J.Sci.Soc.Thailand, 20(1994) 43-59

THEORETICAL INVESTIGATION OF A PRODUCT INHIBITION MODEL FOR A CONTINUOUS CULTURE: EFFECT OF YIELD TERM AND PARABOLIC SPECIFIC GROWTH RATE

YONGWIMON LENBURY AND BORIBOON NOVAPRATEEP

Department of Mathematics, Faculty of Science, Mahidol University, Rama 6 Road, Bangkok 10400, Thailand.

(Received Jan 15, 1994)

ABSTARCT

The dynamic behavior of a model for the continuous culture subject to product inhibition is investigated theoretically in terms of multiplicity and stability of steady states and existence and stability character of limit cycles. It is shown that bifurcation of periodic solution cannot occur from the washout steady state of the model system. At the point of bifurcation of periodic solution from a nontrivial steady state, however, an increase in the substrate concentration must decrease the specific growth rate and increase the substrate consumption rate. Various boundary conditions are derived which delineate the parameter space into regions of dynamically different behavior. The predicted types of behavior are then illustrated by numerical computation of cells and product concentration trajectories.

INTRODUCTION

Basically, microbial kinetics have varied in diverse ways from a model due to Monod fashioned after Michaelis-Menton kinetics for single enzyme-substrate reactions, in which the yield coefficient Y is assumed constant. The most obvious departure from the predictions of Monod model is in the variation of the stoichiometric coefficient Y, as in the work of Agrawal et al. [1] for example. Dynamic behaviors of the continuous fermentation have also been studied theoretically by several workers for different types of specific growth rate function. In some fermentations inhibition of microbial growth is observed at a high concentration of its product as in, for example, the lactic acid fermentation [2]. A model for such a chemostat in which the growth of a microorganism is inhibited by its product was presented and theoretically studied in a paper by Yano and Koga [2], where the specific growth rate was assumed to have the form

$$\mu(P) = \frac{\mu_m}{[1 + (P/K_p)^n]}$$

and the single - vessel continuous fermentation system is described by the following system of differential equations:

$$\frac{dX}{dt} = \mu(P)X - DX \qquad (1)$$

$$\frac{dP}{dt} = [\eta1 + \eta2\,\mu(P)]X - DP \qquad (2)$$

in the case that the growth limiting substrate S is supplied in sufficient amount so that the concentration change in S has little effect on the rates of change in the cells or product concentration. Here, X (t) denotes the cells concentration at time t; P (t) the product concentration at time t; D the dilution rate; and h1 and h2 are constants for product formation.

Lenbury and Chiaranai [3] later carried out a theoretical study of the two dimensional model with h1 = 0; namely

$$\frac{dX}{dt} = \mu X - DX \qquad X(0) = X0 \qquad (3)$$

$$\frac{dP}{dt} = \frac{\mu X - DP}{Y_p} \qquad P(0) = P0 \qquad (4)$$

If Yp is assumed constant, it can be shown [4] that the system of Eqns. (3) and (4) will not admit periodic behavior. It was also shown by Lenbury and Chiaranai [3] that if Yp is a linear function of the product concentration, sustained oscillation in X and P is possible due to a Hopf bifurcation in the system of differential equations which comprises the model. Some recent studies on these types of models can be found in the work of Alsholm [5] and that of Cheng-Fu [6]. In this paper, we shall therefore consider the system of Eqns. (3) and (4) with

$$Yp = A + BP \qquad (5)$$

where A and B are constants.

Following the work of Poore [7] and Uppal et al. [8, 9] and later that of Agrawal et al. [1] on dynamic behavior of continuous stirred tank biological reactors, the criterion for periodic behavior of continuous cultures originating from Friedrich's [10] sufficient condition for the existence of limit cycles will be derived. We adopt for simplicity the function

$$\mu_m = \mu_0 (1 + P/k_m - P2/k_p) \qquad (6)$$

where m0 , km, and kp are positive constants, which exhibits the same characteristics as the usual product inhibition model [2] in the range where the function has positive value. In fact, the function in (6) results from linearizing the exponential term in the one hump' product inhibition model

$$\mu_m = k(P + 1)\exp(-P/K) \qquad (7)$$

Different types of dynamic behavior of the continuous biological reactor subject to product inhibition, modelled by Eqns. (3) and (4) with (5) and (6), shall be classified in terms of a 'modified Damkohler number' and two other system parameters.

MATERIAL AND METHOD

Introducing for convenience a new set of variables, namely; $x_1 = X / [k_m Y_p(0)]$, $x_2 = P / k_m$, $T = Dt$, $Da = \mu(0) / D$, $M(x_2) = \mu(k_m x_2) / \mu(0)$, $y(x_2) = Y_p(k_m x_2) / Y_p(0)$, $\alpha = k_m^2 / kp$, $\beta = -A / Bkm$, the Eqns. (6) through (9) become

$$\frac{dx_1}{dT} = -x_1 + D_a M(x_2)\, x_1 \qquad (8)$$

$$\frac{dx_2}{dT} = -x_2 + D_a M(x_2)\, x_1 / y(x_2) \qquad (9)$$

$$y(x_2) = (b - x_2) / b \qquad (10)$$

$$M(x_2) = 1 + x_2 - a\, x_2^2 \qquad (11)$$

Letting

$$\Sigma(x_2) = M(x_2) / y(x_2) \qquad (12)$$

$$f_1(x_1, x_2, Da) = -x_1 + DaM(x_2)\, x_1 \qquad (13)$$

$$f_2(x_1, x_2, Da) = -x_2 + Da\Sigma(x_2)\, x_1 \qquad (14)$$

Eqns. (8) and (9) may be recast in vector form as

$$dx / dT = f(x, Da) \qquad (15)$$

We investigate the dynamic as well as steady state behavior of the system described by Eqn. (15). We are particularly interested in the effects of the yield expression and the parabolic specific growth rate on the existence of limit cycles and their stability.

Solving the equation

$$f(x_s, Da) = 0$$

for $x_s = (x_{s1}, x_{s2})$, we obtain the steady state solutions as

(a) trivial (washout) steady state : $x_{s1} = x_{s2} = 0$,

(b) nontrivial steady state (s) : $x_{s1} = y(x_{s2})\, x_{s2}$, $M(x_{s2}) = 1/Da$.

Let J be the Jacobian matrix of f evaluated at the steady state of interest,

$$J(x_s, Da) = \begin{bmatrix} -1 + Da\, M(x_{s2}) & Da\, M'(x_{s2})\, x_{s1} \\ Da\, S(x_{s2}) & -1 + Da\, S'(x_{s2})\, x_{s1} \end{bmatrix} \qquad (16)$$

where the prime denotes differentiation with respect to x2. The necessary and sufficient conditions for local stability of a steady state are that eigenvalues have negative real parts, which are equivalent to

$$\det J > 0 \text{ and } \operatorname{tr} J < 0$$

At the washout steady state,

$$\text{tr } J = -2 + Da \quad (17)$$

$$\det J = 1 - Da. \quad (18)$$

It follows therefore that the washout steady state is stable if $Da < 1$ and a saddle point for $Da > 1$.

For the nontrivial steady states, xs 0,

$$\det J = - D_a M'(x_{s2}) x_{s2} \quad (19)$$

and

$$\text{Tr } J = -1 + Da \Sigma'(x_{s2}) x_{s1} \quad (20)$$

Therefore, the necessary and sufficient conditions for local stability are

$$M'(x_{s2}) < 0 \quad (21)$$

and

$$S'(x_{s2}) < 1 / Da\, x_{s1} \quad (22)$$

Now, Hopf bifurcation occurs at a steady state xs^* if J evaluated at xs^* has purely imaginary eigenvalues, which requires that

$$\det J > 0 \text{ and } \text{tr } J = 0 \quad (23)$$

Due to (17) and (18), the two conditions in (23) cannot be satisfied simultaneously for the washout steady state. Therefore, bifurcation of periodic solution cannot occur here.

For the nontrivial steady states, it is possible to prove the following theorem.

Theorem1 A necessary condition that a Hopf bifurcation of periodic solution occurs from a nontrivial steady state of the system of equations (8) and (9), with (10) and (11), is that $B < 0$.

Proof For a nontrivial steady state, condition (23) for Hopf bifurcation becomes

$$M'(x_{s2}^*) < 0 \quad (24)$$

and

$$D_a \Sigma'(x_{s2}^*) x_{s1}^* - 1 = 0 \quad (25)$$

or, equivalently

$$\Sigma'(xs2^*) = \frac{1 > 0}{x_{s1}^* Da} \quad (26)$$

Conditions (24) and (26) state that, at the point of bifurcation, an increase in the substarte concentration must decrease the specific growth rate and increase the substrate consumption rate. This can be explained by the graphs depicted in Figuṙe 1 which shows possible regions of bifurcation for different specific growth rate and substrate consumption rate curves.

Since $y(x_2) = M(x_2) / \Sigma(x_2)$, conditions (24) and (26) imply that

$$\frac{dy}{dt} = [M'(x_2)\Sigma(x_2) - \Sigma'(x_2)M(x_2)]/\Sigma^2(x_2) < 0$$

which means that the yield coefficient must decrease with the substrate concentration. Hence, no periodic solution is possible if $B \geq 0$.

As a result of the above theorem, we will henceforth assume that $B < 0$ (equivalently $\beta > 0$). Applying conditions (24) and (25) to the functions in Eqns. (10) and (11), we find that for positive det J the following condition must be satisfied

$$1 - 2\alpha x_{s2}^* < 0 \qquad (27)$$

while $\mathrm{tr}\, J = 0$ is equivalent to the requirement that

$$g (x_{s2}^*) = (1 - \alpha\beta) (x_{s2}^*)^2 + 2 x_{s2}^* - \beta = 0 \qquad (28)$$

the other factors in tr J being always positive.

The function $g (x_{s2}^*)$ will have two distinct positive real roots $x_{s2}^* = r_1$ and r_2, with $r_1 < r_2$, if

$$1/\beta > \alpha\beta - 1 > 0 \qquad (29)$$

On the other hand, if $\alpha\beta - 1 < 0$ then $g (x_{s2}^*)$ has only one positive real root r_1. Also, if $\alpha\beta - 1 < 0$ then from Eqn. (28)

$$x_{2s}^* = \beta/2 - (\alpha\beta - 1) (x_{s2}^*)^2 / 2 > \beta/2 > 1 / 2\alpha$$

Therefore, $\det J = 2\alpha x_{s2}^* - 1 > 0$ when $\alpha\beta - 1 < 0$, in which case no bifurcation occurs. In other words, $M' (x_{s2}^*)$, and correspondingly det J , changes signs when

$$\alpha\beta - 1 = 0 \qquad (30)$$

Finally, onset of instability of steady states x_s is realized when $\mathrm{tr}\, J = 0$ and $(\mathrm{tr}\, J)' = 0$ which, from Eqn. (28), occurs when

$$\alpha\beta^2 - \beta - 1 = 0 \qquad (31)$$

STABILITY OF LIMIT CYCLES

Applying the Poincare's criterion and Friedrich's bifurcation theory [10], we may derive the following condition for the stability of the periodic solution which bifurcates from the point $x_{s2} = x_{s2}^*$:

$$3\Sigma''' (x_{s2}^*) x_{s2}^* < \Sigma'' (x_{s2}^*) \{ 1 + 4 M'' (x_{s2}^*) x_{s2}^*/3M'(x_{s2}^*) \} \qquad (32)$$

According to Agrawal *et al.* [9], it can be shown that if a bifurcated periodic solution surrounds an unstable critical point, it is stable. If it surrounds a stable critical point it is unstable. We are now in the position to prove the following theorem.

Theorem2 The limit cycle which bifurcates from the 'upper' bifurcation point $x_{s2}^* = r_2$ is always stable, while the limit cycle which bifurcates from the 'lower' bifurcation point $x_{s2}^* = r_1$ is stable if

$$9 [1 - \beta (\alpha\beta - 1)]^{1/2} r_1^2 < (\beta - r_1)^2 (3 - 14 \alpha r_1) / (3 - 6 \alpha r_1) \qquad (33)$$

Proof

Evaluating M" , Σ" and Σ''' and substituting into Eqn. (32), we arrive at the following stability condition :

$$9[(1 - \alpha\beta) x_{s2}^* + 1] (x_{s2}^*)^2 < \frac{(\beta - x_{s2}^*)^2 (3 - 14\alpha x_{s2}^*)}{(3 - 6\alpha x_{s2}^*)} \qquad (34)$$

From Eqn. (28), we have

$$(1 - \alpha\beta) r_{1,2} + 1 = \pm [1 - \beta (\alpha\beta - 1)]^{1/2} \qquad (35)$$

Therefore, for $x_{s2} = r_2$, the left hand side of the inequality in (34) reads

$$- 9 [1 - \beta (\alpha\beta - 1)]^{1/2} r_2^{\ 2}$$

which is always negative. On the other hand, we need have $1 - 2\alpha x_{s2}^* < 0$ for bifurcation, in which case we must have

$$3 - 14 \alpha x_{s2}^* < 3 - 6 \alpha x_{s2}^* < 0$$

This in turns implies

$$(3 - 14 \alpha x_{s2}^*) / (3 - 6 \alpha x_{s2}^*) > 1$$

and therefore the right hand side of (33) is always positive. This means that a limit cycle bifurcating from the bifurcation point $x_{s2}^* = r_2$ is always stable.

Now , for the point $x_{s2}^* = r_1$, the stability condition (35) for the limit cycle becomes

$$9 [1 - \beta (\alpha\beta - 1)]^{1/2} r_1^2 < (\beta - r_1)^2 (3 - 14 \alpha r_1) / (3 - 6 \alpha r_1)$$

which is inequality (33).

Substituting the appropriate root r1 in (33), we find that a loss of stability of the periodic solution which bifurcates from xs2* = r1 occurs when

$$\beta = (1 + c) (-14 c^2 + 68 c - 54) / (3 c^2 - 38 c + 27) \qquad (36)$$

where $c = [1 - \beta (\alpha\beta - 1)]^{1/2}$.

LOCATIONS OF BIFURCATION POINTS

Letting w be the 'modified Damkohler number' defined by

$$w = 1 - 1 / Da \qquad (37)$$

we have from (b) that

$$w = \alpha (x_{s2})^2 - x_{s2} \qquad (38)$$

the graph of which can be seen in Figure 2. We see that w = 0 at $x_{s2} = 0$ and $1 / \alpha$.

By condition (29) for two positive real roots we must have

$$\beta\,(\,\alpha\beta - 1\,) \; < \; 1 \quad \text{and} \quad \alpha\beta \; > \; 1$$

so that

$$(\,\alpha\beta - 1\,)\,/\,\alpha^2 \; < \; \beta^2\,(\,\alpha\beta - 1\,) \; < \; \beta$$

Thus, we have

$$r_1\, r_2 \; = \; \beta\,/\,(\,\alpha\beta - 1\,) \; > \; 1\,/\,\alpha^2 \qquad (\,39\,)$$

which means that if $r_1 < 1/\alpha$ then $r_2 > 1/\alpha$. On the other hand , if $r_1 > 1/\alpha$ then $r_2 > r_1 > 1/\alpha$. In other words, r_2 is always greater than the value $1/\alpha$, while r_1 may be either less than or greater than that value. Substituting $1/\alpha$ for $x_{s2}{}^*$ in Eqn. (31) , we find that r_1 will be equal to $1/\alpha$ when

$$\alpha\beta \quad = \frac{1 + 2\,\alpha}{1 + \alpha} \qquad (\,40\,)$$

If $\alpha\beta$ is less than the quantity on the right of Eqn. (40) then $r_1 < 1/\alpha$. As w increases, x_{s2} increases until the value r_1 is reached where tr J = 0, then bifurcation occurs at this critical value $w_1{}^*$ of the modified Damkohler number . If the parametric values α and β satisfy condition (33) also, then the bifurcation originating at this lower critical modified Damkohler number w1* is stable. Between the two critical modified Damkohler numbers $w_1{}^*$ and $w_2{}^*$ at which points tr J = 0 , the steady state is unstable which is represented by a dashed line, while the stable limit cycles existing between these two w*'s are denoted by dots. The distance between the dot and the dashed line approximately represents the average amplitude (in x_2) of the limit cycle surrounding the unstable steady state.

BEHAVIOR CLASSIFICATION

From the above discussions, we have found that the two system parameters α and β determine the stability regions of bifurcating periodic solutions. Figure 2 shows the (α , β) plane divided into 5 regions by the graphs of Eqns. (30) , (31) , (36) and (40) . Following the representation used by Uppal *et al.* [10] we also show in Figure 3 typical steady state and limit cycle plots of x_{x2} vs w for each region. There can be as many as eleven different types of qualitative phase plane which are possible for different ranges of the modified Damkohler numbers w. These are labelled A through K in Table 1.

In region I, there is no bifurcation ($\alpha\beta^2 - \beta - 1 > 0$). Three types of phase plane are possible : A , B and C. The type A shows only one stable washout steady state. The type B shows one stable washout, one unstable normal and one stable normal, while the type C shows an unstable washout (saddle point) and a stable normal.

In region II , $\alpha\beta^2 - \beta - 1 > 0$ and so bifurcation occurs. Since this region is above the graph of Eqn. (36) , unstable bifurcation originates at the lower modified Damkohler number $w_1{}^*$, with stable bifurcation originating at the upper modified Damkohler number $w_2{}^*$. This region is also bounded below by the graph of Eqn. (40) and therefore $r_1 > 1/\alpha$. Thus, in this region, two cases are possible, IIa and IIb, permitting seven types of phase

TABLE 1. Typical phase plots.

	A	B	C	D	E	F	G	H	I	J	K
Stable washout (node)	1	1	0	0	0	0	1	1	1	1	1
Unstable washout (saddle pt.)	0	0	1	1	1	1	0	0	0	0	0
Stable normal (node or focus)	0	1	1	1	0	1	0	1	0	1	0
Unstable normal (saddle pt. or focus)	0	1	0	0	1	0	1	1	2	1	2
Stable limit cycle	0	0	0	1	1	0	0	1	1	0	0
Unstable limit cycle	0	0	0	1	0	1	0	1	0	1	0
Total invariants	1	3	2	4	3	3	2	5	4	4	3

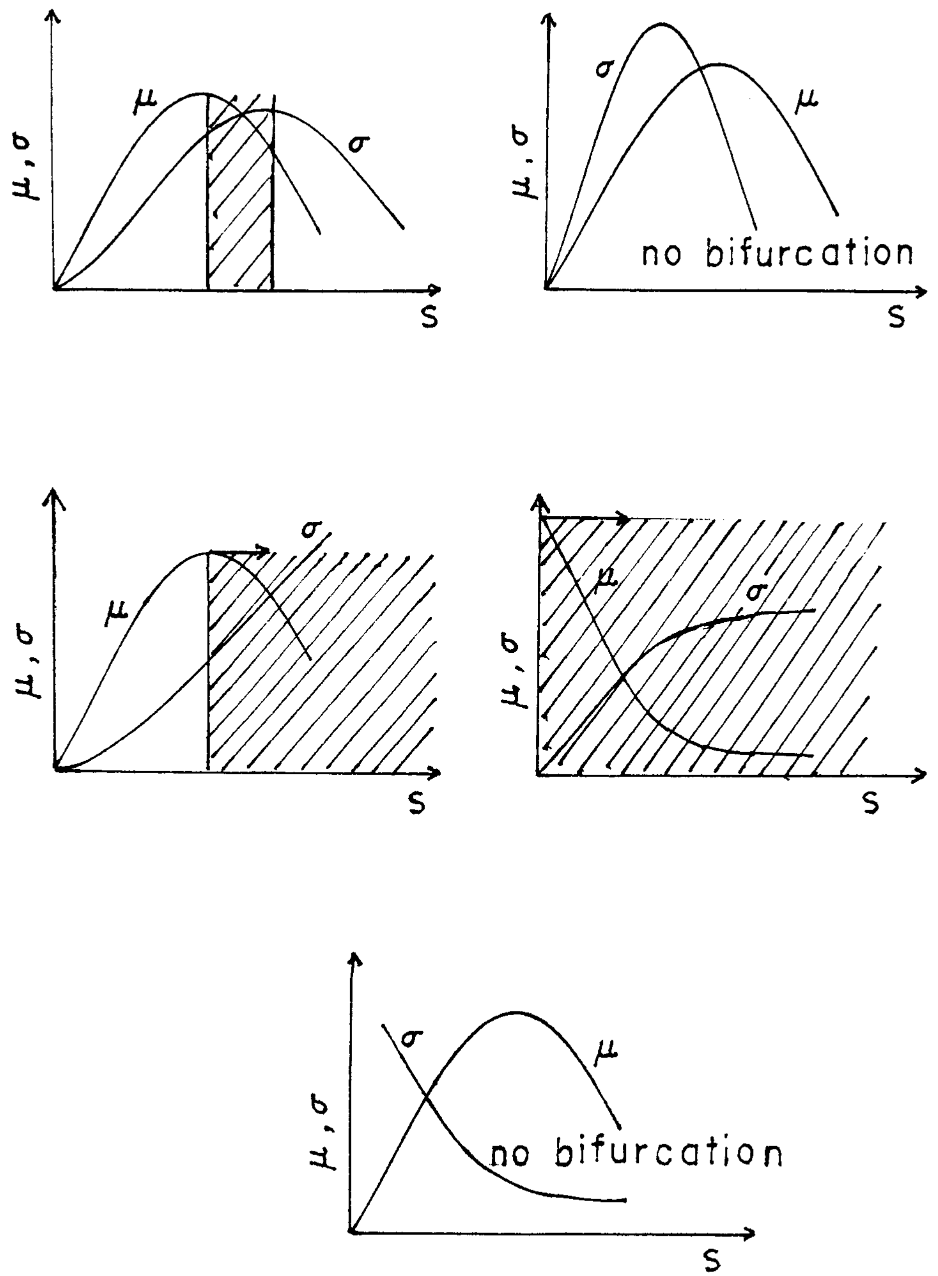

Fig. 1 Possible regions of bifurcation (shaded) for various specific growth rate and substrate consumption rate functions.

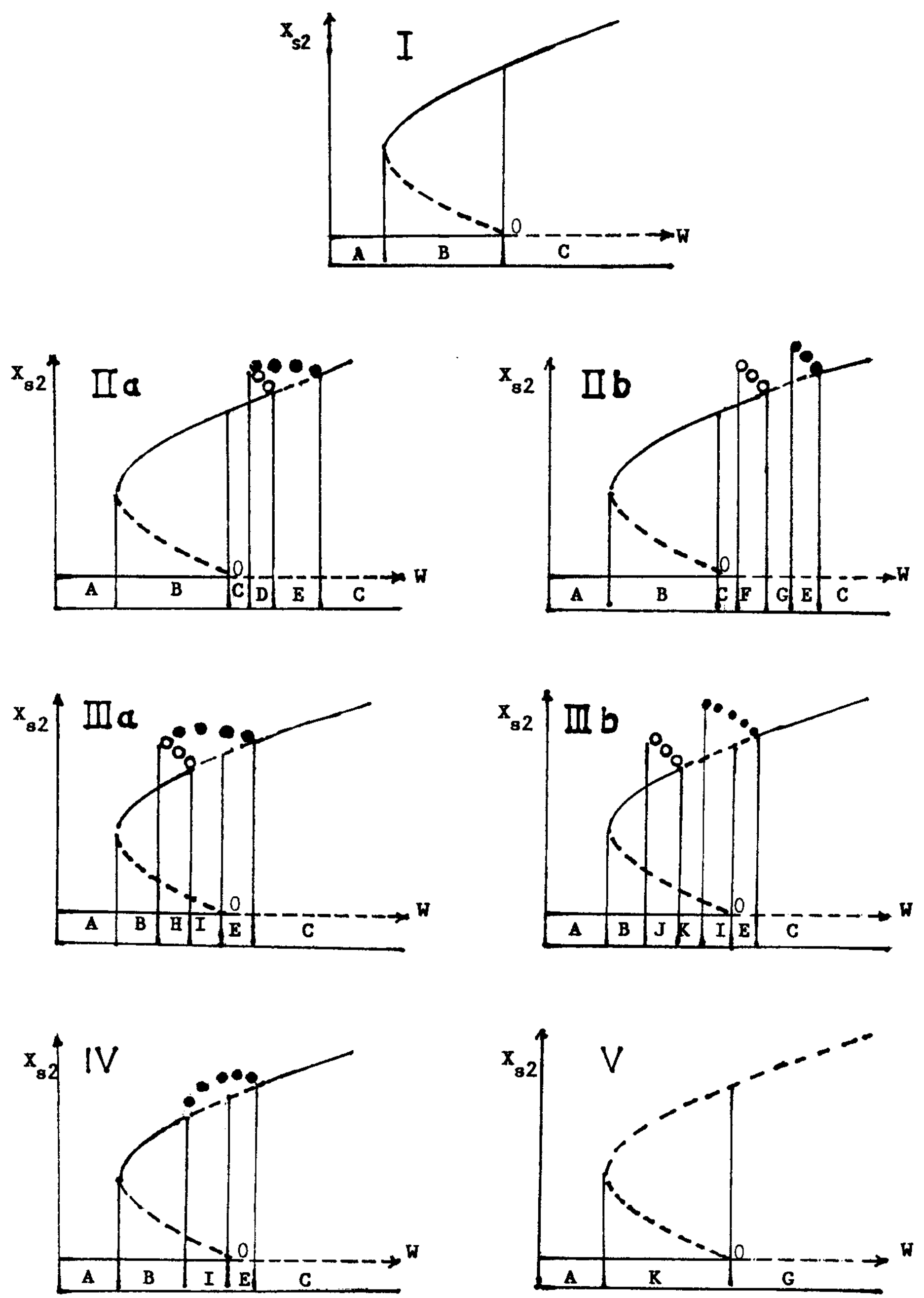

Fig. 2 Typical plots of w vs x_{s2} for each region in the (α , β) plane.

————	stable steady state,
- - - - - -	unstable steady state,
● ● ●	stable limit cycle,
○ ○ ○	unstable limit cycle.

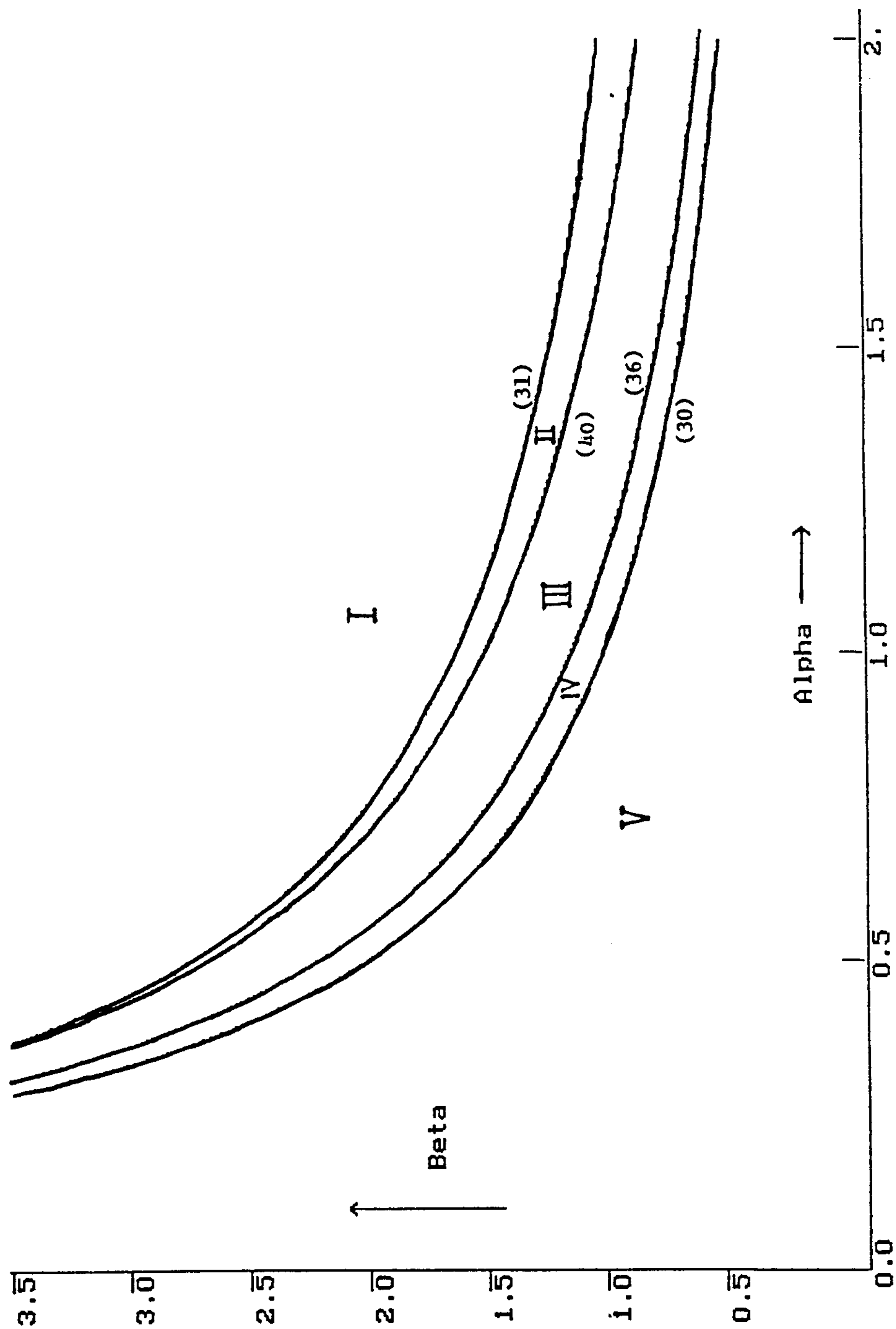

Fig. 3 The (α , β) plane delineated by graphs of Eqns.(30), (31), (36), and (40) into 5 regions of qualitatively different dynamic behavior.

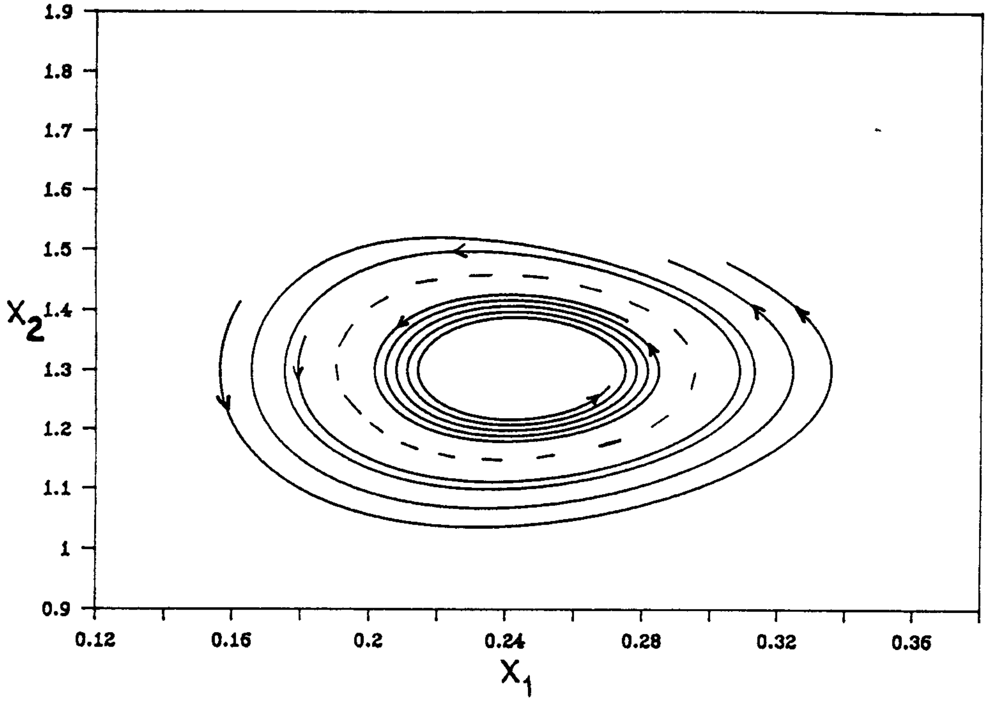

Fig. 4 Computer simulation of the system model with α = 1.0, β =1.6 and Da = 0.61 (Region II, type F) showing solution trajectories tanding away from the unstable limit cycle.

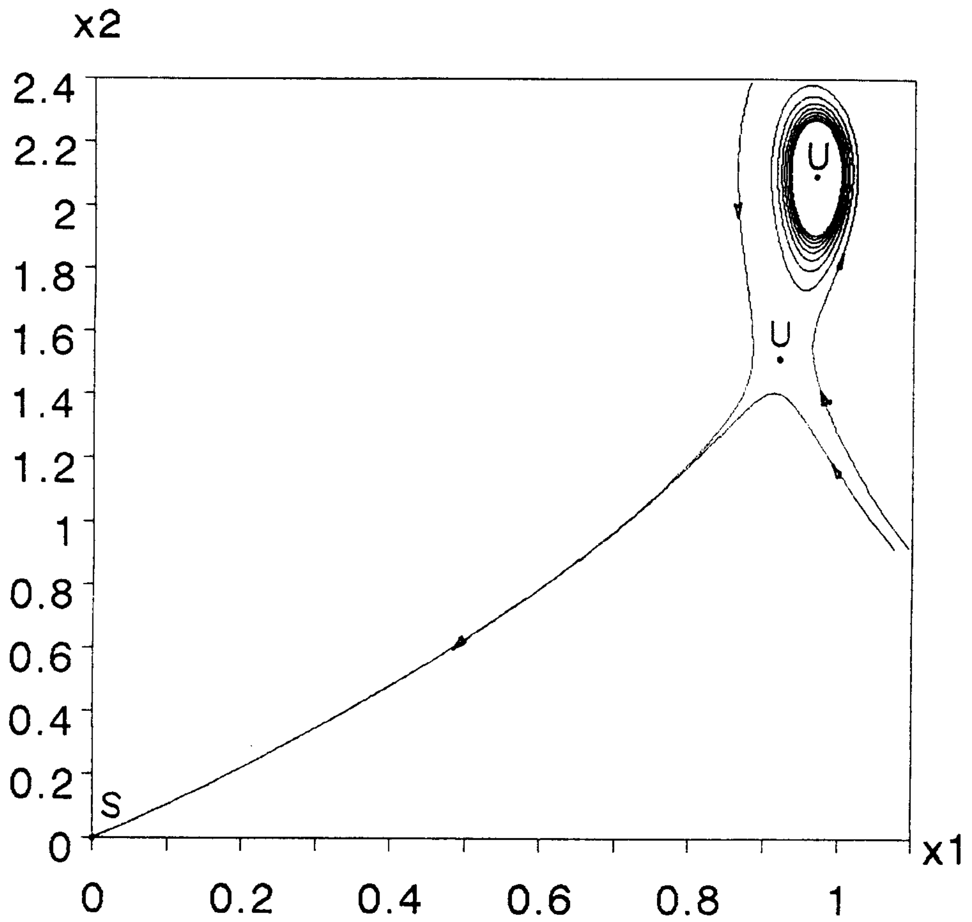

Fig. 5 Computer simulation of the system model with α =0.273997, β = 3.9 and Da = 1.891370559 (Region IV, type I) showing solution trajectories pushed away from the saddle point towards the stable limit cycle or the stable washout steady state.

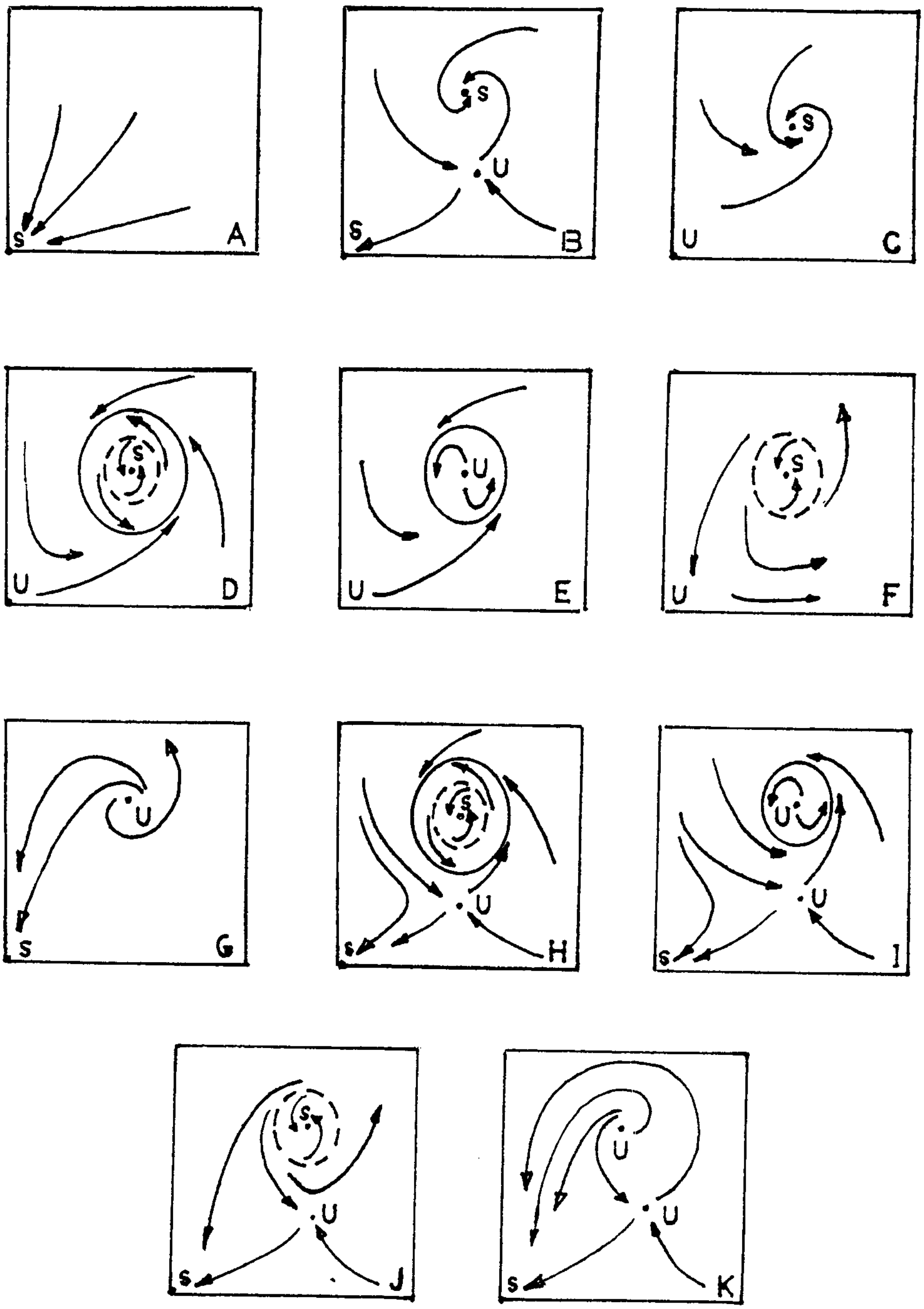

Fig. 6 Typical phase space plots of types A through K in Table 1.

plane, A through G. The type D shows one unstable washout (saddle point) , a stable normal surrounded by one unstable limit cycle inside a stable one which bifurcates from the upper modified Damkohler number w_2*. The type E shows one unstable washout, one unstable normal (focus) and a stable limit cycle which surrounds the steady state. The type F shows one unstable washout, one stable normal and one unstable limit cycle. The type G shows one unstable washout and one unstable normal.

Region III is bounded below by the graph of Eqn. (36) which means that the limit cycle bifurcating at the lower modified Damkohler number is still unstable. It is bounded above by the graph of Eqn.(40) which means that r_1 lies below the value 1/a here and there can be two and below by that of Eqn. (36). Here, r1 lies below the value $1 / \alpha$ and there can be two cases, IIIa and IIIb, in this region admitting eight types of phase plane, A through C, E, and H through K. The type H shows one stable washout, one unstable normal and one stable normal (focus) surrounded by an unstable limit cycle inside a stable limit cycle. The type I shows one stable washout and two unstable normals one of which is a focus surrounded by a stable limit cycle. The type J shows one stable washout, one unstable normal, one stable normal and an unstable limit cycle. The type K shows one stable washout and two unstable normals.

Region IV is one of stable bifurcation at the lower modified Damkohler number w_1* since the stability condition (33) is satisfied . There, five types of phase plane trajectories are possible, A through C , E and I.

Finally, in region V $\alpha\beta - 1 < 0$ and no bifurcation occurs. Tr J becomes positive at x_{s2} for which $M'(x_{s2}) < 0$ so that the nonwashout steady states are always unstable. Thus, there are 3 possible types of phase plane in this region, A, G and K.

Figure 4 shows computer simulation of the system model for $\alpha = 1.0$ and $\beta = 1.6$, where the solution trajectories of the type F are seen to tend away from the unstable limit cycle whose approximate position is represented by the dashed line. In Figure 5, a computer simulation of the system model is presented for $\alpha = 0.273997$ and $\beta = 3.9$ in region IV and Da = 1.891370559 of the type I, showing the predicted three steady states, a stable washout, a saddle point, and an unstable focus surrounded by a stable limit cycle.Trajectories are seen to be pushed away from the saddle point, either towards the stable washout steady state or towards the stable limit cycle.

To summerise, typical plots of all eleven possible types of phase space, labelled A through K in Table 1, are depicted in Figure 6.

CONCLUSIONS

We have theoretically investigated steady state multiplicity and existence of limit cycle behavior of a continuous bio-reactor subject to product inhibition modelled by two mass balance equations over cells and product, in which the supply of substrate is assumed to be of a surplus amount so that the concentration change of S has little effect on the rates of change in X and P .

It is found that bifurcation to periodic solutions can occur only at the nontrivial steady state and not at the washout steady state. At the nontrivial steady state, bifurcation of periodic solution occurs only if an increase of the substrate concentration leads to a decrease of the specific growth rate and an increase of the substrate consumption rate. Asymptotically stable limit cycles exist for a significant range of the modified Damkohler number at appropriate system parametric values. While it is possible for bifurcation to originate at two modified Damkohler numbers w_1^* and w_2^*, the one originating at the upper modified Damkohler number w_2^* is always stable.

Employing a simple product inhibition form of the specific growth rate which results from linearizing the so called " one hump " function involving two parameters, phase plane trajectories have been completely classified and numerical examples given. It was also shown that for bifurcation to occur ,the yield coefficient must decrease with the substrate concentration justifying our use of a simple linearly decreasing yield coefficient Y_p (P) which was sufficient to allow limit cycle behavior. In practice, the yield coefficient is known to vary for many organisms [1] and various researchers have adopted such linear form for the yield expression in their works with models of continuous fermentation processes [2, 5]. It is also reasonable to expect that a high product concentration will have an inhibitory effect on the yield.

Introducing the modified Damkohler number, our analysis shows that, in changing its value, the product inhibition model considered in this paper yields five dynamically different regions in the parameter plane and up to a combination of five possible invariants in a phase plane. Such high variety in dynamic behaviour which the model can simulate indicates how, inspite of its simplicity, the model is able to give new and valuable insights to the complexity of continuous microbial cultures.

ACKNOWLEDGEMENTS

Appreciation is rendered to the National Research Council of Thailand and Thai Oil Company Limited for their financial support.

REFERENCES

1. P. Agrawal, S. Lee, H. C. Lim and D. Ramakrishna (1982). Theoretical Investigations of Dynamic Behavior of Isothermal Continuous Stirred Tank Biological Reactors. *Chem. Engng. Sci.* **37**, 453 - 462.
2. T. Yano and S. Koga (1973). Dynamic Behavior of the Chemostat Subject to Product Inhibition. J. Gen. Appl. Microbiol. **19** (2), 97 - 114 .
3. Y.Lenbury and C.Chiaranai (1987). Bifurcation Analysis of a Product Inhibition Model of a Continuous Fermentation Process.Appl. Microbiol. *Biotechnol* **25**:532-534.
4. Y. Lenbury and C. Chiaranai (1987). Direction of the Sustained Oscillation Trajectoriy in the Cell - Product Phase Plane Describing Product Inhibition on Continuous Fermentation Systems. *Acta Biotechnol.* **7** (5) 433 - 437.
5. P. Alsholm (1992). Non - existence of periodic solutions in a model of continuous fermentation. *Proc. R. Soc. Lond.* **A 438**, 311-318.
6. J. Cheng-Fu, Existence and uniqueness of limit cycles in continuous cultures of microorganisms with nonconstant yield factor. Preprint, Universita degli studi di Bari, Italy.
7. Poore, B. A. (1973). A model Equation Arising from Chemical Reactor Theory. *Arch. Rat. Mech. Anal.* **52** , 358 - 388.
8. A.Uppal, W. H.Ray and A. B. Poore (1974). On the Dynamic Behavior of Continuous Stirred Tank Reactors. *Chem. Engng. Sci.* **29**, 967 - 985.
9. A. Uppal, W. H. Ray and A. B. Poore (1976). The Classification of the Dynamic Behavior of Continuous Stirred Tank Reactors - Influence of Residence Time. *Chem. Engng. Sci.* **31** , 205 - 214.
10. K. O. Friedrichs, Advanced Ordinary Differential Equations. Gordon & Breach, New York 1965.