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ORIGINAL PAPER

Dynamic analysis of lactic acid fermentation with impulsive input

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Abstract In this paper, a mathematical model for the lactic acid fermentation in membrane bioreactor is investigated. Using the Floquet's theorem and small amplitude perturbation method, we obtain the biomass-free periodic solution is locally stable if some conditions are satisfied. The permanent conditions of the system are also given. Furthermore, in a certain limiting case it is shown that a nontrivial periodic solution emerges via a supercritical bifurcation. Finally, our findings are confirmed by means of numerical simulations.

Keywords Lactic acid fermentation · Impulsive input · Asymptotically stable · Periodic solution · Permanent · Bifurcation

1 Introduction

Lactic acid is an important organic acid that has both food and industrial applications [1,2]. Lactic acid has received much consideration as a precursor of the biodegradable plastic, polylactic acid. As the physical properties of polylactic acid depend on the isomeric composition of lactic acid, the production of optically pure lactic acid is essential [3]. In industry, Lactic acid is usually produced by using batch fermentation. But it suffers relatively low productivity due to end-product inhibition [4]. Lactic acid is a primary metabolite, and it is well known that the production of lactic acid

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is strictly dependent on cell growth and the final biomass. Membrane cell-recycle bioreactor (MCRB) could solve these problems satisfactorily. The efficiency of the MCRB was demonstrated in a number of previous studies on the enhancement of lactic acid productivity [4,5]. During the practical industry product, manufacturers always consider how to keep a sustainable and steady output of lactic acid. Therefore, we need to investigate the effect of substrate input on the output of the lactic acid.

In fact, many inputs are not continuous, which brings to sudden changes to the system. For example, we put the reactants into the reaction vessel in between some time during many chemical reactions. Systems with such sudden perturbation are involving in impulsive differential equation which has been studied in the literatures. Impulsive perturbation makes systems more intractable except that in some instance, the models can be rewritten as simple discrete-time mapping or difference equation when the corresponding continuous models can be solved explicitly. That is why most of the investigations related to impulsive systems are focused on the basic theory of impulsive equations and seldom give applications on the fermentation kinetics.

Stimulated by Fig. 1 [6], we consider the following model of the lactic acid fermentation in membrane bioreactor.

$$\begin{cases} \frac{dS}{dt} = -\frac{QS}{V} - \frac{\mu S x}{\delta_1\left(K_s+S+\frac{S^2}{k_1}\right)} + \left(\frac{K_D}{\delta_1} - m\right)x, & \\ \frac{dx}{dt} = \frac{\mu S x}{K_s+S+\frac{S^2}{k_1}} - \left(K_D + \frac{Q_1}{V}\right)x, & t \neq nT, \\ \frac{dP}{dt} = \frac{\delta_2 \mu S x}{\delta_1\left(K_s+S+\frac{S^2}{k_1}\right)} - \left(\frac{\delta_2 K_D}{\delta_1} - \delta_2 m\right)x - \frac{QP}{V}, & \\ \Delta S = \frac{QS^0}{V}, & \\ \Delta x = 0, & t = nT, \\ \Delta P = 0, & \end{cases} \tag{1.1}$$

where T is the impulsive period, $n = \{1, 2, \ldots\}$. x is the biomass concentration (g/L); S is the substrate concentration (g/L); S^0 is the initial substrate concentration (g/L); P is the lactic acid concentration (g/L); Q_1 is the volumetric bleed flow-rate (L/h); V is the reactor volume; δ_1 and δ_2 are the yield coefficients (g/g); m is the maintenance coefficient (h^{-1}); μ is the maximal specific growth rate of biomass (h^{-1}); K_D is the death coefficient (h^{-1}); K_s and k_1 are the kinetic coefficients. From the practical view of fermentation, we only consider system (1.1) in the positive region: $D = \{(S, x, P) | S, x, P \geq 0\}$.

The aim of this work is to study the dynamical behaviors of lactic acid fermentation with pulsed input, and investigate how the substrate input affects the dynamical behaviors of unforced continuous system.

We notice that the variable P does not appear in the first two equations of (1.1). This allows us to consider the following system:

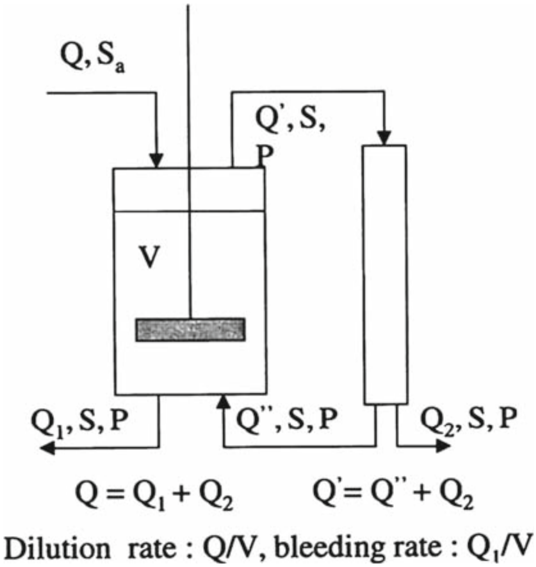

Fig. 1 Principles of cultivations during continuous fermentation using the bioreactor equipped with the membrane module operating under partial cell recycling

$$\begin{cases} \frac{dS}{dt} = -\frac{QS}{V} - \frac{\mu S x}{\delta_1\left(K_s + S + \frac{S^2}{k_1}\right)} + \left(\frac{K_D}{\delta_1} - m\right)x, & \\ & t \neq nT, \\ \frac{dx}{dt} = \frac{\mu S x}{K_s + S + \frac{S^2}{k_1}} - \left(K_D + \frac{Q_1}{V}\right)x, & \\ \Delta S = \frac{QS^0}{V}, & \\ & t = nT. \\ \Delta x = 0, & \end{cases} \tag{1.2}$$

2 Biomass-free periodic solution and its stability

Considering the following subsystem

$$\begin{cases} \frac{dS}{dt} = -\frac{Q}{V}S, & t \neq nT, \\ S(t^+) = S(t) + \frac{Q}{V}S^0, & t = nT. \end{cases} \tag{2.1}$$

We can find a unique positive periodic solution $\widetilde{S}(t) = \frac{QS^0}{V}\frac{\exp\left(-\frac{Q}{V}(t-nT)\right)}{1-\exp\left(-\frac{Q}{V}T\right)}$, $t \in (nT, (n+1)T]$. Similar to Liu [7], it can be shown that $\widetilde{S}(t)$ is globally asymptotically stable by using stroboscopic map.

As a consequence, system (1.2) always has a biomass-free periodic solution $(\widetilde{S}(t), 0)$.

Theorem 2.1 *The biomass-free periodic solution* $(\widetilde{S}(t), 0)$ *is locally stable if*

$$\int_0^T \frac{\mu k_1 \widetilde{S}(t)}{K_s k_1 + k_1 \widetilde{S}(t) + \widetilde{S}^2(t)} dt < \frac{(K_D V + Q_1)T}{V}.$$

Proof The local stability of the periodic solution may be determined by considering the behavior of small amplitude perturbations of the solution. Define

$$S(t) = u(t) + \widetilde{S}(t), \quad x(t) = v(t).$$

The linearization of the first and second equations of (1.2) can be written as:

$$\begin{pmatrix} \dot{u}(t) \\ \dot{v}(t) \end{pmatrix} \begin{pmatrix} -\frac{Q}{V} & -\dfrac{\mu k_1 \widetilde{S}(t)}{\delta_1 (K_s k_1 + k_1 \widetilde{S}(t) + S^2(t))} + \dfrac{K_D - \delta_1 m}{\delta_1} \\ 0 & \dfrac{\mu k_1 \widetilde{S}(t)}{K_s k_1 + k_1 \widetilde{S}(t) + \widetilde{S}^2(t)} - \dfrac{K_D V + Q_1}{V} \end{pmatrix} \begin{pmatrix} u(t) \\ v(t) \end{pmatrix}. \tag{2.2}$$

Let $\phi(t)$ is the fundamental solution matrix, then $\phi(t)$ satisfies

$$\frac{d\phi(t)}{dt} = \begin{pmatrix} -\frac{Q}{V} & -\dfrac{\mu k_1 \widetilde{S}(t)}{\delta_1 (K_s k_1 + k_1 \widetilde{S}(t) + S^2(t))} + \dfrac{K_D - \delta_1 m}{\delta_1} \\ 0 & \dfrac{\mu k_1 \widetilde{S}(t)}{K_s k_1 + k_1 \widetilde{S}(t) + \widetilde{S}^2(t)} - \dfrac{K_D V + Q_1}{V} \end{pmatrix} \phi(t), \tag{2.3}$$

and $\phi(0) = I$ is the identity matrix. The linearization of the third and fourth equations of system (1.2) becomes

$$\begin{pmatrix} u(nT^+) \\ v(nT^+) \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \begin{pmatrix} u(nT) \\ v(nT) \end{pmatrix}.$$

Thus, the monodromy matrix of (2.3) is

$$M = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \phi(T).$$

From (2.3), we have $\phi(T) = \phi(0) \exp \int_0^T A dt \triangleq \phi(0) \exp(\overline{A})$, where $\phi(0)$ is the identity matrix. Let λ_1, λ_2 be eigenvalues of matrix M then

$$\lambda_1 = \exp\left(-\frac{Q}{V} T\right) < 1,$$
$$\lambda_2 = \exp \int_0^T \left(\left(\frac{\mu k_1 \widetilde{S}(t)}{K_s k_1 + k_1 \widetilde{S}(t) + \widetilde{S}^2(t)} - \frac{K_D V + Q_1}{V} \right) dt \right).$$

Therefore, all eigenvalues of M, namely, $\lambda_i (i = 1, 2)$ have absolute values less than one if and only if

$$\int_0^T \frac{\mu k_1 \widetilde{S}(t)}{K_s k_1 + k_1 \widetilde{S}(t) + \widetilde{S}^2(t)} dt < \frac{(K_D V + Q_1) T}{V}.$$

According to the Floquet theorem [8], we have $(\widetilde{S}(t), 0)$ is locally asymptotically stable.

The proof is completed. □

Remark 2.1 The biomass-free periodic solution $(\widetilde{S}(t), 0)$ is unstable if

$$\int_0^T \frac{\mu k_1 \widetilde{S}(t)}{K_s k_1 + k_1 \widetilde{S}(t) + \widetilde{S}^2(t)} dt > \frac{(K_D V + Q_1)T}{V}.$$

3 Permanence

Firstly we show that all solutions of (1.2) are uniformly ultimately bounded.

Theorem 3.1 *There exists a constant $M > 0$ such that $S(t) \le M$, $x(t) \le M$ for each positive solution $(S(t), x(t))$ of (1.2) with t large enough.*

Proof Define a function $W(t) = S(t) + \frac{x(t)}{\delta_1}$ and the upper right derivative of $W(t)$ along a solution of (1.2) is described as

$$\begin{cases} D^+ W(t) \le -\alpha W, \; t \ne nT, \\ \Delta W = \frac{QS^0}{V}, \qquad t = nT, \end{cases} \tag{3.1}$$

where $\alpha = \min\{\frac{Q}{V}, \frac{Q_1 + mV\delta_1}{\delta_1 V}\}$. We obtain

$$W(t) \le W(0^+)e^{-\alpha t} + \frac{QS^0}{V} \frac{e^{-\alpha(t-T)}}{1 - e^{-\alpha T}} + \frac{QS^0 e^{\alpha T}}{V(e^{\alpha T} - 1)} \to \frac{QS^0 e^{\alpha T}}{V(e^{\alpha T} - 1)}, \quad t \to \infty. \tag{3.2}$$

By the definition of $W(t)$, we obtain that each positive solution of (1.2) is uniformly ultimately bounded.

Next we give the conditions of permanence.

□

Theorem 3.2 *System (1.2) is permanent provided $K_D > m\delta_1$ and*

$$\ln \frac{(M^2 + k_1 K_s)\left(1 - e^{-\frac{QT}{V}}\right) + \frac{Qk_1 S^0}{V}}{(M^2 + k_1 K_s)\left(1 - e^{-\frac{QT}{V}}\right) + \frac{Qk_1 S^0}{V} e^{-\frac{QT}{V}}} > \frac{Q(K_D V + Q_1)T}{\mu V^2}.$$

Proof Suppose $(S(t), x(t))$ is a solution of (1.2) with positive initial value. From Theorem (3.1), we may assume $S(t) \le M$, $x(t) \le M$, $t \ge 0$ and $M > 0$. From system (1.2), we can see that

$$\frac{dS}{dt} \ge -\frac{QS}{V} - \frac{\mu MS}{\delta_1 K_s}.$$

Considering the comparison system

$$\begin{cases} \frac{dw}{dt} = -\left(\frac{Q}{V} + \frac{\mu M}{\delta_1 K_s}\right) w, & t \neq nT, \\ \Delta w = \frac{QS^0}{V}, & t = nT, \end{cases} \tag{3.3}$$

let $m_1 = \frac{\frac{QS^0}{V} e^{-\left(\frac{Q}{V}+\frac{\mu M}{\delta_1 K_s}\right)T}}{1-e^{-\left(\frac{Q}{V}+\frac{\mu M}{\delta_1 K_s}\right)T}} - \varepsilon_1$, $\varepsilon_1 > 0$. According to comparison theorem, we have $S(t) \geq m_1$ for t large enough.

In the following, we want to find m_2 such that $x(t) \geq m_2$ for t large enough. We shall do it in the following two steps for convenience.

Step I: Let $m_2 > 0$ and ε_2 be small enough such that

$$\rho = \frac{\mu V}{Q} \ln \frac{\left(K_s k_1 + M^2 - k_1\varepsilon_2\right)\left(1 - e^{-\frac{Q}{V}}\right) + \frac{k_1 QS^0}{V}}{\left(K_s k_1 + M^2 - k_1\varepsilon_2\right)\left(1 - e^{-\frac{Q}{V}}\right) + \frac{k_1 QS^0}{V} e^{-\frac{QT}{V}}}$$
$$+ \frac{k_1 \mu V \varepsilon_2}{Q\left(K_s k_1 + M^2 - k_1\varepsilon_2\right)} \ln \frac{\left(K_s k_1 + M^2 - k_1\varepsilon_2\right)\left(1 - e^{-\frac{QT}{V}}\right) + \frac{k_1 QS^0}{V}}{\left(K_s k_1 + M^2 - k_1\varepsilon_2\right)\left(e^{\frac{QT}{V}} - 1\right) + \frac{k_1 QS^0}{V}}$$
$$- \frac{(K_D V + Q_1)\, T}{V} > 0.$$

We will prove $x(t) < m_2$ cannot hold for all $t \geq 0$. Otherwise,

$$\frac{dS}{dt} \geq -\left(\frac{Q}{V} + \frac{\mu m_2}{\delta_1 K_s}\right) S,$$

we have $S(t) \geq z(t)$ and $z(t) \to z^*(t)$, $t \to \infty$. Where $z(t)$ is the solution of

$$\begin{cases} \frac{dz}{dt} = -\left(\frac{Q}{V} + \frac{\mu m_2}{\delta_1 K_s}\right) z, & t \neq nT, \\ \Delta z = \frac{QS^0}{V}, & t = nT, \end{cases} \tag{3.4}$$

and

$$z^*(t) = \frac{QS^0 \exp\left(\left(-\frac{Q}{V} - \frac{\mu m_2}{\delta_1 K_s}\right)(t-nT)\right)}{V(1-\exp\left(\left(-\frac{Q}{V} - \frac{\mu m_2}{\delta_1 K_s}\right)T\right)}),\ t \in (nT, (n+1)T],$$

therefore, there exists a $n_1 > 0$, $t > n_1 T$ such that $S(t) \geq z(t) > z^*(t) - \varepsilon_2$ and we have

$$\frac{dx}{dt} \geq \frac{k_1 \mu \left(\widetilde{S}(t) - \varepsilon_2\right)}{(K_s k_1 + k_1 \left(\widetilde{S}(t) - \varepsilon_2\right) + M^2} - \frac{K_D V + Q_1}{V} x, \tag{3.5}$$

integrating (3.5) on $t \in (nT, (n+1)T]$, $n > n_2 > n_1 > 0$, we obtain that

$$x((n+1)T) \geq x(nT)\exp\left(\int_{nT}^{(n+1)T}\left(\frac{k_1\mu\left(\widetilde{S}(t)-\varepsilon_2\right)}{K_s k_1 + k_1\left(\widetilde{S}(t)-\varepsilon_2\right)+M^2} - \frac{K_D V + Q_1}{V}\right)dt\right),$$

therefore, $x((n+1)T) \geq x(nT)\exp(\rho)$. Then $x((N_1+k)T) \geq x(N_1T)\exp(k\rho) \to \infty$ as $k \to \infty$, which is a contradiction to the boundedness of $x(t)$. Therefore, there is a $t_1 > 0$ such that $x(t_1) \geq m_2$. If $x(t) \geq m_2$ for all $t > t_1$, then our aim is obtained. Otherwise $x(\bar{t}) < m_2$ for some $t > t_1$. Setting $t^* = \inf_{t>t_1}\{x(t) < m_2\}$, then we have $x(t) \geq m_2$ for $t \in [t_1, t^*)$ and $x(t^*) = m_2$ since $x(t)$ is continuous.

Step II: Suppose $t^* \in (n_1T, (n_1+1)T]$, $n_1 \in N$, select $n_2 \in N$, $n_3 \in N$ such that

$$n_2T \geq \frac{1}{-\frac{Q}{V} - \frac{\mu m_2}{\delta_1 K_s}} \ln \frac{\varepsilon_2}{M + \frac{QS^0}{V}},$$
$$\exp(\eta(n_2+1)T)\exp(n_3\rho) > 1,$$

where $\eta = \frac{k_1\mu m_1}{K_s k_1 + k_1 m_1 + M^2} - \frac{K_D V + Q_1}{V} < 0$. Let $T' = n_2T + n_3T$, we claim that there must be a $t' \in ((n_1+1)T, (n_1+1)T + T']$ such that $x(t) \geq m_2$. Otherwise $x(t) \geq m_2$ for $t \in ((n_1+1)T, (n_1+1)T + T']$. Consider (3.4) with $z((n_1+1)T^+) = S((n_1+1)T^+)$, then we have

$$z(t) = \left(z\left((n_1+1)T^+\right) - \frac{QS^0}{V\left(1-\exp\left(\left(-\frac{Q}{V} - \frac{\mu m_2}{\delta_1 K_s}\right)T\right)\right)}\right) \times \exp\left(-\left(\frac{Q}{V} + \frac{\mu m_2}{\delta_1 K_s}\right)(t-(n_1+1)T)\right) + z^*(t),$$

for $t \in (nT, (n+1)T]$, $n_1 + 1 < n \leq n_1 + 1 + n_2 + n_3$. Then

$$|z(t) - z^*(t)| \leq \left(M + \frac{QS^0}{V}\right)\exp\left(-\left(\frac{Q}{V} + \frac{\mu m_2}{\delta_1 K_s}\right)(t-(n_1+1)T)\right) < \varepsilon_2,$$

and $x(t) \geq z(t) > z^*(t) - \varepsilon_2$ for $(n_1+1+n_2)T \leq t \leq (n_1+1)T + T'$, which implies (3.5) holds. For $(n_1+n_2+1)T \leq t \leq (n_1+1)T + T'$, as in step I, we have $x((n_1+n_2+n_3+1)T) \geq x((n_1+n_2+1)T)\exp(n_3\rho)$, there are two cases for $t \in (t^*, T]$.

Case (a) If $x(t) < m_2$ for $t \in (t^*, T]$, then $x(t) < m_2$ for all $t \in (t^*, (n_1+n_2+1)T]$, system (1.2) gives

$$\frac{dx}{dt} \geq x(t)\left(\frac{k_1\mu m_1}{K_s k_1 + k_1 m_1 + M^2} - \frac{K_D V + Q_1}{V}\right), \tag{3.6}$$

integrating (3.6) on $(t^*, (n_1 + n_2 + 1)T]$, which yields $x((n_1 + n_2 + 1)T) \geq m_2 \exp(\eta(n_2 + 1)T)\exp(n_3\rho) > m_2$, which is a contraction. Let $\bar{t} = \inf_{t>t^*}\{x(t) \geq m_2\}$, then $x(\bar{t}) = m_2$ and (3.6) holds for $t \in [t^*, \bar{t})$. Then integrating (3.6) on $[t^*, \bar{t})$ yields $x(t) \geq x(t^*)\exp(\eta(t - t^*)) \geq m_2 \exp(\eta(1 + n_2 + n_3)T) \triangleq \overline{m}_2$. For $t > \bar{t}$, the same argument can be continued since $x(\bar{t}) \geq m_2$. Hence $x(t) \geq \overline{m}_2$ for all $t > t_1$. Similarly, we can prove case (b).

Incorporating into Theorem 3.1, the proof is completed. □

4 The bifurcation of a nontrivial periodic solution

In the following, we shall study the loss of stability phenomenon mentioned in Remark 2.1 and prove that it is due to the onset of nontrivial periodic solutions obtained via a supercritical bifurcation in the limiting case, that is,

$$\int_0^T \frac{\mu k_1 \widetilde{S}(t)}{K_s k_1 + k_1 \widetilde{S}(t) + \widetilde{S}^2(t)} dt = \frac{(K_D V + Q_1)T}{V}.$$

To this purpose, we shall employ a fixed point argument. We denote by $\Phi(t, U_0)$ the solution of the (unperturbed) system consisting of the first two equations of (1.2) for the initial data $U_0 = (u_0^1, u_0^2)$; also, $\Phi = (\Phi_1, \Phi_2)$. We define the mapping $I_1, I_2 : R^2 \to R^2$ by

$$I_1(x_1, x_2) = x_1 + \frac{QS^0}{V}, \quad I_2(x_1, x_2) = x_2$$

and the mapping $F_1, F_2 : R^2 \to R^2$ by

$$F(x_1, x_2) = -\frac{Qx_1}{V} - \frac{k_1 \mu x_1 x_2}{\delta_1 \left(K_s k_1 + k_1 x_1 + x_1^2\right)} + \frac{K_D - m\delta_1}{\delta_1} x_2,$$
$$F_2(x_1, x_2) = \frac{k_1 \mu x_1 x_2}{K_s k_1 + k_1 x_1 + x_1^2} - \frac{K_D V + Q_1}{V} x_2.$$

Furthermore, let us define $\Psi : [0, \infty) \times R^2 \to R^2$ by

$$\Psi(T, U_0) = I(\Phi(T, U_0)); \ \Psi(T, U_0) = (\Psi_1(T, U_0), \Psi_2(T, U_0)).$$

It is easy to see that Ψ is actually the stroboscopic mapping associated to the system (1.2), which puts in correspondence the initial data at 0_+ with the subsequent state of the system $\Psi(T^+, U_0)$ at T_+, where T is the stroboscopic time snapshot.

We reduce the problem of finding a periodic solution of (1.2) to a fixed problem. Here, U ia a periodic solution of period T for (1.2) if and only if its initial value $U(0) = U_0$ is a fixed point for $\Psi(T, \cdot)$. Consequently, to establish the existence of nontrivial periodic solutions of (1.2), one needs to prove the existence of the nontrivial fixed points of Ψ.

We are interested in the bifurcation of nontrivial periodic solutions near $(\widetilde{S}(t), 0)$. Assume that $X_0 = (x_0, 0)$ is starting point for the trivial periodic solution $(\widetilde{S}(t), 0)$, where $x_0 = \widetilde{S}(0^+)$. To find a nontrivial periodic solution of period τ with initial value X, we need to solve the fixed point problem $X = \Psi(\tau, X)$, or denoting $\tau = T + \widetilde{\tau}$, $X = X_0 + \widetilde{X}$,

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

Let us define

$$N(\widetilde{\tau}, \widetilde{X}) = X_0 + \widetilde{X} - \Psi(T + \widetilde{\tau}, X_0 + \widetilde{X}) = (N_1(\widetilde{\tau}, \widetilde{X}), N_2(\widetilde{\tau}, \widetilde{X})). \tag{4.1}$$

At the fixed point $N(\widetilde{\tau}, \widetilde{X}) = 0$. Let us denote

$$D_X N(0, (0, 0)) = \begin{pmatrix} a_0' & b_0' \\ c_0' & d_0' \end{pmatrix}.$$

It follows that

$$a_0' = 1 - \exp\left(-\frac{Q}{V}T\right) > 0, \tag{4.2}$$

$$b_0' = e^{-\frac{QT}{V}} \int_0^T e^{\frac{Qs}{V}} \left(\frac{K_D - \delta_1 m}{\delta_1} - \frac{k_1 \mu \widetilde{S}(s)}{\delta_1(K_s k_1 + k_1 \widetilde{S}(s) + \widetilde{S}^2(s))}\right) \frac{\partial \Phi_2}{\partial x_2}(s, X_0)ds, \tag{4.3}$$

$$c_0' = 0, \tag{4.4}$$

$$d_0' = 1 - e^{\int_0^T \left(\frac{k_1 \mu \widetilde{S}(s)}{K_s k_1 + k_1 \widetilde{S}(s) + \widetilde{S}^2(s)} - \frac{K_D V + Q_1}{V}\right) ds}. \tag{4.5}$$

(See Appendix 1 for details). A necessary condition for the bifurcation of nontrivial periodic solutions near $(\widetilde{S}(t), 0)$ is then

$$\det[D_X N(0, (0, 0))] = 0.$$

Since $D_X N(0, (0, 0))$ is an upper triangular matrix and $1 - \exp(-\frac{Q}{V}T) > 0$ always, it consequently follows that $d_0' = 0$ is necessary for the bifurcation. It is easy to see that $d_0' = 0$ is equivalent to $\int_0^T \frac{\mu k_1 \widetilde{S}(t)}{K_s k_1 + k_1 \widetilde{S}(t) + \widetilde{S}^2(t)} dt = \frac{(K_D V + Q_1)T}{V}$. It now remains to show that this necessary condition is also sufficient. This assertion represents the statement of the following theorem, which is our main result.

Theorem 4.1 *A supercritical bifurcation occurs at* $\int_0^T \frac{\mu k_1 \widetilde{S}(t)}{K_s k_1 + k_1 \widetilde{S}(t) + \widetilde{S}^2(t)} dt = \frac{(K_D V + Q_1)T}{V}$, *in the sense that there is* $\varepsilon > 0$ *such that for all* $0 < \widetilde{\varepsilon} < \varepsilon$ *there is a stable positive nontrivial periodic solution of* (1.2) *with period* $T + \widetilde{\varepsilon}$.

Proof With the above notations, it is that

$$\dim\left(Ker[D_X N(0,(0,0))]\right) = 1,$$

and a basis in $Ker\,[D_X N\,(0,(0,0))]$ is $\left(-\frac{b_0'}{a_0'}, 1\right)$. Then the equation $N\left(\widetilde{\tau}, \widetilde{X}\right) = 0$ is equivalent to

$$N_1\,(\widetilde{\tau}, \alpha Y_0 + z E_0) = 0,\; N_2\,(\widetilde{\tau}, \alpha Y_0 + z E_0) = 0,$$

where $E_0 = (1,0),\ Y_0 = \left(-\frac{b_0'}{a_0'}, 1\right)$. $\widetilde{X} = \alpha Y_0 + z E_0$ represents the direct sum decomposition of $\widetilde{X}$ using the projections onto $Ker[D_X N(0,(0,0))]$ (the central manifold) and $Im[D_X N(0,(0,0))]$ (the stable manifold).

Let us define

$$f_1(\widetilde{\tau}, \alpha, z) = N_1(\widetilde{\tau}, \alpha Y_0 + z E_0),\;\; f_2(\widetilde{\tau}, \alpha, z) = N_2(\widetilde{\tau}, \alpha Y_0 + z E_0).$$

Firstly, we see that

$$\frac{\partial f_1}{\partial z}(0,0,0) = \frac{\partial N_1}{\partial x_1}(0,(0,0)) = a_0' \neq 0.$$

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

$$f_1(\widetilde{\tau}, \alpha, z(\widetilde{\tau}, \alpha)) = N_1(\widetilde{\tau}, \alpha Y_0 + z(\widetilde{\tau}, \alpha) E_0) = 0. \tag{4.6}$$

Moreover,

$$\frac{\partial z}{\partial \alpha}(0,0) = -\left(\frac{\partial N_1(0,0)}{\partial x_1}\right)^{-1} \frac{\partial N_1(0,0)}{\partial x_2} + \frac{b_0'}{a_0'} = 0.$$

Then $N(\widetilde{\tau}, \widetilde{X}) = 0$ if and only if

$$f_2(\widetilde{\tau}, \alpha) = N_2\left(\widetilde{\tau}, \left(-\frac{b_0'}{a_0'}\alpha + z(\widetilde{\tau}, \alpha), \alpha\right)\right) = 0. \tag{4.7}$$

The Eq. 4.7 is called the “determining equation” and the number of its solutions equals the number of periodic solutions of (1.2). We now proceed to solving (4.7). Let us denote

$$f(\widetilde{\tau}, \alpha) = f_2(\widetilde{\tau}, \alpha, z).$$

First, it is to see that $f(0, 0) = N_2(0, (0, 0) = 0$. We determine the Taylor expansion of f around (0, 0). For this, we compute the first order partial derivatives $\frac{\partial f}{\partial \widetilde{\tau}}(0, 0)$ and $\frac{\partial f}{\partial \alpha}(0, 0)$ and observe that

$$\frac{\partial f}{\partial \widetilde{\tau}}(0, 0) = \frac{\partial f}{\partial \alpha}(0, 0) = 0.$$

(See Appendix 2 for the proof of this fact). Furthermore, it is observed in Appendix 3 that

$$A = \frac{\partial^2 f}{\partial \widetilde{\tau}^2}(0, 0) = 0, \ B = \frac{\partial^2 f}{\partial \alpha \partial \widetilde{\tau}}(0, 0), \ C = \frac{\partial^2 f}{\partial \alpha^2}(0, 0),$$

and hence

$$f(\widetilde{\tau}, \alpha) = B\alpha\widetilde{\tau} + C\frac{\alpha^2}{2} + o(\widetilde{\tau}, \alpha)(\widetilde{\tau}^2 + \alpha^2).$$

By denoting $\widetilde{\tau} = l\alpha$ (where $l = l(\alpha)$), we obtain that (4.7) is equivalent to

$$Bl + C\frac{l^2}{2} + o(\alpha, l\alpha)(1 + l^2) = 0. \tag{4.8}$$

Next, we consider the solution of system (4.8), we will do it in the following two steps for convenience.

Step I: When $B = \frac{\partial^2 f}{\partial \alpha \partial \widetilde{\tau}}(0, 0) > 0$, we have two cases:

Case (1) Suppose $\frac{\partial^2 f}{\partial \alpha^2}(0, 0) < 0$, by denoting $\widetilde{\tau} = l\alpha$ (where $l = l(\alpha)$). Since $B > 0$ and $C < 0$, this equation is solvable with respect to l as a function of α. Moreover, here $l \approx -\frac{2B}{C} > 0$.

Case (2) Suppose $\frac{\partial^2 f}{\partial \alpha^2}(0, 0) > 0$, by denoting $\widetilde{\tau} = l\alpha$ (where $l = l(\alpha)$). Similarly we have $l \approx -\frac{2B}{C} < 0$.

Step II: When $B = \frac{\partial^2 f}{\partial \alpha \partial \widetilde{\tau}}(0, 0) < 0$, we also have two cases:

Case (1) Suppose $\frac{\partial^2 f}{\partial \alpha^2}(0, 0) < 0$. Since $B < 0$ and $C < 0$, this equation is solvable with respect to l as a function of α. Moreover, here $l \approx -\frac{2B}{C} < 0$.

Case (2) Suppose $\frac{\partial^2 f}{\partial \alpha^2}(0, 0) < 0$, by denoting $\widetilde{\tau} = l\alpha$ (where $l = l(\alpha)$). Similarly we have $l \approx -\frac{2B}{C} > 0$.

This implies that there is a supercritical bifurcation to a nontrivial periodic solution near a period T which satisfies the sufficient condition for the bifurcation

$$\int_0^T \frac{\mu k_1 \widetilde{S}(t)}{K_s k_1 + k_1 \widetilde{S}(t) + \widetilde{S}^2(t)} dt = \frac{(K_D V + Q_1)\, T}{V}.$$

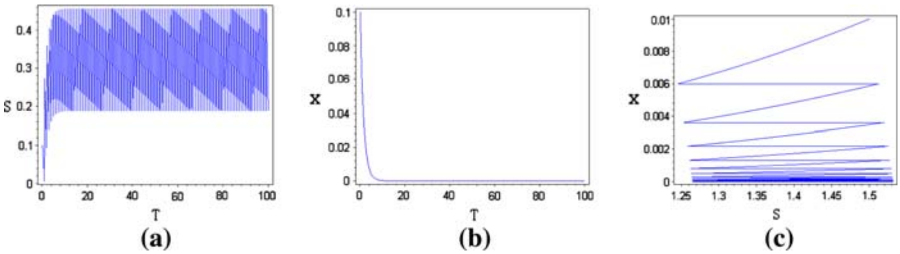

Fig. 2 Dynamical behavior of the system (1.2) with $T = 1$, $V = 3$, $Q = 0.8$, $S^0 = 1$, $\mu = 0.3$, $m = 0.1$, $K_s = 1$, $K_D = 0.5$, $k_1 = 1$, $Q_1 = 0.5$, $\delta_1 = 0.2$. **a** Time-series of the substrate concentration of system (1.2). **b** Time-series of the biomass concentration of system (1.2). **c** Phase portrait of system (1.2)

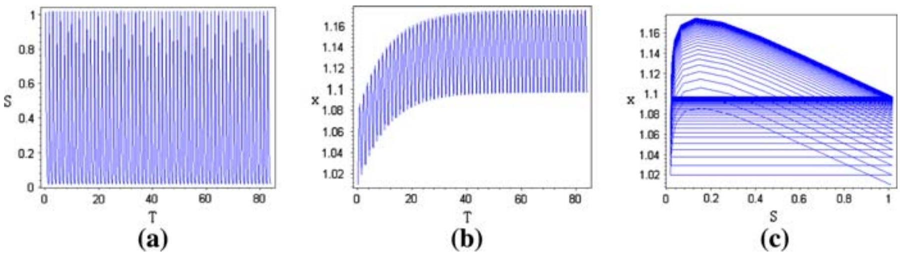

Fig. 3 Dynamical behavior of the system (1.2) with $T = 1.4$, $V = 2$, $Q = 0.4$, $S^0 = 5$, $\mu = 0.2$, $Q_1 = 0.1$, $k_1 = 1$, $m = 0.1$, $K_s = 1$, $\delta_1 = 0.2$, $K_D = 0.1$. **a** Time-series of the substrate concentration of system (1.2). **b** Time-series of the biomass concentration of system (1.2). **c** Phase portrait of system (1.2)

It is noteworthy that since this periodic solution appears via a supercritical bifurcation, the nontrivial periodic solution is stable. That is, there is $\varepsilon > 0$ such that for all $0 < \alpha < \varepsilon$ there is a stable positive nontrivial periodic solution of (1.2) with period $T + \widetilde{\tau}(\alpha)$ which starts in $X_0 \pm \alpha Y_0 + z(\widetilde{\tau}(\alpha), \alpha)E_0$. Here, $X_0, Y_0, E_0, z, \widetilde{\tau}$ are as defined above. □

5 Discussion

The model for the lactic acid fermentation process is developed and used by J. Boudrant et al. [6]. To simulate the oscillatory behavior of an experimental fermentor, we incorporate the impulsive input substrate. From Theorem 2.1, we obtain that the biomass-free periodic solution $(\widetilde{S}(t), 0)$ is locally asymptotically stable (In Fig. 2) if $\int_0^T \frac{k_1\mu\widetilde{S}(s)}{K_s k_1 + k_1\widetilde{S}(s) + \widetilde{S}^2(s)} ds < \frac{K_D V + Q_1}{V}$. The system (1.2) is permanent if $\int_0^T \frac{k_1\mu\widetilde{S}(s)}{K_s k_1 + k_1\widetilde{S}(s) + M^2} ds > \frac{K_D V + Q_1}{V}$, which is also simulated in Fig. 3. From Theorem 2.1 and Remark 2.1, we obtain that $\int_0^T \frac{k_1\mu\widetilde{S}(s)}{K_s k_1 + k_1\widetilde{S}(s) + \widetilde{S}^2(s)} ds = \frac{K_D V + Q_1}{V}$ is a critical value. Using the bifurcation theorem, we show that once a threshold condition is reached, a stable nontrivial periodic solution emerges via a supercritical bifurcation.

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Appendix 1: the first order partial derivatives of Φ_1, Φ_2

By formally deriving the equation

$$\frac{d}{dt}(\Phi(t, X_0)) = F(\Phi(t, X_0)),$$

which characterized the dynamics of the unperturbed flow associated to the first two equations in (1.2), one obtains that

$$\frac{d}{dt}\left[D_X\Phi(t, X_0)\right] = D_X F(\Phi(t, X_0))D_X\Phi(t, X_0). \tag{5.1}$$

This relation will be integrated in what follows in order to compute the components of $D_X\Phi(t, X_0)$ explicitly. Firstly, it is clear that

$$\Phi(t, X_0) = (\Phi_1(t, X_0), 0).$$

Then we deduce that (5.1) takes the particular form

$$\begin{aligned}\frac{d}{dt}\begin{pmatrix}\frac{\partial\Phi_1}{\partial x_1} & \frac{\partial\Phi_1}{\partial x_2}\\ \frac{\partial\Phi_2}{\partial x_1} & \frac{\partial\Phi_2}{\partial x_2}\end{pmatrix}(t, X_0)\\ = \begin{pmatrix}-\frac{Q}{V} & -\frac{k_1\mu\widetilde{S}(t)}{\delta_1(K_s k_1+k_1\widetilde{S}(t)+\widetilde{S}^2(t))}+\frac{K_D-\delta_1 m}{\delta_1}\\ 0 & \frac{k_1\mu\widetilde{S}(t)}{K_s k_1+k_1\widetilde{S}(t)+\widetilde{S}^2(t)}-\frac{K_D V+Q_1}{V}\end{pmatrix}\begin{pmatrix}\frac{\partial\Phi_1}{\partial x_1} & \frac{\partial\Phi_1}{\partial x_2}\\ \frac{\partial\Phi_2}{\partial x_1} & \frac{\partial\Phi_2}{\partial x_2}\end{pmatrix}(t, X_0),\end{aligned} \tag{5.2}$$

the initial condition for (5.2) at $t = 0$ being

$$D_X\Phi(0, X_0) = I_2. \tag{5.3}$$

Here, I_2 is the identity matrix in $M_2(R)$. It follows that

$$\frac{\partial\Phi_2(t, X_0)}{\partial x_1} = \exp\left(\int\limits_0^t\left(\frac{k_1\mu\widetilde{S}(s)}{K_s k_1 + k_1\widetilde{S}(s) + \widetilde{S}^2(s)} - \frac{K_D V + Q_1}{V}\right)ds\right)\frac{\partial\Phi_2(0, X_0)}{\partial x_1}.$$

This implies, using the initial condition (5.3), that

$$\frac{\partial\Phi_2(t, X_0)}{\partial x_1} = 0, \quad \text{for } t \geq 0. \tag{5.4}$$

To compute $\frac{\partial\Phi_1(t,X_0)}{\partial x_1}$, $\frac{\partial\Phi_1(t,X_0)}{\partial x_2}$ and $\frac{\partial\Phi_2(t,X_0)}{\partial x_2,}$. From (5.2) one obtain that

$$
\begin{aligned}
\frac{d}{dt}\left(\frac{\partial\Phi_1(t,X_0)}{\partial x_1}\right) &= -\frac{Q}{V}\frac{\partial\Phi_1(t,X_0)}{\partial x_1},\\
\frac{d}{dt}\left(\frac{\partial\Phi_1(t,X_0)}{\partial x_2}\right) &= -\frac{Q}{V}\frac{\partial\Phi_1(t,X_0)}{\partial x_2}\\
&\quad + \left(\frac{K_D-\delta_1 m}{\delta_1} - \frac{k_1\mu\widetilde{S}(t)}{\delta_1\left(K_s k_1 + k_1\widetilde{S}(t) + \widetilde{S}^2(t)\right)}\right)\frac{\partial\Phi_2(t,X_0)}{\partial x_2},\\
\frac{d}{dt}\left(\frac{\partial\Phi_2(t,X_0)}{\partial x_2}\right) &= \left(\frac{k_1\mu\widetilde{S}(t)}{K_s k_1 + k_1\widetilde{S}(t) + \widetilde{S}^2(t)} - \frac{K_D V + Q_1}{V}\right)\frac{\partial\Phi_2(t,X_0)}{\partial x_2}.
\end{aligned}
$$

According to the initial condition, we obtain that

$$
\begin{aligned}
\frac{\partial\Phi_1(t,X_0)}{\partial x_1} &= e^{-\frac{Q}{V}t},\\
\frac{\partial\Phi_1(t,X_0)}{\partial x_2} &= e^{-\frac{Qt}{V}}\int_0^t e^{\frac{Qs}{V}}\left(\frac{K_D-\delta_1 m}{\delta_1}\right.\\
&\qquad \left. - \frac{k_1\mu\widetilde{S}(s)}{\delta_1\left(K_s k_1 + k_1\widetilde{S}(s) + \widetilde{S}^2(s)\right)}\right)\frac{\partial\Phi_2}{\partial x_2}(s,X_0)ds,\\
\frac{\partial\Phi_2(t,X_0)}{\partial x_2} &= e^{\int_0^t\left(\frac{k_1\mu\widetilde{S}(s)}{K_s k_1 + k_1\widetilde{S}(s) + \widetilde{S}^2(s)} - \frac{K_D V + Q_1}{V}\right)ds}.
\end{aligned}
$$

From (4.1), we obtain that

$$
D_X N(0,(0,0)) = I_2 - D_X\psi(T,X_0),
$$

which implies

$$
D_X N(0,(0,0)) = \begin{pmatrix} a_0' & b_0' \\ 0 & d_0' \end{pmatrix}.
$$

Appendix 2: the first order partial derivatives of f

$$\frac{\partial f}{\partial \alpha}(\widetilde{\tau}, \alpha) = \frac{\partial}{\partial \alpha}\left(\alpha - \Psi_2(T + \widetilde{\tau}, X_0 + \alpha Y_0 + z\left(\widetilde{\tau}, \alpha\right) E_0)\right)$$
$$= 1 - \left(\frac{\partial \Phi_2}{\partial x_1}(T + \widetilde{\tau}), X_0 + \alpha Y_0 + z(\widetilde{\tau}, \alpha) E_0\right)\left(-\frac{b_0'}{a_0'} + \frac{\partial z(\widetilde{\tau}, \alpha)}{\partial \alpha}\right)$$
$$+ \frac{\partial \Phi_2}{\partial x_2}\left(\widetilde{\tau}, X_0 + \alpha Y_0 + z(\widetilde{\tau}, \alpha) E_0)\right),$$

but

$$\frac{\partial \Phi_2}{\partial x_1}(T + \widetilde{\tau}, X_0 + \alpha Y_0 + z(\widetilde{\tau}, \alpha) E_0) = 0$$

and

$$d_0' = 1 - \frac{\partial \Phi_2}{\partial x_2}(T, X_0) = 0.$$

When $d_0' = 0$, then we obtain

$$\frac{\partial f}{\partial \alpha}(0, 0) = 0.$$

On the other hand,

$$\frac{\partial f(\widetilde{\tau}, \alpha)}{\partial \widetilde{\tau}} = \frac{\partial}{\partial \widetilde{\tau}}(\alpha - \Psi_2(T + \widetilde{\tau}, X_0 + \alpha Y_0 + z(\widetilde{\tau}, \alpha) E_0))$$
$$= -\frac{\partial \Phi_2}{\partial \widetilde{\tau}}(T + \widetilde{\tau}, X_0 + \alpha Y_0 + z(\widetilde{\tau}, \alpha) E_0)$$
$$-\frac{\partial \Phi_2}{\partial x_1}(T + \widetilde{\tau}, X_0 + \alpha Y_0 + z(\widetilde{\tau}, \alpha) E_0).$$

Since $\frac{\partial \Phi_2}{\partial x_1}(T + \widetilde{\tau}, X_0 + \alpha Y_0 + z(\widetilde{\tau}, \alpha) E_0)) = 0$ and $\frac{\partial \Phi_2}{\partial \widetilde{\tau}}(T + \widetilde{\tau}, X_0 + \alpha Y_0 + z\left(\widetilde{\tau}, \alpha\right) E_0)) = 0$. Therefore, we have $\frac{\partial f}{\partial \widetilde{\tau}}(0, 0) = 0$.

Appendix 3: second partial derivatives of f

Denote $A = \frac{\partial^2 f}{\partial \widetilde{\tau}^2}(0, 0),\ B = \frac{\partial^2 f}{\partial \widetilde{\tau} \partial \alpha}(0, 0),\ C = \frac{\partial^2 f}{\partial \alpha^2}(0, 0).$

Take $\eta(\widetilde{\tau}) = T + \widetilde{\tau}$, $\eta_1(\widetilde{\tau}, \alpha) = x_0 - \frac{b_0'}{a_0'} + z(\widetilde{\tau}, \alpha)$ and $\eta_2(\widetilde{\tau}, \alpha) = \alpha$. Next we calculate these quantities in terms of the parameters of the equation.

Calculation of A

We have

$$
\begin{aligned}
\frac{\partial^2 f(\widetilde{\tau},\alpha)}{\partial\widetilde{\tau}^2} &= \frac{\partial^2}{\partial\widetilde{\tau}^2}(\eta_2 - I_2\circ\Phi(\eta,\eta_1,\eta_2))(\widetilde{\tau},\alpha)\\
&= -\frac{\partial^2}{\partial x_1^2}\left(\frac{\partial\Phi_1(\eta,\eta_1,\eta_2)}{\partial\widetilde{\tau}} + \frac{\partial\Phi_1(\eta,\eta_1,\eta_2)}{\partial x_1}\frac{\partial z}{\partial\widetilde{\tau}}\right)^2\\
&\quad -\frac{\partial^2 I_2}{\partial x_1\partial x_2}\frac{\partial\Phi_2(\eta,\eta_1,\eta_2)}{\partial\widetilde{\tau}}\left(\frac{\partial\Phi_1(\eta,\eta_1,\eta_2)}{\partial\widetilde{\tau}} + \frac{\partial\Phi_1(\eta,\eta_1,\eta_2)}{\partial x_1}\frac{\partial z}{\partial\widetilde{\tau}}\right)\\
&\quad -\frac{\partial^2 I_2}{\partial x_1\partial x_2}\frac{\partial\Phi_2}{\partial x_1}\frac{\partial z}{\partial\widetilde{\tau}}\left(\frac{\partial\Phi_1(\eta,\eta_1,\eta_2)}{\partial\widetilde{\tau}} + \frac{\partial\Phi_1(\eta,\eta_1,\eta_2)}{\partial x_1}\frac{\partial z}{\partial\widetilde{\tau}}\right)\\
&\quad -\frac{\partial I_2}{\partial x_1}\left(\frac{\partial^2\Phi_1(\eta,\eta_1,\eta_2)}{\partial\widetilde{\tau}^2} + 2\frac{\partial^2\Phi_1(\eta,\eta_1,\eta_2)}{\partial x_1\partial\widetilde{\tau}}\frac{\partial z}{\partial\widetilde{\tau}}\right)\\
&\quad -\frac{\partial I_2}{\partial x_1}\left(\frac{\partial^2\Phi_1(\eta,\eta_1,\eta_2)}{\partial x_1^2}\left(\frac{\partial z}{\partial\widetilde{\tau}}\right)^2 + \frac{\partial\Phi_1(\eta,\eta_1,\eta_2)}{\partial x_1}\frac{\partial^2 z}{\partial\widetilde{\tau}^2}\right)\\
&\quad -\frac{\partial^2 I_2}{\partial x_2\partial x_2}\frac{\partial\Phi_1(\eta,\eta_1,\eta_2)}{\partial\widetilde{\tau}}\left(\frac{\partial\Phi_2(\eta,\eta_1,\eta_2)}{\partial\widetilde{\tau}} + \frac{\partial\Phi_2(\eta,\eta_1,\eta_2)}{\partial x_1}\frac{\partial z}{\partial\widetilde{\tau}}\right)\\
&\quad -\frac{\partial^2 I_2}{\partial x_2\partial x_2}\frac{\partial\Phi_1(\eta,\eta_1,\eta_2)}{\partial\widetilde{\tau}}\frac{\partial z}{\partial\widetilde{\tau}}\left(\frac{\partial\Phi_2(\eta,\eta_1,\eta_2)}{\partial\widetilde{\tau}} + \frac{\partial\Phi_2(\eta,\eta_1,\eta_2)}{\partial x_1}\frac{\partial z}{\partial\widetilde{\tau}}\right)\\
&\quad -\frac{\partial^2 I_2}{\partial x_2^2}\left(\frac{\partial\Phi_2(\eta,\eta_1,\eta_2)}{\partial\widetilde{\tau}} + \frac{\partial\Phi_2(\eta,\eta_1,\eta_2)}{\partial x_1}\frac{\partial z}{\partial\widetilde{\tau}}\right)^2\\
&\quad -\frac{\partial I_2}{\partial x_2}\left(\frac{\partial^2\Phi_2(\eta,\eta_1,\eta_2)}{\partial\widetilde{\tau}^2} + 2\frac{\partial^2(\eta,\eta_1,\eta_2)}{\partial x_1\partial\widetilde{\tau}}\frac{\partial z}{\partial\widetilde{\tau}}\right)\\
&\quad -\frac{\partial I_2}{\partial x_2}\left(\frac{\partial^2\Phi_2(\eta,\eta_1,\eta_2)}{\partial x_1^2}\left(\frac{\partial z}{\partial\widetilde{\tau}}\right)^2 + \frac{\partial\Phi_2(\eta,\eta_1,\eta_2)}{\partial x_1}\frac{\partial z}{\partial\widetilde{\tau}}\right).
\end{aligned}
$$

Since $\frac{\partial^2 I_2}{\partial x_2^2} = \frac{\partial\Phi_2}{\partial x_2} = \frac{\partial\Phi_2}{\partial\widetilde{\tau}} = \frac{\partial^2\Phi_2}{\partial\widetilde{\tau}\partial x_1} = 0$ for $(\widetilde{\tau},\alpha) = (0,0)$, then

$$A = -\frac{\partial I_2}{\partial x_2}\frac{\partial^2\Phi_2(T,x_0)}{\partial\widetilde{\tau}^2},$$

on the other hand, we have $\frac{\partial^2\Phi_2(t,X_0)}{\partial\widetilde{\tau}^2} = 0$, therefore, we obtain $A = 0$.

Calculation of C

We have

$$\frac{\partial^2 f}{\partial\alpha^2}(\widetilde{\tau},\alpha) = \frac{\partial^2}{\partial^2}(\eta_2 - I_2\circ\Phi(\eta,\eta_1,\eta_2))$$

and

$$
\begin{aligned}
\frac{\partial^2 f}{\partial \alpha^2}(\widetilde{\tau},\alpha) = {} & \frac{\partial^2 I_2}{\partial x_1^2}\left(\frac{\partial \Phi_1(\eta,\eta_1,\eta_2)}{\partial_1}\left(-\frac{b_0'}{a_0'}+\frac{\partial z(\widetilde{\tau},\alpha)}{\partial \widetilde{\tau}}\right)+\frac{\partial \Phi_1(\eta,\eta_1,\eta_2)}{\partial x_2}\right)^2 \\
& -\frac{\partial^2 I_2}{\partial x_1 \partial x_2}\left(\frac{\partial \Phi_1(\eta,\eta_1,\eta_2)}{\partial x_1}\left(-\frac{b_0'}{a_0'}+\frac{\partial z(\widetilde{\tau},\alpha)}{\partial \widetilde{\tau}}\right)-\frac{\partial \Phi_1(\eta,\eta_1,\eta_2)}{\partial x_2}\right) \\
& \times\left(\frac{\partial \Phi_2(\eta,\eta_1,\eta_2)}{\partial x_2}\left(-\frac{b_0'}{a_0'}+\frac{\partial z(\widetilde{\tau},\alpha)}{\partial \alpha}\right)\right) \\
& -\frac{\partial^2 I_2}{\partial x_1 \partial x_2}\left(\frac{\partial \Phi_1(\eta,\eta_1,\eta_2)}{\partial x_1}\left(-\frac{b_0'}{a_0'}+\frac{\partial z(\widetilde{\tau},\alpha)}{\partial \alpha}\right)\right)\frac{\partial \Phi_2(\eta,\eta_1,\eta_2)}{\partial x_2} \\
& -\frac{\partial^2 I_2}{\partial x_1 \partial x_2}\frac{\partial \Phi_1(\eta,\eta_1,\eta_2)}{\partial x_2}\frac{\partial \Phi_2(\eta,\eta_1,\eta_2)}{\partial x_2} \\
& -\frac{\partial I_2}{\partial x_1}\left(\frac{\partial^2 \Phi_1(\eta,\eta_1,\eta_2)}{\partial x_1^2}\left(-\frac{b_0'}{a_0'}+\frac{\partial z(\widetilde{\tau},\alpha)}{\partial \alpha}\right)^2\right) \\
& -2\frac{\partial I_2}{\partial x_1}\frac{\partial^2(\eta,\eta_1,\eta_2)}{\partial x_1 \partial x_2}\left(-\frac{b_0'}{a_0'}+\frac{\partial z(\widetilde{\tau},\alpha)}{\partial \alpha}\right) \\
& -\frac{\partial I_2}{\partial x_1}\left(\frac{\partial \Phi_1(\eta,\eta_1,\eta_2)}{\partial x_1}\left(\frac{\partial z(\widetilde{\tau},\alpha)}{\partial \alpha^2}\right)^2+\frac{\partial^2 \Phi_1(\eta,\eta_1,\eta_2)}{\partial x_2^2}\right) \\
& -\frac{\partial^2 I_2}{\partial x_1 \partial x_2}\left(\frac{\partial \Phi_1(\eta,\eta_1,\eta_2)}{\partial x_1}\left(-\frac{b_0'}{a_0'}+\frac{\partial z(\widetilde{\tau},\alpha)}{\partial \alpha}\right)+\frac{\partial \Phi_1(\eta,\eta_1,\eta_2)}{\partial x_2}\right) \\
& \times\left(\frac{\partial \Phi_2(\eta,\eta_1,\eta_2)}{\partial x_1}\left(-\frac{b_0'}{a_0'}+\frac{\partial z(\widetilde{\tau},\alpha)}{\partial \alpha}\right)\right) \\
& -\frac{\partial^2 I_2}{\partial x_1 \partial x_2}\left(\frac{\partial \Phi_1(\eta,\eta_1,\eta_2)}{\partial x_1}\left(-\frac{b_0'}{a_0'}+\frac{\partial z(\widetilde{\tau},\alpha)}{\partial \alpha}\right)\right)\frac{\partial \Phi_2(\eta,\eta_1,\eta_2)}{\partial x_2} \\
& -\frac{\partial^2 I_2}{\partial x_1 \partial x_2}\frac{\partial \Phi_1(\eta,\eta_1,\eta_2)}{\partial x_2}\frac{\partial \Phi_2(\eta,\eta_1,\eta_2)}{\partial x_2} \\
& -\frac{\partial^2 I_2}{\partial x_2^2}\left(\frac{\partial \Phi_2(\eta,\eta_1,\eta_2)}{\partial x_1}\left(-\frac{b_0'}{a_0'}+\frac{\partial z(\widetilde{\tau},\alpha)}{\partial \alpha}\right)+\frac{\partial \Phi_2(\eta,\eta_1,\eta_2)}{\partial x_2}\right)^2 \\
& -\frac{\partial I_2}{\partial x_2}\left(\frac{\partial^2 \Phi_2(\eta,\eta_1,\eta_2)}{\partial x_1^2}\left(-\frac{b_0'}{a_0'}+\frac{\partial z(\widetilde{\tau},\alpha)}{\partial \alpha}\right)^2\right) \\
& -2\frac{\partial I_2}{\partial x_2}\frac{\partial^2 \Phi_2(\eta,\eta_1,\eta_2)}{\partial x_1 \partial x_2}\left(-\frac{b_0'}{a_0'}+\frac{\partial z(\widetilde{\tau},\alpha)}{\partial \alpha}\right) \\
& -\frac{\partial I_2}{\partial x_2}\left(\frac{\partial \Phi_2(\eta,\eta_1,\eta_2)}{\partial x_1}\frac{\partial^2 z(\widetilde{\tau},\alpha)}{\partial \alpha^2}+\frac{\partial^2 \Phi_2(\eta,\eta_1,\eta_2)}{\partial x_2^2}\right).
\end{aligned}
$$

On the one hand, for determining C, we must calculate the following terms:

$$
\frac{\partial^2 \Phi_2(T,X_0)}{\partial x_1 \partial x_2},\ \frac{\partial^2 \Phi_2(T,X_0)}{\partial x_2^2}.
$$

We have

$$\frac{d}{dt}\left(\frac{\partial^2\Phi_2(t,X_0)}{\partial x_1\partial x_2}\right)=\left(\frac{k_1\mu\widetilde{S}(t)}{k_1K_s+k_1\widetilde{S}(t)+\widetilde{S}^2(t)}-\frac{K_DV+Q_1}{V}\right)\frac{\partial^2\Phi_2(t,X_0)}{\partial x_1\partial x_2}+\frac{k_1\mu\left(k_1K_s-\widetilde{S}^2(t)\right)}{\left(K_sk_1+k_1\widetilde{S}(t)+\widetilde{S}^2(t)\right)^2}\frac{\partial\Phi_1(t,X_0)}{\partial x_1}\frac{\partial\Phi_2(t,X_0)}{\partial x_2}.$$

Since

$$\frac{\partial\Phi_2(0,X_0)}{\partial x_1\partial x_2}=0.$$

We obtain that

$$\frac{\partial^2\Phi_2(t,X_0)}{\partial x_1\partial x_2}=\exp\left(\int_0^t\left(\frac{k_1\mu\widetilde{S}(s)}{\left(K_sk_1+k_1\widetilde{S}(s)+\widetilde{S}^2(s)\right)}-\frac{K_DV+Q_1}{V}\right)ds\right)\times\int_0^t\frac{k_1\mu(k_1K_s-\widetilde{S}^2(s))}{\left(K_sk_1+k_1\widetilde{S}(s)+\widetilde{S}^2(s)\right)^2}\frac{\partial\Phi_1(s,X_0)}{\partial x_1}ds.$$

Also, by a similar argument,

$$\frac{d}{dt}\left(\frac{\partial^2\Phi_2(t,X_0)}{\partial x_2^2}\right)=\left(\frac{k_1\mu\widetilde{S}(t)}{K_sk_1+k_1\widetilde{S}(t)+\widetilde{S}^2(t)}-\frac{K_DV+Q_1}{V}\right)\frac{\partial^2\Phi_2(t,X_0)}{\partial x_2^2}+\frac{\mu k_1\left(k_1K_s-\widetilde{S}^2(t)\right)}{\left(K_sk_1+k_1\widetilde{S}(t)+\widetilde{S}^2(t)\right)^2}\frac{\partial\Phi_1(t,X_0)}{\partial x_2}\frac{\partial\Phi_2(t,X_0)}{\partial x_2},$$

and since

$$\frac{\partial^2\Phi_2(0,X_0)}{\partial x_2^2}=0.$$

One may deduce that

$$\frac{\partial^2\Phi_2(t,X_0)}{\partial x_2^2}=\exp\left(\int_0^t\left(\frac{k_1\mu\widetilde{S}(s)}{K_sk_1+k_1\widetilde{S}(s)+\widetilde{S}^2(s)}-\frac{K_DV+Q_1}{V}\right)ds\right)\times\int_0^t\frac{k_1\mu\left(k_1K_s-\widetilde{S}^2(s)\right)}{\left(K_sk_1+k_1\widetilde{S}(s)+\widetilde{S}^2(s)\right)^2}\frac{\partial\Phi_1(s,X_0)}{\partial x_2}ds.$$

Therefore, we have

$$
\begin{aligned}
C &= 2\frac{b_0'}{a_0'} \cdot \frac{\partial^2 \Phi_2(T, X_0)}{\partial x_1 \partial x_2} - \frac{\partial^2 \Phi_2(T, X_0)}{\partial x_2^2} \\
&= 2\frac{b_0'}{a_0'} \exp\left(\int_0^T \left(\frac{k_1 \mu \widetilde{S}(s)}{K_s k_1 + k_1 \widetilde{S}(s) + \widetilde{S}^2(s)} - \frac{K_D V + Q_1}{V}\right) ds\right) \\
&\quad \times \int_0^T \frac{\mu k_1 (k_1 K_s - \widetilde{S}^2(s))}{\left(K_s k_1 + k_1 \widetilde{S}(s) + \widetilde{S}^2(s)\right)^2} \frac{\partial \Phi_1(s, X_0)}{\partial x_1} ds \\
&\quad - \exp\left(\int_0^T \left(\frac{k_1 \mu \widetilde{S}(s)}{K_s k_1 + k_1 \widetilde{S}(s) + \widetilde{S}^2(s)} - \frac{K_D V + Q_1}{V}\right) ds\right) \\
&\quad \times \int_0^T \frac{\mu k_1 (k_1 K_s - \widetilde{S}^2(s))}{\left(K_s k_1 + k_1 \widetilde{S}(s) + \widetilde{S}^2(s)\right)^2} \frac{\partial \Phi_1(s, X_0)}{\partial x_2} ds.
\end{aligned}
$$

Similarly, we also obtain that

$$
\begin{aligned}
B &= -\left(\frac{\partial^2 \Phi_2(T, X_0)}{\partial x_1 \partial x_2} \cdot \frac{1}{a_0'} \cdot \frac{\partial \Phi_1(T, X_0)}{\partial \widetilde{\tau}} + \frac{\partial \Phi_2(T, X_0)}{\partial \widetilde{\tau} \partial x_2}\right) \\
&= -\left(\left(\exp\left(\int_0^T \left(\frac{k_1 \mu \widetilde{S}(s)}{K_s k_1 + k_1 \widetilde{S}(s) + \widetilde{S}^2(s)} - \frac{K_D V + Q_1}{V}\right) ds\right)\right.\right. \\
&\quad \times \int_0^T \frac{k_1 \mu \left(k_1 K_s - \widetilde{S}^2(s)\right)}{\left(K_s k_1 + k_1 \widetilde{S}(s) + \widetilde{S}^2(s)\right)^2} \frac{\partial \Phi_1(s, X_0)}{\partial x_1} ds \frac{1}{a_0'} \dot{\widetilde{S}}(T) \\
&\quad - \left(\frac{k_1 \mu \widetilde{S}(T)}{\left(K_s k_1 + k_1 \widetilde{S}(T) + \widetilde{S}^2(T)\right)} - \frac{K_D V + Q_1}{V}\right) \\
&\quad \left.\left. \times \exp\left(\int_0^T \left(\frac{k_1 \mu \widetilde{S}(s)}{\left(K_s k_1 + k_1 \widetilde{S}(s) + \widetilde{S}^2(s)\right)} - \frac{K_D V + Q_1}{V}\right) ds\right)\right)\right) \\
&= \exp\left(\int_0^T \left(\frac{k_1 \mu \widetilde{S}(s)}{K_s k_1 + k_1 \widetilde{S}(s) + \widetilde{S}^2(s)} - \frac{K_D V + Q_1}{V}\right) ds\right) \\
&\quad \times \left(\int_0^T \left(\frac{k_1 \mu (K_s k_1 - \widetilde{S}^2(s))}{\left(K_s k_1 + k_1 \widetilde{S}(s) + \widetilde{S}^2(s)\right)^2} - \frac{K_D V + Q_1}{V}\right) ds\right) \frac{Q \widetilde{S}(T)}{V a_0'}
\end{aligned}
$$

$$-\left(\frac{k_1\mu\widetilde{S}(T)}{K_sk_1+k_1\widetilde{S}(T)+\widetilde{S}^2(T)}-\frac{K_DV+Q_1}{V}\right)$$
$$\times\exp\left(\int_0^T\left(\frac{k_1\mu\widetilde{S}(s)}{\left(K_sk_1+k_1\widetilde{S}(s)+\widetilde{S}^2(s)\right)}-\frac{K_DV+Q_1}{V}\right)ds\right)\Bigg).$$

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