

$$\frac{\partial \Psi(W_f, X_1, S_F)}{\partial W_f} = \frac{W_f \frac{\partial T}{\partial W_f} - T}{W_f^2}.$$

Denote

$$\Phi(W_f, X_1, S_F) = W_f \frac{\partial T}{\partial W_f} - T.$$

Then we have $\Phi(0, X_1, S_F) = 0$. Since

$$\frac{\partial \Phi(W_f, X_1, S_F)}{\partial W_f} = \frac{S_{\max} W_f}{\mu_m}\left[\frac{S_F + K_S}{S_F(S_{\max} - S_F)}\frac{1}{(1-W_f)^2} - \frac{K_S}{S_{\max} S_F}\frac{(aX_1)^2}{[S_F - a(1-W_f)X_1]^2} - \frac{S_{\max} + K_S}{S_{\max}(S_{\max} - S_F)}\frac{(aX_1)^2}{[S_{\max} - S_F + a(1-W_f)X_1]^2}\right].$$

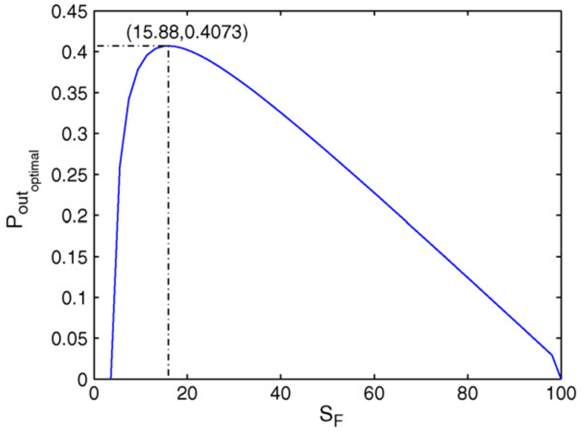

Fig. 9. The dependence of $P_{\text{out}_{\text{optimal}}}$ on S_F for $Y_{x/S_{\max}} = 0.5[g/g]$ (*i.e.*,$a = 2$), $\mu_m = 0.3[1/h]$, $S_{\max} = 100\,[g/l]$ and $X_1 = 1.8\,[g/l]$.

It can be easily shown that $\partial\Phi(W_f, X_1, S_F)/\partial W_f \ge 0$ for $2aX_1 \le S_F \le S_{\max}$. Then we have $\Phi(W_f, X_1, S_F) \ge \Phi(0, X_1, S_F) = 0$, which implies that $\partial\Psi/\partial W_f \ge 0$ or $\partial P_{\text{out}}/\partial W_f \le 0$. Hence, the objective function achieves its maximum when $W_f \to 0$.

Proposition 4. *For given X_1 and S_F, there is*

$$P_{\text{out}_{\text{optimal}}} = \lim_{W_f \to 0} P_{\text{out}}(W_f, X_1, S_F) = \frac{\mu_m X_1}{\Lambda(X_1, S_F)}, \quad (11)$$

where

$$\Lambda(X_1, S_F) = \frac{K_S}{S_F}\frac{aX_1}{S_F - aX_1} + \frac{S_{\max} + K_S}{S_F - S_{\max}}\frac{aX_1}{S_{\max} - S_F + aX_1} + \frac{S_{\max}(S_F + K_S)}{S_F(S_{\max} - S_F)}$$

and $X_1 \le X_{\text{critical}}$.

The maximum of $P_{\text{out}_{\text{optimal}}}$ can be achieved by finding the minimum of $\Lambda(X_1, S_F)$ with respect to S_F. Take the first partial derivative of $\Lambda(X_1, S_F)$ with respect to S_F and let $\Lambda'(X_1, S_F) = 0$, we have $S_F^* = aX_1 - K_S + S^*$ and

$$\Lambda_{\min} = \frac{S^* S_{\max}}{(S_{\max} + K_S - S^*)(S^* - K_S)},$$

where $S^* = \sqrt{K_S^2 + K_S S_{\max}}$. Therefore, for given X_1, the maximal biomass productivity is

$$P_{\text{out}_{\text{optimal}}} = \frac{\mu_m(S_{\max} + K_S - S^*)(S^* - K_S)}{S^* S_{\max}} X_1 = \mu(S^* - K_S)X_1.$$

Fig. 9 displays the dependence of $P_{\text{out}_{\text{optimal}}}$ on S_F for given X_1. From Fig. 9 it can be seen that the maximal $P_{\text{out}_{\text{optimal}}}$ is achieved at $S_F = 15.88\,[g/l]$, and the maximum is $P_{\text{out}_{\text{optimal}}} = 0.4073[g/lh]$.

Proposition 5. *For given X_1, when the substrate inhibition does not occur (i.e., $S^* = \sqrt{K_S^2 + K_S S_{\max}} \gg K_S$ for $S_{\max} \to \infty$), there is $\mu_{\max} = \mu_m$* and

$$P_{\text{out}_{\text{optimal}}} = \mu(S^* - K_S)X_1 \to \mu_{\max}X_1 = \mu_m X_1.$$

6. Conclusions

The article put forward a new model of a continuous bioprocess with impulsive substrate dosing and impulsive medium removing. To ensure the models universality, the flexible sigmoid function was proposed to describe the dependence of the biomass yield on the substrate concentration. Moreover it was demonstrated how to establish coefficients for this function. According to Proposition 1, it was shown that the stability of the bioprocess (i.e., the existence of the positive period-1 solution), depends on the biomass yield, and does not depend on the microorganisms' growth rate. According to Proposition 2 it was shown that the period of the positive period-1 solution, depends both on the biomass yield and the microorganisms' growth rate. The article also cited the following bioprocess parameter changes in the selected biomass oscillation cycle: (a) the substrate concentration (S), (b) the biomass concentration (X), (c) the biomass yield ($Y_{X/S}$), (d) the specific growth rate (μ), and (e) the biomass productivity (defined as $P_{in} = \mu X$). In addition, the complete expression of the biomass oscillations period was given, by which the continuous culture model with an impulsive state feedback control can be altered to a model with periodic control. Lastly, it was shown that during the biomass productivity optimization, the impulsive bioprocess strived for a continuous bioprocess (Proposition 4). In this case the maximum biomass productivity was received, but the possibility of a synchronization of the bioprocesses was lost. Analytical results based on a formal mathematical analysis of the bioreactor dynamics offer the possibility of establishing general and more systematic operation and control strategies based on the counteraction of the mechanisms underlying the adverse effects of bioreactor dynamics.

Appendix A.

Before introducing the main results, we give the definition of period-1 solution, periodic-2 solution and Analogue of Poincare criterion first. Assume the closed curve is the orbit of the periodic solution $(\xi(t), \eta(t))$ of system (3).

Definition 1. [27] $(\xi(t), \eta(t))$ is said to be period-1 solution if in a minimum cycle time, there is one impulse effect. Similarly, $(\xi(t), \eta(t))$ is said to be period-2 solution if in a minimum cycle time, there are two impulse effects.

Definition 2. [27] Γ is said to be orbitally stable, if for any $\varepsilon > 0$, there exists $\delta > 0$, with the proviso that every solution $(\xi(t), \eta(t))$ of system (3) whose distance from Γ is less than δ at $t = t_0$, will remain within a distance less than ε from Γ for all $t \geq t_0$. Such a Γ is said to be orbitally asymptotically stable if, in addition, the distance of $(\xi(t), \eta(t))$ from Γ tends to zero as $t \to \infty$. Moreover, if there exist positive constants α, β and a real constant h such that $\rho((\xi(t), \eta(t), \Gamma) < \alpha e^{-\beta t})$ for $t > t_0$, then Γ is said to be orbitally asymptotically stable and enjoys the property of asymptotic phase.

Lemma 1. [27] *(Analogue of Poincare' Criterion) The T-periodic solution $X = \xi(t), S = \eta(t)$ of system*

$$\begin{cases} \dfrac{dS}{dt} = P(S, X),\ \dfrac{dX}{dt} = R(S, X), & \text{if} \quad \phi(S, X) \neq 0 \\ \Delta S = \alpha(S, X),\ \Delta X = \beta(S, X), & \textit{if} \quad \phi(S, X) = 0 \end{cases} \tag{A.1}$$

is orbitally asymptotically stable and enjoys the property of asymptotic phase if the multiplier μ_2 satisfies the condition $|\mu_2| < 1$; and the T-periodic solution $X = \xi(t), S = \eta(t)$ is unstable if $|\mu_2| > 1$. Where

$$\mu_2 = \prod_{k=1}^{q} \Delta_k \exp\left(\int_0^T \left[\frac{\partial P}{\partial S}(\xi(t), \eta(t)) + \frac{\partial R}{\partial X}(\xi(t), \eta(t)) \right] \mathrm{d}t \right),$$

$$\Delta_k = \frac{P_+ \left((\partial\beta/\partial X)(\partial\phi/\partial S) - (\partial\beta/\partial S)(\partial\phi/\partial X) + (\partial\phi/\partial S) \right)}{P(\partial\phi/\partial S) + R(\partial\phi/\partial X)} + \frac{R_+ \left((\partial\alpha/\partial S)(\partial\phi/\partial X) - (\partial\alpha/\partial X)(\partial\phi/\partial S) + (\partial\phi/\partial X) \right)}{P(\partial\phi/\partial S) + R(\partial\phi/\partial X)},$$

$P_+ = P(\xi(\tau_k^+), \eta(\tau_k^+))$, $R_+ = R(\xi(\tau_k^+), \eta(\tau_k^+))$ and $P, R, \partial\alpha/\partial S, \partial\alpha/\partial X, \partial\beta/\partial S, \partial\beta/\partial X, \partial\phi/\partial S, \partial\phi/\partial X$ are calculated at the point $(\xi(\tau_k), \eta(\tau_k))$.

Let $X = \xi(t)$, $S = \eta(t)$ be a T- period-1 solution of system (3). Denote $\xi_0 = \xi(t_0^+)$, $\eta_0 = \eta(t_0^+)$, $\xi_1 = \xi(t_0 + T) = X_1$, $\eta_1 = \eta(t_0 + T)$, $\xi_1^+ = \xi((t_0 + T)^+)$ and $\eta_1^+ = \eta((t_0 + T)^+)$. Then from the T- periodicity, we have

$$\xi_1^+ = \xi((t_0 + T)^+) = \xi(t_0^+) = \xi_0, \quad \eta_1^+ = \eta((t_0 + T)^+) = \eta(t_0^+) = \eta_0.$$

Thus

$$\begin{aligned} \xi_0 - \xi_1 &= \xi((t_0 + T)^+) - \xi(t_0 + T) = -W_f X_1, \\ \eta_0 - \eta_1 &= \eta((t_0 + T)^+) - \eta(t_0 + T) = W_f(S_F - \eta_1). \end{aligned}$$

i.e.,

$$\xi_0 = (1 - W_f)X_1, \quad \eta_0 = W_f S_F + (1 - W_f)\eta_1. \tag{A.2}$$

Similarly, let $X = \bar{\xi}(t)$, $S = \bar{\eta}(t)$ be a period-2 solution of system (3). Denote $\bar{\xi}_0 = \bar{\xi}(t_0^+)$, $\bar{\eta}_0 = \bar{\eta}(t_0^+)$, $t_0 < t_1 < t_0 + T$, $\bar{\xi}_1 = \bar{\xi}(t_1) = X_1$, $\bar{\eta}_1 = \bar{\eta}(t_1)$, $\bar{\xi}_1^+ = \bar{\xi}(t_1^+)$, $\bar{\eta}_1^+ = \bar{\eta}(t_1^+)$, $\bar{\xi}_2 = \bar{\xi}(t_0 + T) = X_1$, $\bar{\eta}_2 = \bar{\eta}(t_0 + T)$, $\bar{\xi}_2^+ = \bar{\xi}((t_0 + T)^+)$ and $\bar{\eta}_2^+ = \bar{\eta}((t_0 + T)^+)$. Then from the T-periodicity, we have

$$\bar{\xi}_2^+ = \bar{\xi}((t_0 + T)^+) = \bar{\xi}(t_0^+) = \bar{\xi}_0, \quad \bar{\eta}_2^+ = \bar{\eta}((t_0 + T)^+) = \bar{\eta}(t_0^+) = \bar{\eta}_0.$$

Thus we have

$$\begin{aligned} \bar{\xi}_0 &= (1 - W_f)X_1, \quad \bar{\eta}_0 = W_f S_F + (1 - W_f)\bar{\eta}_2, \\ \bar{\xi}_1^+ &= (1 - W_f)X_1, \quad \bar{\eta}_1^+ = W_f S_F + (1 - W_f)\bar{\eta}_1. \end{aligned} \tag{A.3}$$

A.1. The proof of Proposition 1

Proof. By Eq. (5) we have

$$X(t) = \frac{1}{ab} \ln\left(\frac{ae^{bS_0} + 1}{ae^{bS(t)} + 1} \right) + X_0.$$

If the impulsive effect happens, the condition

$$\frac{1}{ab} \ln\left(\frac{ae^{bS_0} + 1}{a + 1} \right) + X_0 \geq X_1 \tag{A.4}$$

is necessary.

For $t \in (t_0, t_0 + T]$, the solution $S = \xi(t), X = \eta(t)$ of system (3) satisfies that

$$\xi(t) - \xi_0 = \frac{1}{ab} \ln(ae^{b\eta_0} + 1) - \frac{1}{ab} \ln(ae^{b\eta(t)} + 1).$$

In particular, for $t = t_0 + T$, we have

$$\xi(t_0 + T) - \xi_0 = \frac{1}{ab} \ln(ae^{b\eta_0} + 1) - \frac{1}{ab} \ln(ae^{b\eta(t_0 + T)} + 1),$$

or

$$X_1 - \xi_0 = \frac{1}{ab} \ln(ae^{b\eta_0} + 1) - \frac{1}{ab} \ln(ae^{b\eta_1} + 1).$$

In view of (A.2) we have

$$W_f X_1 = \frac{1}{ab} \ln\left(\frac{ae^{b\eta_0} + 1}{ae^{b\eta_1} + 1} \right) = \frac{1}{ab} \ln\left(\frac{ae^{b(W_f S_F + (1 - W_f)\eta_1)} + 1}{ae^{b\eta_1} + 1} \right)$$

which can be rewritten as

$$e^{abW_fX_1}(ae^{b\eta_1}+1)-ae^{W_fbS_F}e^{b(1-W_f)\eta_1}=1.$$

Denote $\lambda=abW_fX_1,\ A=ae^{bW_fS_F},\ B=e^{\lambda},\ C=aX_1/\lambda,\ u=e^{b\eta_1}$. Since $\eta_1>0$ is equivalent to $u>1$, then there exists a positive period-1 solution if and only if the following equation

$$aBu-Au^{1-W_f}+B-1=0 \tag{A.5}$$

exists a root which is larger than 1. Let $f(u)=aBu-Au^{1-W_f}+B-1$. Then we have

$$f(1)=aB-A+B-1,$$
$$\lim_{u\to\infty}f(u)=\lim_{u\to\infty}u^{1-W_f}(aBu^{W_f}-A)+B-1=+\infty.$$

To take the first derivative of $f(u)$ with respect to u, we have

$$f'(u)=aB-(1-W_f)Au^{-W_f}=0,$$

by solving the equation we have

$$u^*=\sqrt[W_f]{\frac{(1-W_f)A}{aB}}.$$

Case 1 $f(1)<0$, i.e.,

$$S_F>C\ln\left(\frac{(a+1)B-1}{a}\right)=\Gamma_1(X_1) \tag{A.6}$$

As shown in Fig. A.1a).

By the intermediate value property of function there exists a unique $u_1>1$ such that $f(u_1)=0$.

Case 2 $f(1)\geq 0$, i.e.,

$$S_F\leq C\ln\left(\frac{(a+1)B-1}{a}\right)=\Gamma_1(X_1) \tag{A.7}$$

In this case, there exists a root of Eq. (A.5) which is larger than 1 if and only if $u^*>1, f(u^*)\leq 0$, as shown in Fig. A.1(b).

By $u^*>1$, we have

$$S_F>C\ln\left(\frac{B}{1-W_f}\right)=\Gamma_2(X_1) \tag{A.8}$$

Since $f(u^*)=(\frac{(1-W_f)A}{aB})^{(1/W_f-1)}(-W_fA)+B-1$, then $f(u^*)\leq 0$ if and only if

$$A\geq\left(\frac{B-1}{W_f}\right)^{W_f}\left(\frac{aB}{1-W_f}\right)^{1-W_f},$$

i.e.,

$$S_F\geq C\ln\left(\frac{1}{a}\left(\frac{B-1}{W_f}\right)^{W_f}\left(\frac{aB}{1-W_f}\right)^{1-W_f}\right)=\Gamma_3(X_1).$$

In a word, for given critical level X_1 and the feeding substrate concentration S_F, we have the following conclusions:

(I) If $S_F>\Gamma_1(X_1)$, there exists a unique root $u_1>\max\{1,u^*\}$ of Eq. (A.2), in this case there exists a unique positive period-1 solution of system (3);
(II) If $\max\{\Gamma_2(X_1),\Gamma_3(X_1)\}<S_F\leq\Gamma_1(X_1)$, there exists two roots $1<u_1<u^*<u_2$ of Eq. (A.2), in this case there exist two positive period-1 solution of system (3);
(III) If $S_F=\Gamma_3(X_1)>\Gamma_2(X_1)$, there exists a unique root $u_3=u^*$ of Eq. (A.2), in this case there exists a unique positive period-1 solution of system (3).

Next, we prove that system (3) has no period-2 solution. Suppose that system (3) has a positive period-2 solution, which is denoted by $(\bar{\xi}(t),\bar{\eta}(t))$. Then for $t\in(t_0,t_1]$, by Eq. (5) we have

$$\bar{\xi}(t)-\bar{\xi}_0=\frac{1}{ab}[\ln(ae^{b\bar{\eta}_0}+1)-\ln(ae^{b\bar{\eta}(t)}+1)]. \tag{A.9}$$

For $t\in(t_1,t_2]$, we have

$$\bar{\xi}(t)-\bar{\xi}_1^+=\frac{1}{ab}[\ln(ae^{b\bar{\eta}_1^+}+1)-\ln(ae^{b\bar{\eta}(t)}+1)]. \tag{A.10}$$

Substitute $t=t_1$ into Eq. (A.9), we have

$$\bar{\xi}_1-\bar{\xi}_0=\frac{1}{ab}[\ln(ae^{b\bar{\eta}_0}+1)-\ln(ae^{b\bar{\eta}_1}+1)]. \tag{A.11}$$

Substitute $t=t_0+T$ into Eq. (A.9), we have

$$\bar{\xi}_2-\bar{\xi}_1^+=\frac{1}{ab}[\ln(ae^{b\bar{\eta}_1^+}+1)-\ln(ae^{b\bar{\eta}_2}+1)]. \tag{A.12}$$

Subtract Eq. (A.11) from Eq. (A.12) we have

$$(\bar{\xi}_2-\bar{\xi}_1)+(\bar{\xi}_0-\bar{\xi}_1^+)=\frac{1}{ab}\ln(\frac{(ae^{b\bar{\eta}_1}+1)(ae^{b\bar{\eta}_1^+}+1)}{(ae^{b\bar{\eta}_0}+1)(ae^{b\bar{\eta}_2}+1)})$$

By the definition of period-2 solution, we have $\bar{\xi}_2=\bar{\xi}_1,\ \bar{\xi}_0=\bar{\xi}_1^+$, $\bar{\eta}_0=W_fS_F+(1-W_f)\bar{\eta}_2,\ \bar{\eta}_1^+=W_fS_F+(1-W_f)\bar{\eta}_1$ and $\bar{\eta}_1\neq\bar{\eta}_2$. So we have

$$\frac{ae^{b\bar{\eta}_1}+1}{ae^{b\bar{\eta}_2}+1}=\frac{ae^{b(W_fS_F+(1-W_f)\eta_2)}+1}{ae^{b(W_fS_F+(1-W_f)\eta_1)}+1} \tag{A.13}$$

Denote $x=e^{b\bar{\eta}_1}, y=e^{\bar{\eta}_2}$. Then Eq. (A.13) is equivalent to

$$(ax+1)(Ax^{1-W_f}+1)=(ay+1)(Ay^{1-W_f}+1).$$

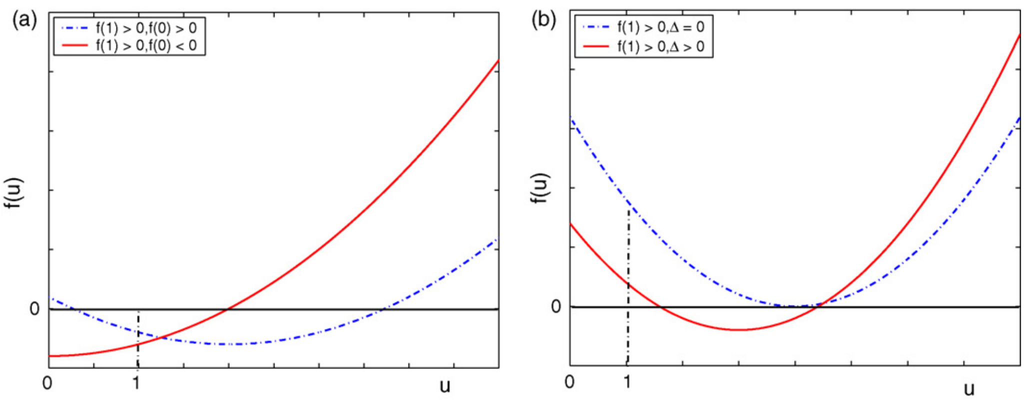

Fig. A.1. The illustration of function $f(u)$ for case a) $f(1)<0$; case (b) $f(1)>0$.

Let $P(u) = (au + 1)(Au^{1-W_f} + 1)$. Then

$$P'(u) = a(Au^{1-W_f} + 1) + A(1 - W_f)u^{-W_f}(au + 1) > 0.$$

So $P(x) = P(y)$ if and only if $x = y$, i.e., $\bar{\eta}_1 = \bar{\eta}_2$, which leads to a contradiction. Therefore, there do not exist positive period-2 solution for the system (3). This completes the proof of Proposition 1. □

A.2. The proof of Proposition 3

Proof. According to Lemma 1 we calculate the multiplies of system (3) in variations corresponding to the T-periodic solution $(\xi(t), \eta(t))$. Denote $A(\xi_0, \eta_0)$, $B(\xi_1, \eta_1)$, where $\xi_0 = (1 - W_f)X_1$, $\xi_1 = X_1$, $\eta_0 = W_f S_F + (1 - W_f)\eta_1$. In system (3), since

$$P(S, X) = -(a + e^{-bS})\frac{\mu_m S}{K_S + S}\left(1 - \frac{S}{S_{\max}}\right)X,\ R(S, X) = \frac{\mu_m S}{K_S + S}\left(1 - \frac{S}{S_{\max}}\right)X,$$
$$\alpha(S, X) = W_f(S_F - S),\ \beta(S, X) = -W_f X,\ \phi(S, X) = X - X_1,$$

then we have

$$\frac{\partial P}{\partial S} = \frac{\mu_m b}{S_{\max}}\frac{e^{-bS}S(S_{\max} - S)}{K_S + S}X - (a + e^{-bS})[\frac{\mu_m K_S}{S_{\max}}\frac{S_{\max} - S}{(K_S + S)^2} - \frac{\mu_m}{S_{\max}}\frac{S}{K_S + S}]X,$$
$$\frac{\partial R}{\partial X} = \frac{\mu_m}{S_{\max}}\frac{S(S_{\max} - S)}{K_S + S},\ \frac{\partial \alpha}{\partial S} = \frac{\partial \beta}{\partial X} = -W_f,\ \frac{\partial \alpha}{\partial X} = \frac{\partial \beta}{\partial S} = \frac{\partial \phi}{\partial S} = 0,\ \frac{\partial \phi}{\partial X} = 1.$$

Therefore

$$\begin{aligned}\Delta_1 &= \frac{P_+\left((\partial\beta/\partial X)(\partial\phi/\partial S) - (\partial\beta/\partial S)(\partial\phi/\partial X) + (\partial\phi/\partial S)\right)}{P(\partial\phi/\partial S) + R(\partial\phi/\partial X)}\\ &\quad + \frac{R_+\left((\partial\alpha/\partial S)(\partial\phi/\partial X) - (\partial\alpha/\partial X)(\partial\phi/\partial S) + (\partial\phi/\partial X)\right)}{P(\partial\phi/\partial S) + R(\partial\phi/\partial X)}\\ &= \frac{R_+(1 - W_f)}{R} = (1 - W_f)\frac{\xi_0}{\xi_1}\frac{\eta_0}{\eta_1}\frac{K_S + \eta_1}{K_S + \eta_0}\frac{S_{\max} - \eta_0}{S_{\max} - \eta_1},\\ \mu_2 &= \Delta_1 \exp\left(\int_0^T \left[\frac{\partial P}{\partial S}(\xi(t), \eta(t)) + \frac{\partial R}{\partial X}(\xi(t), \eta(t))\right] \mathrm{d}t\right)\\ &= \Delta_1 \exp\left(\int_0^T \frac{\mu_m}{S_{\max}}\frac{S(S_{\max} - S)}{K_S + S}\mathrm{d}t + \int_0^T \frac{\mu_m b}{S_{\max}}\frac{e^{-bS}S(S_{\max} - S)}{K_S + S}X\mathrm{d}t\right)\\ &\quad \cdot \exp\left(-\int_0^T (a + e^{-bS})\left[\frac{\mu_m K_S}{S_{\max}}\frac{S_{\max} - S}{(K_S + S)^2} - \frac{\mu_m}{S_{\max}}\frac{S}{K_S + S}\right]X\mathrm{d}t\right)\\ &= \Delta_1\frac{\xi_1}{\xi_0}\frac{\eta_1}{\eta_0}\frac{K_S + \eta_0}{K_S + \eta_1}\frac{a + e^{-b\eta_1}}{a + e^{-b\eta_0}}\frac{S_{\max} - \eta_1}{S_{\max} - \eta_0} = (1 - W_f)\frac{a + e^{-b\eta_1}}{a + e^{-b\eta_0}}\end{aligned}$$

Since $\eta_0 = W_f S_F + (1 - W_f)\eta_1$, then we have

$$\begin{aligned}\mu_2 &= (1 - W_f)\left(\frac{a + e^{-b\eta_1}}{a + e^{-b(W_f S_F + (1 - W_f)\eta_1)}}\right)\\ &= (1 - W_f)\left(\frac{ae^{b\eta_1} + 1}{ae^{b(W_f S_F + (1 - W_f)\eta_1)} + 1}\right)\left(\frac{e^{b(W_f S_F + (1 - W_f)\eta_1)}}{e^{b\eta_1}}\right)\\ &= (1 - W_f)\frac{1}{B}\frac{Au^{1-W_f}}{au} = \frac{(1 - W_f)A}{aB}\frac{1}{u^{W_f}}.\end{aligned} \tag{A.14}$$

(i) If $S_F > \Gamma_1(X_1)$, there exists a unique positive period-1 solution of system (3), in this case the unique root of Eq. (A.2) satisfies $u_1 > u^* = \sqrt[W_f]{\frac{(1 - W_f)A}{aB}}$, thus

$$\mu_2 = \frac{(1 - W_f)A}{aB}\frac{1}{u^{W_f}} < \frac{(1 - W_f)A}{aB}\left(\frac{1}{u^*}\right)^{W_f} = 1;$$

(ii) If $\max\{\Gamma_2(X_1), \Gamma_3(X_1)\} < S_F \le \Gamma_1(X_1)$, there exist two positive period-1 solutions of system (3), in this case, two roots of Eq. (A.2) satisfy $1 < u_1 < u^* < u_2$. For the period-1 solution corresponding to the root u_1, by Eq. (A.14) we have $\mu_2 > 1$; while for the period-1 solution corresponding to the root u_2, by Eq. (A.14) we have $\mu_2 < 1$;

(iii) If $S_F = \Gamma_3(X_1) > \Gamma_2(X_1)$, there exists a unique positive period-1 solution of system (3), in this case the unique root of Eq. (A.2) satisfies $u_3 = u^*$, hence by Eq. (A.14) we have $\mu_2 = 1$.

In a word, we conclude that

(I) if $S_F > \Gamma_1(X_1)$, there exists a unique positive period-1 solution of system (3), which is orbitally asymptotically stable and enjoys the property of asymptotic phase;

(II) if $\max\{\Gamma_2(X_1), \Gamma_3(X_1)\} < S_F \le \Gamma_1(X_1)$, there exist two positive period-1 solutions of system (3), where one is orbitally asymptotically stable and enjoys the property of asymptotic phase, while the other one is not stable;

(III) if $S_F = \Gamma_3(X_1) > \Gamma_2(X_1)$, there exists a unique positive period-1 solution of system (3), the stability of which cannot be determined by Lemma 1. □

A.3. The constraints in the bioprocess optimization

(a) $0 < W_f \le W_{f_{\max}} < 1$
W_f—the part of biomass which is removed from the bioreactor in each biomass oscillation cycle,
$W_{f_{\max}}$—the maximal part of biomass which is removed from the bioreactor in each biomass oscillation cycle,

(b) $0 < X_1 \le X_{\text{critical}}$
X_1—the set level of the biomass concentration in the bioreactor medium,
X_{critical}—the critical level of biomass concentration in the bioreactor medium,

(c) $\Gamma_1(X_1) \le S_F \le S_{F_{\text{critical}}}$
S_F—the concentration of the feed substrate,
$S_{F_{\text{critical}}}$—the critical level of the dosaged substrate concentration.

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