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# LIMIT CYCLES IN A CONTINUOUS FERMENTATION MODEL

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## Abstract

The existence of limit cycles in a mathematical model for a continuous fermentation process is investigated. Estimation of perimeters and the relative positions of limit cycles are also discussed.

## 1. Introduction

Since the famous papers of Poincaré (1881, 1882, 1885, 1886) and Van der Pol (1926), the problem of limit cycles has attracted more and more attention from mathematicians, physicists, chemists, biologists and other scientists and engineers. At the beginning of this century, David Hilbert made a famous speech on mathematical problems at the International Mathematical Conference in Paris. In his speech, he listed twenty-three problems in the development of mathematics in this century as the most interesting and most important. Among the famous twenty-three Hilbert problems, the sixteenth is about limit cycles, that is, the maximum number of limit cycles of quadratic differential equations. Many years have passed. What happened to those problems? In 1974, the American Mathematical Society invited many mathematicians around the world to a special conference on Hilbert problems. Two massive volumes of titled proceedings, The Advances of Mathematics Due to the Hilbert Problems, were published. The solutions, discussions and developments were summarized one by one for all the twenty-three problems except for one. The exception was the sixteenth problem, which was only a copy of the original problem without a word added. From this we can see how necessary the study of limit cycles is (see, for example, [8]).

Recently, a nonlinear mathematical model for a single species growing in a continuously stirred homogeneous fermentor was studied by Crooke et al. [1,2]. In [1] it was proved that a generally accepted model for fermentation could not exhibit any periodic solution if the substrate yield term in the model was constant. Also, it was shown numerically that when one allows the substrate yield to depend on the substrate concentration in the fermentor under certain conditions on the system parameters (kinetic parameters, dilution rate, etc.), it is possible to have limit cycles in the cell concentration–substrate concentration phase plane. In [2], the Hopf bifurcation of solutions to the model was applied, with the assumptions of Monod kinetics and a variable yield term linearly dependent on the underlying substrate.

In particular, it was shown that the model possesses a one-parameter family of periodic solutions when certain system parameters of the model assume a specific ratio.

However, since bifurcation results can only produce a "small" solution and deal with its properties locally, the global analysis for this model is still necessary. Furthermore, in order to use the Hopf bifurcation theorem, the asymptotical stability of the corresponding equilibrium point is required (see ref. [3], theorem 5.5.1, p. 212, or ref. [4]). Therefore, before applying the Hopf bifurcation theorem one should prove the stability of $(u_0, v_0)$ in the case $\varepsilon = 0$, i.e. $A/C = R$, but this is not done in [2]. In addition, some computation in [2] needs to be modified (see eq. (9), p. 440).

In this paper, we shall employ the thoery of qualitative analysis of differential equations to prove the existence of limit cycles in the continuous fermentation model. Since our proof will not need the assumptions of Monod kinetics and the yield term linearly dependent on the underlying substrate, the model studied in [2] is a special case of ours and will be used as an illustration of our theorem. Moreover, we shall derive estimations of the perimeters of the limit cycles by comparing the curvatures of closed orbits in the model, and consequently discuss the relative position of the limit cycles. Our results may be useful to experimentalists because results have shown that some experimental data suggest that fermentors can exist as oscillatory behavior (see, for example, [1]).

## 2. The model

The following mathematical model works for a single species growing in a continuously stirred homogeneous fermentor which is continuously fed by a nutrient, and where the cells are continuously drawn off.

$$\frac{dX}{dt} = X(\mu(S) - D), \qquad X(0) = X^*,$$

$$\frac{ds}{dt} = D(S_F - S) - \frac{X}{Y(S)}\mu(S), \quad S(0) = S^*. \tag{2.1}$$

Here, $X(t)$ denotes the concentration of the cells, $S(t)$ the concentration of the substrate (nutrient), $Y(S)$ the cell-to-substrate yield (sometimes called the "yield coefficient), $\mu(S)$ the specific growth rate of the cells, $S_F$ the concencentration of the feed substrate, $D$ the ratio of the flow rate of the feed substrate to the volume of the fermentor reacting medium, and $t$ denotes time.

In [2], the Monod kinetics

$$\mu(S) = \frac{\mu_{\max} S}{K_S + S} \tag{2.2}$$

and the linearly dependent

$$Y(S) = A + BS \tag{2.3}$$

are assumed. By introducing the dimensionless variables,

$$\tau = Dt, \quad x = \frac{X}{S_F}, \quad y = \frac{S}{S_F}, \quad a = \frac{\mu_{\max}}{D}, \quad b = \frac{K_S}{S_F}, \quad C = BS_F,$$

applying (2.2) and (2.3), and then using $t$ instead of $\tau$, the model (2.1) is reduced to:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = x\left(\frac{ay}{b+y} - 1\right), \quad \frac{\mathrm{d}y}{\mathrm{d}t} = 1 - y - \frac{axy}{(b+y)(A+Cy)}, \tag{2.4}$$

where $a, b, A$, and $C$ are positive constants [2].

The model that we consider is

$$\frac{\mathrm{d}x}{\mathrm{d}t} = x(g(y) - 1), \quad \frac{\mathrm{d}y}{\mathrm{d}t} = 1 - y - \frac{g(y)}{F(y)}x, \tag{2.5}$$

where $g(y) = \mu(S_F y)$, $F(y) = Y(S_F y)$ which satisfy

$$g(0) = 0, \; g'(y) > 0, \; F(y) > 0, \; F'(y) > 0, \quad for\, y \geq 0. \tag{2.6}$$

Clearly, (2.5) is a generalization of the model (2.4). Our discussion is on the region $\Omega = \{(x, y) | \, x > 0, y > 0\}$.

## 3. Existence of limit cycles

The system (2.5) has two equilibrium points $E_1(0, 1)$ and $E_2(x^*, y^*)$, where

$$y^* = g^{-1}(1), \quad x^* = (1 - y^*)F(y^*). \tag{3.1}$$

The Jacobian of the system (2.5) is

$$J(x, y) = \begin{pmatrix} g(y) - 1, & xg'(y) \\ -\dfrac{g(y)}{F(y)}, & -1 - x\left(\dfrac{g(y)}{F(y)}\right)' \end{pmatrix}. \tag{3.2}$$

Since

$$J(0,1)=\begin{pmatrix} g(1)-1, & 0 \\ -\dfrac{g(1)}{F(1)}, & -1 \end{pmatrix}, \tag{3.3}$$

(0, 1) is a saddle point if

$$g(1)<1. \tag{3.4}$$

Note that (3.4) also implies $x^* > 0$. Then, both $E_1$ and $E_2$ are in $\Omega$.

Since

$$J(x^*,y^*)=\begin{pmatrix} 0 & x^*g'(y^*) \\ -\dfrac{1}{F(y^*)} & -1-x^*\left(\dfrac{g(y)}{F(y)}\right)'\Bigg|_{y=y^*} \end{pmatrix}, \tag{3.5}$$

the characteristic equation is

$$\lambda^2+\left(1+x^*\left(\frac{g(y)}{F(y)}\right)'\Bigg|_{y=y^*}\right)\lambda+\frac{x^*g'(y^*)}{F(y^*)}=0. \tag{3.6}$$

Let

$$P=1+x^*\left(\frac{g(y)}{F(y)}\right)'\Bigg|_{y=y^*}.$$

Clearly, $E_2$ is stable if $P>0$ and unstable if $P<0$.

For the case where $E_2(x^*, y^*)$ is unstable, we will prove that there exists at least one limit cycle in $\Omega$. To this end, we are going to construct an outer boundary of the Bendixson annular region (see fig. 1).

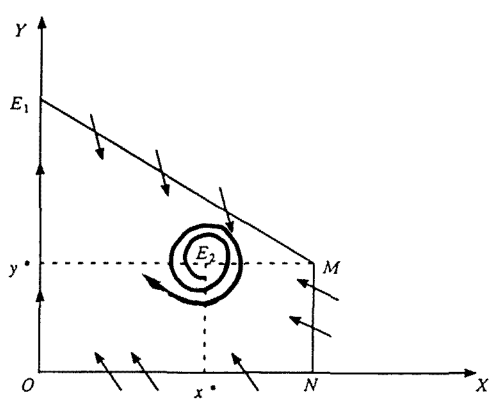


Figure 1.

Let $l_1$ be the line passing the saddle point $E_1(0, 1)$ with the slope $-1/F(1)$:

$$l_1:\ x + F(1)y - F(1) = 0. \tag{3.7}$$

Let $l_2$ be the perpendicular line to the $x$-axis passing $M(F(1)(1-y^*), y^*)$, the point of intersection of $l_1$ and $y = y^*$.

Since there is no equilibrium point when $y > 1$, the following estimation is made only for $0 < y < 1$:

$$\begin{aligned}\frac{\mathrm{d}l_1}{\mathrm{d}t} &= \left.\frac{\mathrm{d}x}{\mathrm{d}t}\right|_{l_1} + F(1)\left.\frac{\mathrm{d}y}{\mathrm{d}t}\right|_{l_1}\\ &= x(g(y)-1) + F(1)\left(1 - y - x\,\frac{g(y)}{F(y)}\right)\\ &= F(1)(1-y)(g(y)-1) + F(1)(1-y) - F(1)(1-y)F(1)\,\frac{g(y)}{F(y)}\\ &= F(1)(1-y)g(y)\left(1 - \frac{F(1)}{F(y)}\right)\\ &< 0.\end{aligned} \tag{3.8}$$

$$\begin{aligned}\frac{\mathrm{d}l_2}{\mathrm{d}t} &= \frac{\mathrm{d}x}{\mathrm{d}t} = x(g(y)-1)\Big|_{x=F(1)(1-y^*)}\\ &= F(1)(1-y^*)(g(y)-1) < 0\end{aligned} \tag{3.9}$$

Furthermore, on the line segment $ON$,

$$\frac{\mathrm{d}y}{\mathrm{d}t} = 1 > 0,$$

and $x = 0$ is a trajectory of (2.5).

Therefore, $OE_1MNO$ constitutes an outer boundary of a Bendixson annular region. By the Poincaré–Bendixson theoreom, there exists at least one limit cycle surrounding the unstable equilibrium point $E_2$.

The above argument can be summarized as:

THEOREM 3.1

Assume $g(1) < 1$ and, if

$$1 + x^*\frac{\mathrm{d}}{\mathrm{d}y}\left(\frac{g}{F}\right)\Big|_{y=y^*} > 0, \tag{3.10}$$

then the equilibrium point $E_2(x^*, y^*)$ of the system (2.5) is stable; if

$$1 + x^* \frac{\mathrm{d}}{\mathrm{d}y}\left(\frac{g}{F}\right)\bigg|_{y=y^*} < 0, \tag{3.11}$$

then $E_2(x^*, y^*)$ is unstable and there exists at least one limit cycle in (2.5) surrounding $E_2$.

For the model (2.4), we have:

THEOREM 3.2

Assume $a > b + 1$ and let

$$R = \frac{b(a - ab - b - 1)}{(a-1)((a-1)^2 + b)}. \tag{3.12}$$

If $A/C > R$, then $E_2$ is stable.

If $A/C < R$, then $E_2$ is unstable and the system (2.4) has at least one limit cycle surrounding $E_2$.

*Proof*

Let

$$g(y) = \frac{ay}{b+y}, \quad F(y) = \frac{1}{A + Cy}.$$

It is easy to see that the assumption (2.6) is satisfied, and

$$x^* = \frac{(a-b-1)(Aa - A + bC)}{(a-1)^2},$$
$$y^* = \frac{b}{a-1}. \tag{3.13}$$

Since

$$1 + x^* \frac{\mathrm{d}}{\mathrm{d}y}\left(\frac{g}{F}\right)\bigg|_{y=y^*}$$
$$= 1 + \frac{(a-b-1)(Aa - A + bC)}{(a-1)^2} \frac{a\left(b + \frac{b}{a-1}\right)\left(A + \frac{Cb}{a-1}\right) - \frac{ab}{a-1}\left(A + \frac{Cb}{a-1}\right) - \frac{abC}{a-1}\left(b + \frac{b}{a-1}\right)}{\left(b + \frac{b}{a-1}\right)^2\left(A + \frac{Cb}{a-1}\right)^2}$$
$$= 1 + \frac{(a-b-1)((a-1)(Aa - A + Cb) - abC)}{ab(Aa - A + Cb)} > 0 \tag{3.9}$$

is equivalent to

$$1+\frac{(a-b-1)(a-1)}{ab}>\frac{(a-b-1)C}{Aa-A+Cb},$$

or

$$((a-1)^2+b)\left((a-1)\frac{A}{C}+b\right)>ab(a-b-1),$$

or

$$(a-1)\frac{A}{C}>\frac{ab(a-b-1)-b((a-1)^2+b)}{(a-1)^2+b},$$

or

$$\frac{A}{C}>\frac{b(a-ab-b-1)}{(a-1)((a-1)^2+b)}=R. \tag{3.14}$$

Similarly,

$$1+x^*\frac{\mathrm{d}}{\mathrm{d}y}\left(\frac{g}{F}\right)\Big|_{y=y^*}<0$$

is equivalent to

$$\frac{A}{C}<R.$$

Thus, we complete the proof of theorem 3.2 by employing theorem 3.1. □

Note: As we mentioned in the beginning of this paper, the use of the Hopf bifurcation theorem needs the assumption of the asymptotical stability of $E_2$ for the case $\varepsilon=0$ or $A/C=R$. Unfortunately, this was not done in [2]. Thus, the analytical proof of the existence of limit cycles was still open. Now, it is completely solved by our theorem 3.2.

## 4. Perimeters and relative positions of limit cycles

In this section, by the comparison of curvatures, we are going to estimate the perimeters of the limit cycles of the model (2.5). Since there are experimental data to suggest that fermentors can exhibit oscillatory behavior [1], to estimate the perimeters of period orbits in the cell concentration–substrate phase plane may be useful to the biochemists.

Rewrite the system (2.5) as

$$\frac{\mathrm{d}x}{\mathrm{d}s} = \frac{x(g(y)-1)}{\sqrt{x^2(g(y)-1)^2+(1-y-\frac{g(y)}{F(y)}x)^2}} = P(x,y),$$

$$\frac{\mathrm{d}y}{\mathrm{d}s} = \frac{1-y-\frac{g(y)}{F(y)}x}{\sqrt{x^2(g(y)-1)^2+(1-y-\frac{g(y)}{F(y)}x)^2}} = Q(x,y), \tag{4.1}$$

where $s$ is the length of the arc.

THEOREM 4.1

Let $C_1$ and $C_2$ be two limit cycles of (4.1) with curvatures $\kappa_1(s)$ and $\kappa_2(s)$, respectively. Let $l_1$ and $l_2$ be the perimeters of $C_1$ and $C_2$. If

$$\kappa_1(s) \geq \kappa_2(s) > 0, \tag{4.2}$$

then

$$l_1 \leq l_2. \tag{4.3}$$

*Proof*

Suppose by proper coordinate transform the relative position of $C_1$ and $C_2$ is as shown in fig. 2:

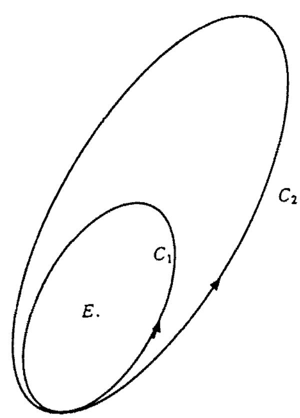


Figure 2.

Since $\kappa_1(s)$ and $\kappa_2(s)$ are positive, $C_1$ and $C_2$ are convex closed right-handed curves. Hence, the index of $C_i$ is 1. That is, for $i = 1, 2$,

$$\frac{1}{2\pi}\int_{C_i}\kappa_i(s)\mathrm{d}s = 1.$$

Assume $l_1 > l_2$. Then,

$$\int_{C_i}\kappa_1(s)\mathrm{d}s = \int_0^{l_2}\kappa_1(s)\mathrm{d}s + \int_{l_2}^{l_1}\kappa_1(s)\mathrm{d}s$$

$$= \int_0^{l_2}\kappa_2(s)\mathrm{d}s.$$

Hence,

$$\int_0^{l_2}(\kappa_1(s) - \kappa_2(s))\mathrm{d}s + \int_{l_2}^{l_1}\kappa_1(s)\mathrm{d}s = 0. \tag{4.5}$$

Since $\kappa_1(s) - \kappa_2(s) \geq 0$, we have

$$\int_{l_2}^{l_1}\kappa_1(s)\mathrm{d}s \leq 0, \tag{4.6}$$

which is a designed contradiction to $\kappa_1(s) > 0$. □

Clearly, the curvature of the curves defined by (4.1) is

$$\kappa(x,y) = \frac{P\left(\frac{\partial Q}{\partial x}P + \frac{\partial Q}{\partial y}Q\right) - Q\left(\frac{\partial P}{\partial x}P + \frac{\partial P}{\partial y}Q\right)}{(P^2+Q^2)^{3/2}}. \tag{4.7}$$

The following corollary is useful for the estimation of the perimeters of limit cycles of (4.1).

COROLLARY 4.2

If there exists $r_1$ and $r_2$ such that

$$\frac{1}{r_1} \geq |\kappa(x,y)| \geq \frac{1}{r_2}, \tag{4.8}$$

then, for any limit cycle, its perimeter satisfies

$$2\pi r_1 \leq l \leq 2\pi r_2. \tag{4.9}$$

Now, for the relative position of the limit cycles, we have:

COROLLARY 4.3

If (4.8) holds, then all the limit cycles of (4.1) must be inside the circle with radius $\pi r_2$ and the center at the corresponding unstable equilibrium point $E_2$.

The inner boundary can be constructed by the same technique as in [5].

The idea used in this section is useful for many other models (for example, the model studied by Huang and Merrill [6,7]).

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