Lawrence Berkeley National Laboratory
Recent Work

Title

Modeling of Fermentation with Continuous Lactic Acid Removal by Extraction Utilizing Reversible Chemical Complexation

Permalink

https://escholarship.org/uc/item/6wf5f58g

Authors

Dai, Y.
King, C.J.

Publication Date

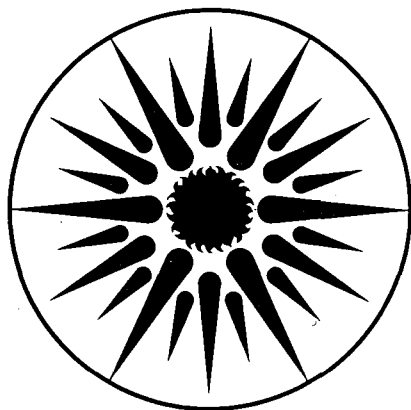1995-07-01

Lawrence Berkeley Laboratory
UNIVERSITY OF CALIFORNIA

ENERGY & ENVIRONMENT DIVISION

Modeling of Fermentation with Continuous
Lactic Acid Removal by Extraction Utilizing
Reversible Chemical Complexation

Y. Dai and C.J. King

July 1995

ENERGY
AND ENVIRONMENT
DIVISION

DISCLAIMER

Modeling of Fermentation with Continuous Lactic Acid Removal by Extraction Utilizing Reversible Chemical Complexation

Youyuan Dai
C. Judson King

Department of Chemical Engineering
University of California

and

Energy and Environment Division
Lawrence Berkeley Laboratory
University of California
Berkeley, CA 94720

July, 1995

MODELING OF FERMENTATION WITH CONTINUOUS LACTIC ACID REMOVAL

BY EXTRACTION UTILIZING REVERSIBLE CHEMICAL COMPLEXATION

Youyuan Dai

C. Judson King

ABSTRACT

Extractive fermentation is a technique that can be used to reduce end-product inhibition by removing fermentation products *in situ* or in an external recycle loop. A model is presented for fermentation with continuous lactic acid removal by extraction utilizing chemical complexation. The model is formulated considering the kinetics of cell growth and the equilibrium distribution of lactic acid between aqueous and organic phases. Simulations have been carried out for different sets of operating conditions. The choice of pH balances faster kinetics at higher pH against lower product concentrations in the solvent and more difficult regeneration. A key need is for liquid extractants or solid sorbents combining stronger uptake ability with economical regeneration and satisfactory biocompatibility.

Key Words: extractive fermentation, lactic acid, process modeling

INTRODUCTION

In many fermentations bioconversion is limited by end-product inhibition. Integration of fermentation with product recovery has been proposed to counteract this problem [1]. Extractive fermentation is one of several technologies of this sort that have been proposed. In this process continuous removal of product is accomplished by solvent extraction, thereby maintaining high specific growth rate of the microorganism and minimizing end-product inhibition. Another potential advantage of an extractive fermentation process is reduction of product recovery costs. Adsorption of the product can provide similar benefits.

Extractive fermentations for production of ethanol and acetone-butanol have been investigated [2-9]. Extractive fermentation has also been explored in recent years as an option for the recovery of high boiling products, such as organic acids. Separation methods based upon volatility, such as distillation and flash evaporation, are infeasible or not economical for recovery of products of such low volatility [10].

Several authors [e.g.,11-15] have studied lactic acid fermentation using *Lactobacillus delbrueckii*. In such processes, an extractant could separate lactic acid from the fermentation broth,

thus increasing the pH value of the broth. This would reduce or eliminate the inhibition effect due to low pH in the fermentation process.

In general, to achieve effective extraction during fermentation, it is necessary to operate under acidic conditions, since it is the carboxylic acid that is the desired product, and not the carboxylate anion. Agents taking up the carboxylate anion are difficult to regenerate and/or do not produce the free acid. At higher values of pH, the efficiency of extraction is reduced, as the carboxylic acid is present to increasing degrees as the carboxylate anion.

However, the pH is also known to influence the kinetics of cell growth. Organic acids have different inhibitory effects on growth of the microorganism, depending on whether they are in an ionic or undissociated form. Undissociated lactic acid causes severe inhibition. Research results show that for *Lactobacillus delbreuckii* lactic acid productivity is considerably improved at pH 5 or greater [16]. Thus there is an inherent conflict between pH below the pK_a of the acid being desirable for separation and pH above the pK_a of the acid being desirable for the fermentation.

Tung and King [17] have proposed separation of lactic acid at pH >

pK$_a$ by extraction with reversible chemical complexation. The key is to use a liquid extractant or solid sorbent that is strongly enough basic to provide substantial capacity even at moderately high values of pH, and yet is regenerable. Of course the extractant or solid sorbent should have sufficient biocompatibility, or else steps must be taken to preclude direct contact of the agent with the cells.

In the present work, a model including the kinetics of cell growth and phase equilibria has been created. Performances of extractive fermentation processes under different operating conditions are simulated, and the simulation results are discussed.
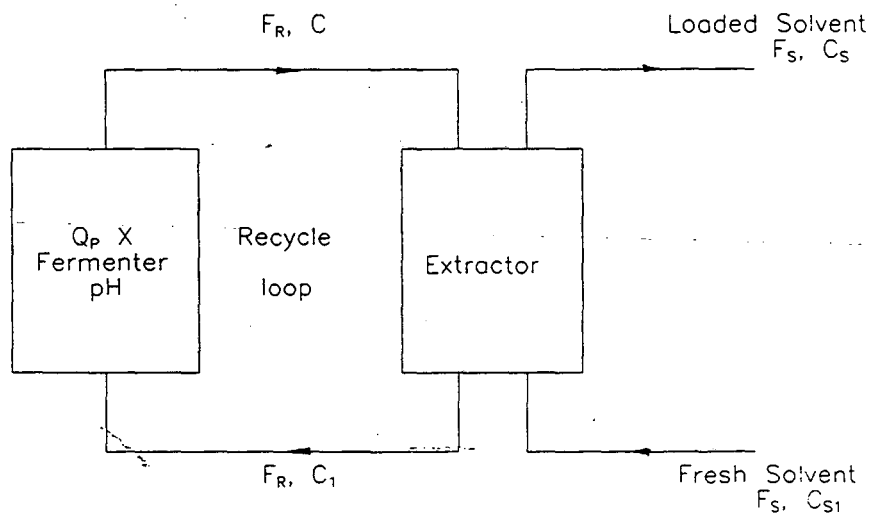
MATHEMATICAL MODEL

Fig. 1   Schematic diagram of extractive fermentation

The schematic of the extractive fermentation system is shown in Figure 1. The fermentation medium is contacted with the solvent continuously to remove lactic acid. The extraction occurs directly in the fermenter or in an external recycle loop. One possible advantage of the external loop is that residues of the extractant or solvent can be removed before the medium is returned to the fermenter. The model has been set up with contact occuring in an external recycle loop. The case of extraction directly within the fermenter corresponds conceptually to an infinite flow rate in the recycle loop.

In the mathematical model the following assumptions are made:

(1) Extraction is by reversible chemical complexation with simple equilibrium and continuous lactic acid removal. A typical amine extractant with a proton-donating diluent is selected. It is assumed that only (1,1) complex formation of lactic acid with the extractant occurs.

(2) To simplify the model the solvent is assumed to be completely biocompatible, or at least the degree of toxicity is independent of pH. (The effect of toxicity from the solvent is discussed later.)

(3) The solvent extracts lactic acid only, i.e., no substrate and/or cells are present in the organic phase.

(4) The solvent and the aqueous phase are totally immiscible.

(5) For an external loop different kinds of extraction

contactors, such as single-stage extraction and countercurrent extraction, can be used. To simplify the model a singe-stage extraction with a designated stage efficiency is considered.

For the fermenter the following equqtions must be satisfied:

$$\partial(C_{(u)}+C_{(L)})/\partial t = Q_P X - F_R[(C_{(u)}+C_{(L)})-(C_{1(u)}+C_{1(L)})]/V \qquad (1)$$

$$\partial(C_{(L)} - C_{(H)})/\partial t = 0 \qquad (2)$$

$$K_a = \frac{C_{(H)}\ C_{(L)}}{C_{(u)}} \qquad (3)$$

For the total lactic acid balance equation (Eq. 1), $C_{(u)}$ and $C_{(L)}$ are free acid concentration and lactate concentration in the exit stream (i.e. concentrations in the broth); $C_{1(u)}$ and $C_{1(L)}$ are the same concentrations at the inlet stream. Q_p is the specific productivity (mol acid per gram cell per hour). X is the cell density (grams cells per liter total volume). $Q_p X$ is the volumetric productivity based on the total volume (medium), and V is the total volume. F_R is the medium recycle flow rate. For a monocarboxylic acid, equation (2) describes the relationship of concentrations of lactate and hydrogen ion ($C_{(H)}$), due to dissociation of free acid. This relationship neglects the involvement of hydrogen ion in the water dissociation equilibrium, an assumption that loses validity as pH approaches 7.

Since under practical conditions 1 mol of glucose metabolized is converted to 2 mol of lactic acid [15], the glucose balance equation can be written as

$$\partial S / \partial t = - Q_p X / 2 \qquad (4)$$

Equations (1), (2) and (4) form a system of partial differential equations describing the problem to be solved. Initial conditions for these partial differential equations are given as:

$$S = S_0, \quad C_{(u)} = C_{0(u)}, \quad C_{(L)} = C_{0(L)} \qquad at \quad t = 0$$

For simulation a forward difference technique is employed. The difference equations are

$$S_{i+1} - S_i / \triangle t = - Q_{Pi} X_i / 2 \qquad (5)$$

$$C_{Ti+1} - C_{Ti} / \triangle t = Q_{Pi} X_i - F_R (C_{Ti} - C_{T1i}) / V \qquad (6)$$

$$C_{(L)i+1} - C_{(H)i+1} = C_{(L)i} - C_{(H)i} \qquad (7)$$

where

$$C_{Ti} = C_{(u)i} + C_{(L)i}$$

As has been demonstrated by previous research on the extraction chemistry of carboxylic acids by amine extractants, the nature of the diluent affects the basicity of the amine and thus the

stability and solution of the complex formed. Specific interactions of the diluent with the complex affect the stoichiometries of the complexes formed. The proton-donating diluents, for example 1-octanol, may form a hydrogen bond with the oxygen on the carboxylic group of the acid-amine complex and thus hamper binding of a second acid onto this complex [18]. For the range of concentration for lactic acid produced by fermentation, we assume that only a (1,1) complex forms for lactic acid with the amine extractant in 1-octanol. An equilibrium description of the system can be written:
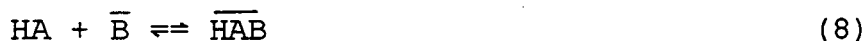
$$HA + \overline{B} \rightleftharpoons \overline{HAB} \qquad (8)$$

where HA corresponds to lactic acid, B to amine extractant, and HAB to complex. Organic phase species are marked with an overbar.

The apparent equilibrium constant, K_{11}, for the overall reaction is:

$$K_{11} = \frac{[\overline{HAB}]}{[HA]\ [\overline{B}]} \qquad (9)$$

where species concentrations are denoted by square brackets and are expressed in molar terms.

The dissociation equilibrium of lactic acid is described as follows:

$$HA \rightleftharpoons H^+ + A^- \qquad (10)$$

The dissociation constant of lactic acid, K_a (Eq.3), is equal to 0.000138 mol/L at 25°C [19].

For extraction-based reversible chemical complexation it is necessary to take into account the transfer of carboxylic acid from water into the amine-free diluent, with which the acid does not interact to form specific complexes or solvates. Because dimerization of the acid is small or non-existent in a polar diluent such as 1-octanol [18], the partition coefficient, P, can be written as

$$P = [\overline{HA}] \ / \ [HA] \qquad (11)$$

where both concentrations have units of moles per liter and organic phase species are marked with an overbar.

Therefore the apparent distribution ratio D of lactic acid between solution and solvent can be written as follows:

$$D = \frac{[\overline{HAB}]}{[HA]} + \frac{[\overline{HA}]}{[HA]}$$

$$= \frac{K_{11} \ B_0}{(1 + K_{11} \ C_{1(u)})} + \phi \ P \qquad (12)$$

where B_0 is the initial concentration of amine extractant and ϕ is a correction factor taken to be the volume fraction diluent in the solvent mixture. Equation (11) ignores simple partioning of the acid into the amine itself.

Tung & King [17] have investigated the extraction of lactic acid into 0.3M Alamine 336 in 1-octanol. From their data, the value of K_{11} is about 182 L/mol. In the simulation this mixed solvent is postulated and that value of K_{11} is used. The partition coefficient of lactic acid between water and 1-octanol (amine-free) is 0.32 [20]. The volume fraction of diluent, ϕ, is 0.85.

Assuming that the acid concentration in inlet solvent is C_{S1}, the following equations must be satisfied for the extractor:

$$C_{(u)} = C_{1(u)} + m \ (D \ C_{1(u)} - C_{S1}) \ F_S \ / \ F_R \qquad (13)$$

$$C_{(L)} - C_{1(L)} = C_{(H)} - C_{1(H)} \qquad (14)$$

$$K_a = \frac{C_{1(H)} \ C_{1(L)}}{C_{1(u)}} \qquad (15)$$

where

$$m = \frac{C_S - C_{S1}}{D \ C_{1(u)} - C_{S1}} \qquad (16)$$

m represents the stage efficiency in the single-stage extractor. F_S and C_S represent the solvent flow rate and the acid concentration

in solvent leaving the extractor. Equation (14) describes the charge balance in the aqueous phase ignoring the effect of water dissociation equilibrium.

If $C_{(u)}$, $C_{(H)}$, $C_{(L)}$, C_{S1}, F_S, F_R and B_0 are known, we can obtain D, $C_{1(u)}$, C_S, $C_{1(H)}$ and $C_{1(L)}$ using equations (12), (13), (14), (15) and (16).

However, the productivity term $Q_P X$ is not a constant because the specific productivity (Q_P) and the cell density (X) vary during the course of extractive fermentation. Yabannavar and Wang[15] have studied the fermentation kinetics of *Lactobacillus delbrueckii*. They have indicated that the term $Q_P X$ can be calculated from the specific growth rate (μ) and the initial cell density (X_0).

Incorporating the Monod dependence on substrate and growth inhibition by the free lactic acid and lactate (in molar concentration), the specific growth rate (μ) is given as [15]:

$$\mu = \frac{0.52\ S}{0.000056+S}[1 - \frac{C_{(L)}}{0.940}][\exp(-C_{(u)} / 0.023)] \quad (17)$$

Applying the Luedeking and Piret model[21], Yabannavar and Wang have derived the relation of the specific productivity (in molar concentration) to the specific growth rate (μ) [15]:

$$Q_P = 0.077(\mu) + 0.0033 \qquad\qquad (18)$$

From the specific growth rate (μ) and the original cell density X_0 (per medium volume), the increasing cell density $X(t)$ (per medium volume) can be calculated [15]:

$$X(t) = X_0 \exp[\mu\, t] \qquad\qquad (19)$$

Equation (19) can be written in forward difference form:

$$X_{i+1} = X_i \exp[\mu_i\, \Delta t] \qquad\qquad (20)$$

Equations (17), (18), (19) and (20) allow us to evaluate $Q_P X$ at various conditions.

The model has been implemented into a computer program. In the simulation an appropriate constant solvent flow rate F_s has been selected by trial and error method so that the time average value of pH during the period of T, in which 99% glucose has been consumed, is maintained at approximately same as the initial value of pH. No buffering agent is employed.

The model developed above has been tested under different fermentation conditions. The fixed model parameters used are summarized in Tables 1.

Table 1. Fixed Model Parameters

Parameter	Value	Unit
K_{11}	182.0	mol/L
V	1.0	L
S_0	45.0	g/L
C_{S1}	0.0	g/L
m	0.9	

RESULTS AND DISCUSSION

Given initial values of pH_0, the simulations of the extractive fermentation at different operating conditions are carried out. Constant values of F_s are used for different initial values of pH, so that the time average value of pH during operation period T, in which 99% glucose has been consumed, is equal approximately to initial value of pH_0. pH_E, μ, $Q_P X$ and C_S are time average values during operation period T. pH_E is pH value in the aqueous phase of the extractor.

The results confirm that the higher pH value at which the extractive fermentation is performed, the faster the growth rate of the microorganism, the higher the lactic acid productivity, and the lower the acid concentration in the solvent (see Figures 2 and 3).

The medium recycle flow rate is an important parameter that affects the difference in pH between the fermenter and extractor. The pH in

the extractor approaches that in the fermenter for a very large medium recycle flow rate (see Figure 4).

However, operating an extractive fermentation at higher pH entails some adverse effects. Besides there being lower acid concentration in the solvent, regeneration of the extract becomes more difficult
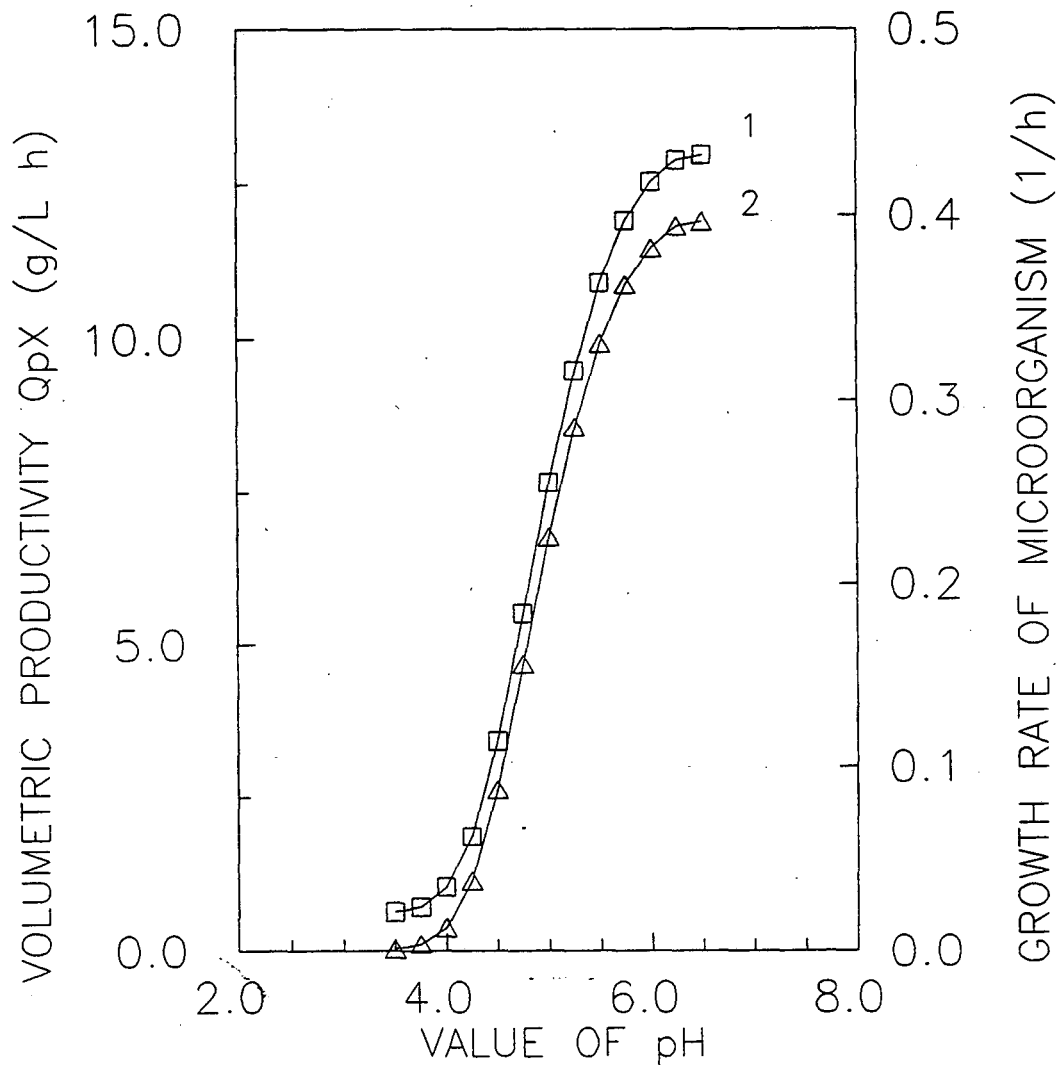

Fig. 2 Extractive Fermentation at Different pH Values
1. Volumetric Productivity Q_PX 2.Growth Rate of Microorganism μ,
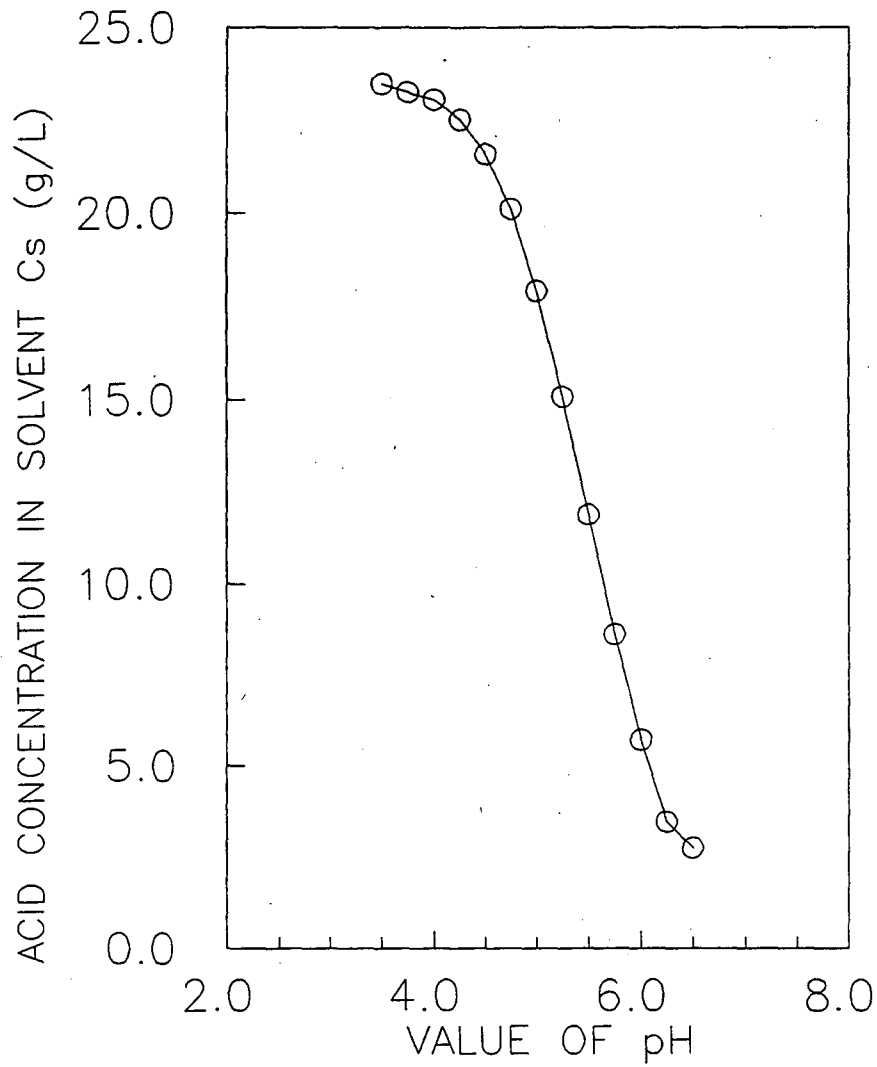X_0=2 g/L, C_0=18 g/L, S_0=45 g/L, F_R=1000 L/h

Fig. 3 Acid Concentration in Solvent C_s for
Extractive Fermentation at Different pH Values
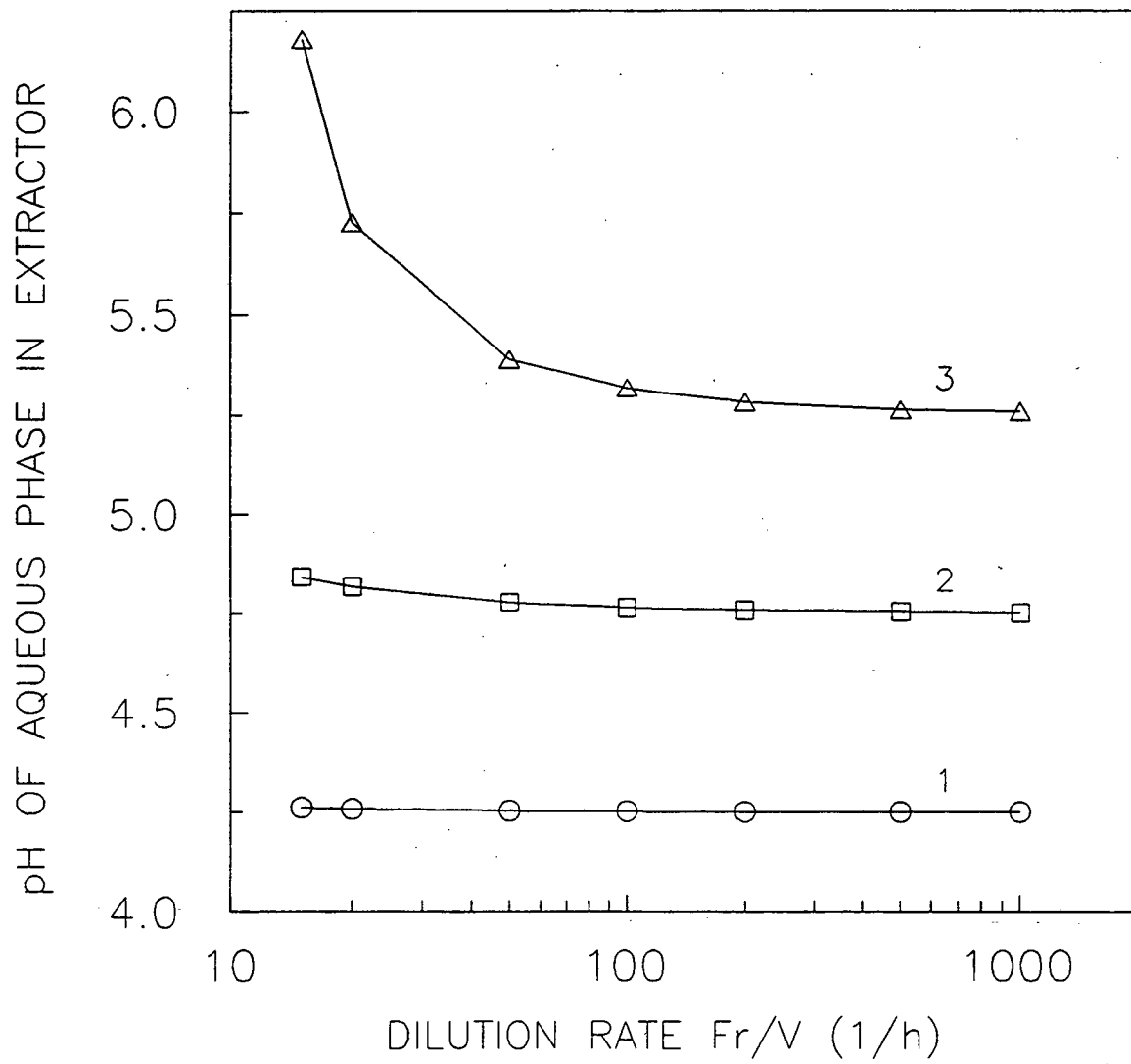X_0=2 g/L, C_0=18 g/L, S_0=45 g/L, F_R=1000 L/h

Fig. 4 Effect of Dilution Rate on pH in Extractor
pH in Fermenter: 1. pH=4.25, 2. pH=4.75, 3. pH=5.25

at higher values of pH. If the same regeneration method, such as back-extraction by an aqueous base solution, is employed, the equipment size and solvent recycle amount are increased, and at some value of pH regeneration may become impossible. There should, therefore, be an optimal value of pH.

From the simulation results (Figure 2), it is apparent that the growth rate of mucroorganism and the productivity increase sharply between pH 4.5 to 5.5. On the other hand, the decreasing acid concentration in the solvent at higher values of pH is closely related to the extraction equilibrium relationship. For 0.3 M Alamine (in 1-octanol), the lactic acid concentration in the solvent decreases sharply from pH 4.5 to 6.0 (Figure 3).

On the other hand, it is necessary to maintain a finite recycle rate, called as dilution rate (= F_R/V), so as to remove the end-product continuously, keeping the pH in the fermenter approximately constant without consumption of other chemicals. The recycle rate required is related to the pH in the fermenter. If the extractive fermentation is operated at a higher value of pH, the recycle rate would be increased considerably (Figure 4) because the undissociated acid concentration, which is the recovered species, is very low. But, it is impractical to employ too a large recycle rate for extractive fermentation because of large capital investment and large energy consumption.

Weighing the advantages of the improved productivity at a higher pH against the disadvantages, the optimal value of pH is likely to be in the range 4.50 - 5.50.

To analyze the effects on extraction fermentation of different pH values the following four sets of operating conditions were postulated to simulate the performances of processes. In the simulation the recycle rate (F_R/V) is constant at 10 h^{-1}.

Simulation results for these four situation are summarized in Table 2.

Table 2. Comparison of Performances
at Four Kind of Operating Conditions

Parameter	Situation 1	Situation 2
pH	4.25 ± 0.10	5.0 ± 0.20
Cell density	from 2 g/L to 4.94 g/L in 24 h	from 2 g/L to 6.98 g/L in 5.5 h
productivity	1.86 g/L h	7.61 g/L h
Total acid produced	44.7 g/L in 24h	41.9 g/L in 5.5 h
acid concentration in the solvent	22.4 g/L	16.0 g/L

Parameter	Situation 3	Situation 4
pH	5.0 ± 0.20	5.0 ± 0.20
Cell density	from 4 g/L to 8.94 g/L in 3.5 h	from 2 g/L to 7.05 g/L in 4.5 h
productivity	11.76 g/L h	9.11 g/L h
Total acid produced	41.2 g/L in 3.5 h	41.0 g/L in 4.5 h
acid concentration in the solvent	14.5 g/L	12.6 g/L

Situation 1. The initial cell density is 2 g/L. The initial lactic acid concentration in the broth is 18.0 g/L. The initial value of pH is 4.25, and the solvent flow rate is 0.083 L/h. The simulation result is shown in Figure 5. For these conditions, the mathematical model predicts that the time in which 99% glucose has been consumed is 24.1 h. The cell density increases from an initial value of 2 g/L to a final value of 4.94 g/L. The total lactic acid production is estimated to be 44.5 g per liter of the medium during that period. The total lactic acid concentration in the broth is maintained at approximately 18.0 g/L. The value of pH varies between 4.15 and 4.35. Taking into account the total lactic acid production during the 24 h, the productivity is found to be 1.86 g/L h, and the lactic acid concentration in the exit solvent stream is about 22.4 g/L.

Situation 2. The same initial cell density (2 g/L) is used. The initial acid concentration in the broth is also 18.0 g/L, but the initial pH value is 5.0, and the solvent flow rate is 0.293 L/h. The simulation result from these conditions is shown in Figure 6. The time in which 99% glucose has been consumed decreases to 5.8 h. The cell density increases quickly from 2 g/L to a final value of 6.98 g/L gel. The lactic acid produced is about 41.9 g per liter medium, and the productivity is found to be 7.61 g/L h, a considerable improvement. The pH is maintained at 5.0 ± 0.2. The lactic acid concentration in the solvent is 16.0 g/L.

Situation 3. The same initial acid concentration in the broth (18.0g/L) is used. The initial cell density is 4 g/L. The initial pH value is 5.0, and the solvent flow rate is 0.48 L/h. The simulation results from these conditions are shown in Figure 7. The time in which 99% glucose has been consumed is 3.8 h. The cell density increases during the fermentation from 4 g/L to 8.94 g/L. The total lactic acid produced is about 41.2g per liter medium, and the productivity is found to be 11.76 g/L h. The pH is maintained at 5.0 ± 0.2. The acid concentration in the solvent is 14.5 g/L, a somewhat lower product concentration than in Situation 2.

Situation 4. The initial cell density is 2 g/L. The initial pH value is 5.0, the solvent flow rate is 0.45 L/h, and the initial lactic acid concentration is 13.5 g/L. The advantage of starting with a lower initial lactic acid concentration is shown in Figure 8. As expected, the time in which 99% glucose has been consumed is reduced to 4.8 h. The cell density increases quickly from 2 g/L to 7.05 g/L. During that period the lactic acid produced is about 41.0 g per liter medium, and the productivity is 9.11 g/L h. The pH is maintained at 5.0 ± 0.2. The lactic acid concentration in the solvent is 12.6 g/L, a substantially lower product concentration.
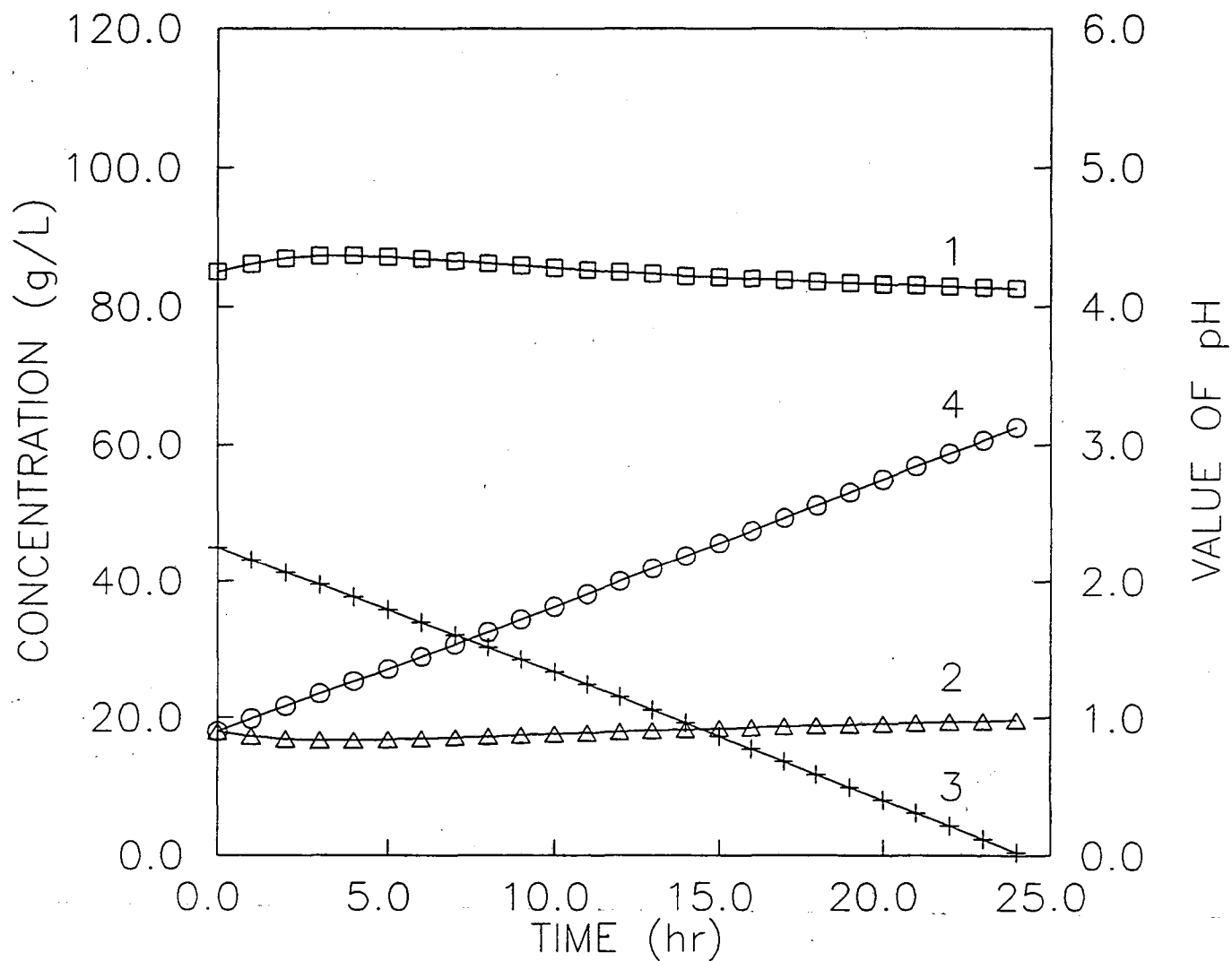
Fig. 5 Performance at pH of 4.25 (Situation 1)
1. Value of pH, 2. Acid Concentration in Broth (g/L),
3. Glucose Concentration in Broth (g/L), 4. Total Acid
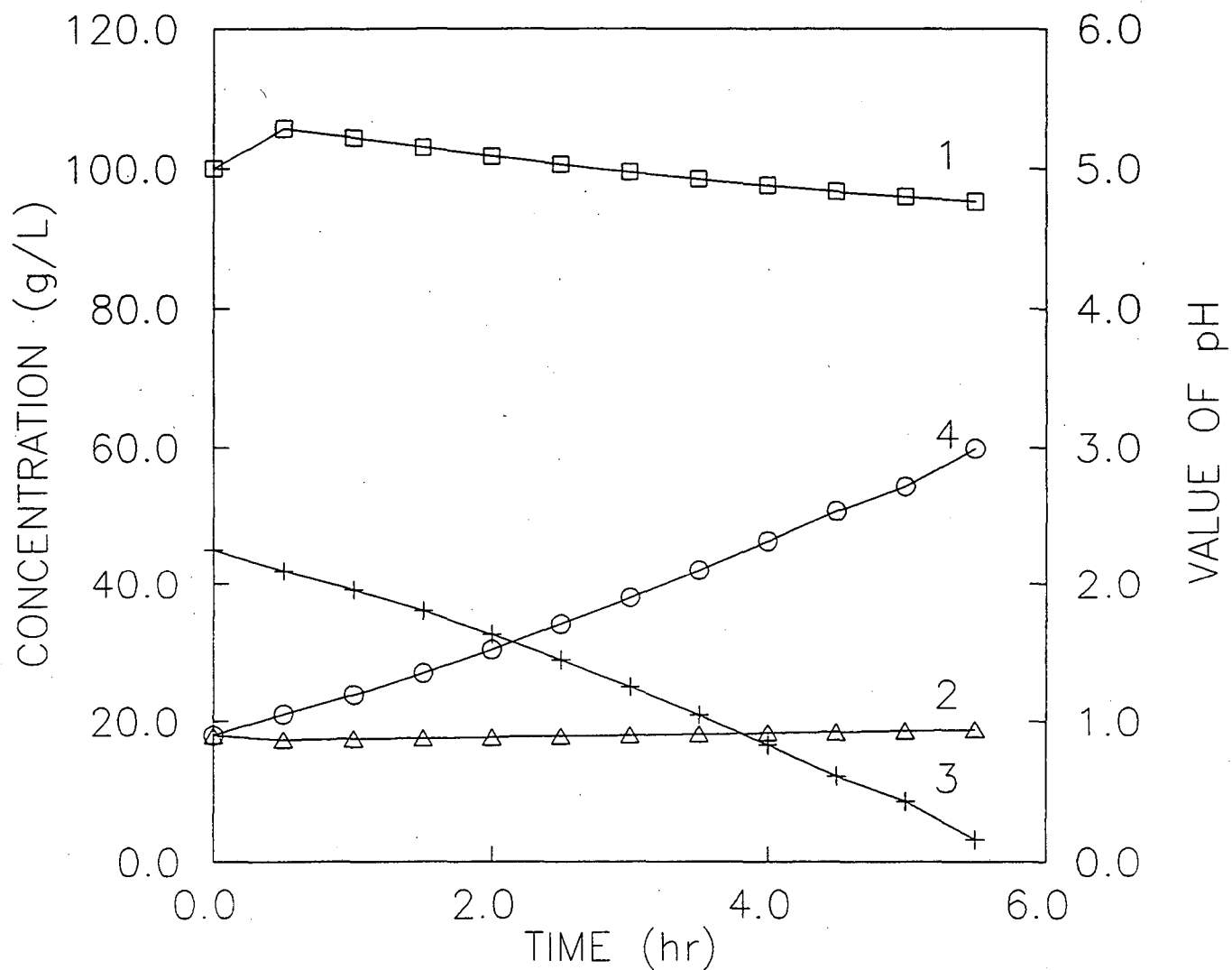Concentration (g/L), X_0= 2 g/L, C_0= 18 g/L, S_0= 45 g/L

Fig. 6 Performance at pH of 5.0 (Situation 2)
1. Value of pH, 2. Acid Concentration in Broth (g/L),
3. Glucose Concentration in Broth (g/L), 4. Total Acid
Concentration (g/L), X_0= 2 g/L, C_0= 18 g/L, S_0= 45 g/L

Fig. 7 Performance at pH of 5.0 (Situation 3)
1. Value of pH, 2. Acid Concentration in Broth (g/L),
3. Glucose Concentration in Broth (g/L), 4. Total Acid
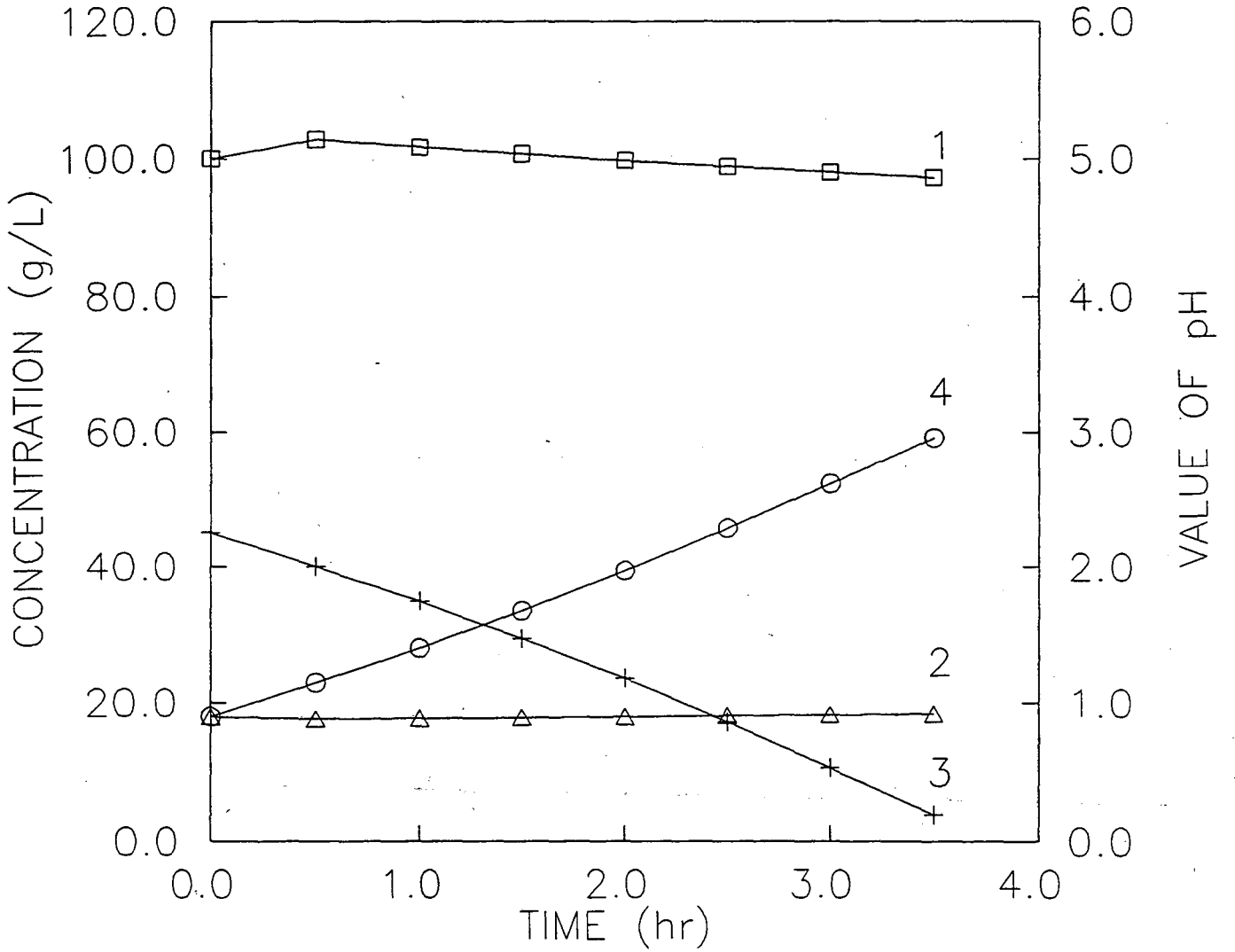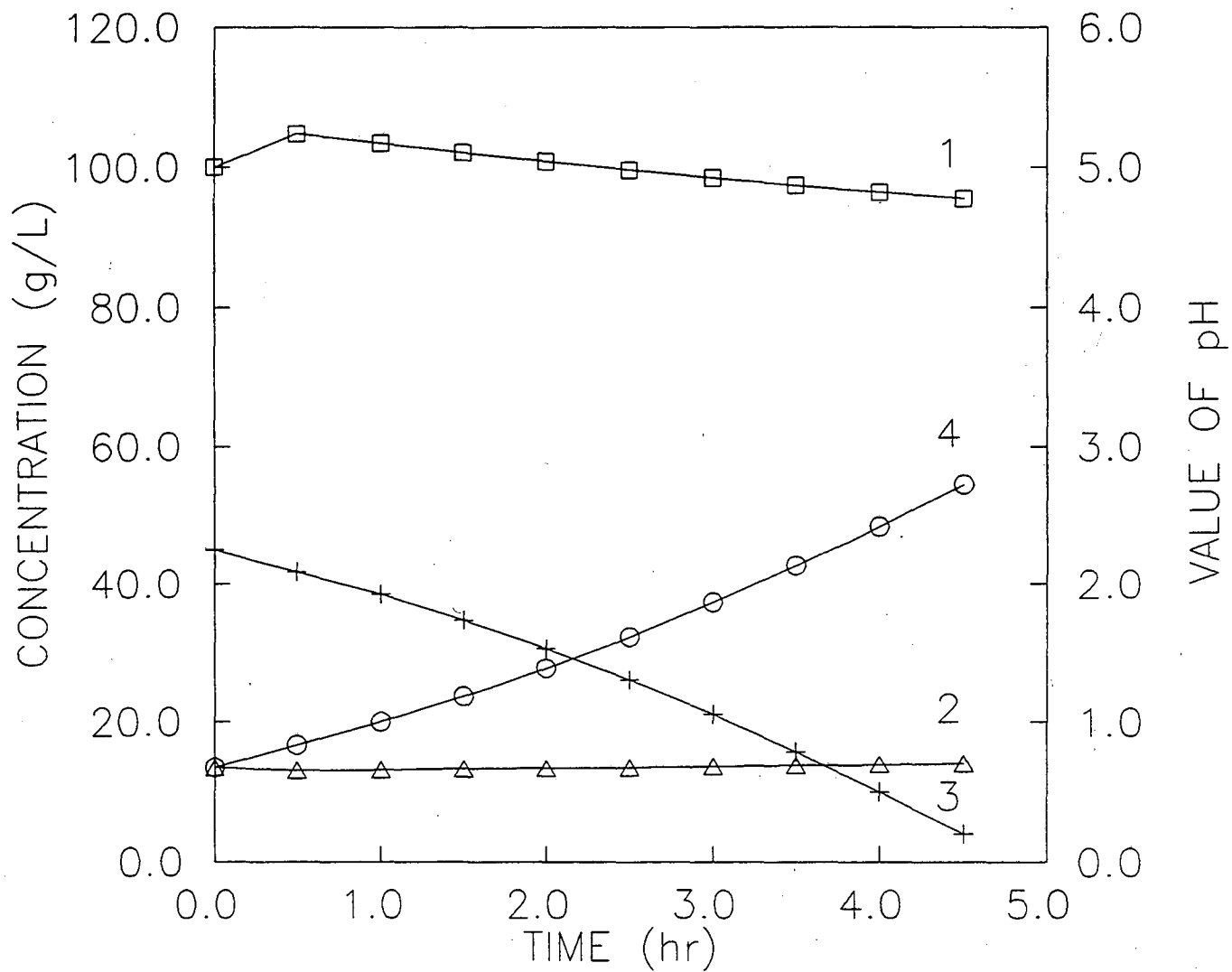Concentration (g/L), $X_0 = 4$ g/L, $C_0 = 18$ g/L, $S_0 = 45$ g/L

Fig. 8 Performance at pH of 5.0 (Situation 4)
1. Value of pH, 2. Acid Concentration in Broth (g/L),
3. Glucose Concentration in Broth (g/L), 4. Total Acid
Concentration (g/L), X_0= 2 g/L, C_0= 13.5 g/L, S_0= 45 g/L

Analyzing the simulation results for different operating conditions, several significant problems should be discussed and emphasized.

(1) It is obvious that fermentation to produce lactic acid operates more effectively at a higher value of pH. In Situation 2, due to the reduced lactic acid inhibition, cell density showed an increase of 249% in 5.5 h at an increased pH of 5.0. And the lactic acid productivity is 4 times as large as that at an pH of 4.25.

(2) An increase of the initial cell density can improve the lactic acid productivity. But to maintain the pH at a higher value one needs a higher solvent flow rate, so that the product concentration in the solvent will not increase. Decreasing the lactic acid concentration in the broth from 18.0 g/L to 13.5 g/L increases the lactic acid productivity somewhat. However, since the lactic acid concentration in the broth is low, the equilibrium concentration in the solvent is decreased.

(3) The key to increasing extraction efficiency is to identify liquid extractants or solid sorbents that are strongly enough basic to sustain capacity to several pH units above the pK_a of lactic acid. In other words, the value of K_{11} (Eq.12) should be higher. However, an extractive fermentation operating at an increased value of pH can bring about lower acid concentration in

the solvent. Regeneration of the extract at a higher value of pH can also be difficult. Also, to maintain a higher pH in fermenter requires a very large medium recycle rate. The optimal operating value of pH has to be chosen considering the overall economics of the process.

Two other points in the model may be questioned.

(1) In the mathematical model complete biocompatibility between solvent and the microorganism is assumed. In fact, most solvents are inhibitory to some extent toward yeast cells. Through experimental research on toxicity of the solvent, a distinction has been made between a broth containing dissolved organic solvent and a broth containing a second immiscible phase of solvent [22]. It appears that the toxic effect of solvent at the molecular level is less than that at the phase level. Membrane extraction [14] and immobilization techniques [15,23] have been used to protect against toxic effects at the phase level.

Some solid sorbents, such as weak-base ion-exchange resins, complex with organic acids. The use of solid sorbents can reduce or eliminate toxic effects on acid-producing bacteria.

(2) The model assumes that the solvent extracts lactic acid only, i.e., that there is no competition from other solutes. In actual

applications extraction of substrate (glucose) and by-products need to be considered. The existence of sugars and by-products in product can affect not only the purity of lactic acid but also the color of the product.

CONCLUSION

A mathematical model for extraction fermentation with continuous lactic acid removal has been presented. This model considers the kinetics of cell growth and the phase equilibrium for extraction of lactic acid, based upon chemical complexation. Different simulations were performed to evaluate the performances of processes under different operating conditions.

Simulation results show that the lactic acid productivity can be improved by using higher initial cell density or higher cell/medium ratio. Because undissociated lactic acid causes severe inhibition, an extractive fermentation process performs better at higher values of pH. But higher pH complicates recovery of the product and increases dilution. Consequently, there is an optimal value of pH. The key problem to be overcome lies in the search for liquid extractants or sorbents conbiming strong extraction ability with economical regeneration and satisfactory biocompatibility.

ACKNOWLEDGMENT

NOMENCLATURE

$C_{(H)}$ proton concentration at exit stream, mol/L

$C_{1(H)}$ proton concentration at inlet stream, mol/L

$C_{(L)}$ lactate concentration at exit stream, mol/L

$C_{1(L)}$ lactate concentration at inlet stream, mol/L

C_s lactic acid concentration in the exit solvent, mol/L

C_{S1} lactic acid concentration in the inlet solvent mol/L

$C_{(u)}$ undissociated acid concentration at exit stream, mol/L

$C_{1(u)}$ undissociated acid concentration at exit stream, mol/L

B_0 initial concentration of extractant, mol/L

D distribution coefficient of lactic acid

F_R external recycled flow rate of medium, L/h

F_S solvent flow rate, L/h

K_a actic acid dissociation constant, mol/L

K_{11} apparent association equilibrium constant, L/mol

m extraction stage efficiency

P   partition coefficient

Q_P specific productivity, mol/g h

S   glucose concentration, g/L

t   time, h

V   total working volume in the fermentor, L

X   cell density g/L

Greek letters

μ specific growth rate, h^{-1}

ϕ correction factor in equation (10)

REFERENCES

1. Daugulis,A.J., Biotech, Prog., 2,113 (1987)

2. Minier,M., and G.Goma, Biotech. Ltrs., 3,405 (1981)

3. Minier,M., and G.Goma, Biotech. Bioeng. 24,1565 (1982)

4. Maiorella,B.L., H.W.Blanch, and C.R.Wilke, Biotech.Bioeng., 26,1003 (1984)

5. Cho,T., and M.L.Shuler, Biotech. Prog., 2,53 (1986)

6. Daugulis,A.J.,D.E.Swaine, F,Kollerup, and C.A.Groom, Biotech.Ltrs. 9,425 (1987)

7. Roffler,S.R., H.W.Blanch, and C.R.Wilke, Bioproc. Eng., 2,181 (1987)

8. Ishii,S., M.Taya, and T.Kobayashi, J. Chem. Eng. Japan, 18,125 (1985)

9. Taya,M., S.Ishii, and T.Kobayashi, J. Ferment. Technol., 63,181 (1985)

10. Ng,T.K., R.M.Busche, C.C.McDonald, and R.N.F.Hardy, science, 219,733 (1983)

11. Yabannavar,V.M., and D.I.C.Wang, Biotech. Bioeng., 37,1095 (1992)

12. Davison,B.N., and J.E.Thompson, Appl. Biochem.Biotech.,34/35, 431 (1992)

13. Seevaratnam,S., O.Holst, S.Hjorleifsdottir, and B.Mattiasson, Bioproc. Eng., 6,35 (1991)

14. Wang,C.J., R.K.Bajpai, and E.L.Iannotti, Appl.Biochem. Biotech., 28/29, 589 (1991)

15. Yabannavar,V.M., and D.I.C.Wang, Biotech. Bioeng., 37, 544 (1991)

16. Vickroy,T.B., "Lactic Acid", in Comprehensive Biotechnology, Vol.3, Blanch,H.W., Drew,S. and D.I.C. Wang, Eds., Pergamon Press, New York, Chapter 38, 761-776 (1985)

17. Tung,L.A., and C.J.King, Ind. Eng. Chem. Res. 33, 3217-3223 (1994)

18. Kertes,A.S., and C.J.King, Biotech. Bioeng., 28,269 (1986)

19. Lange's Handbook of Chemistry, 13th ed., Dean,J.A. Ed., McGraw-Hill, New York (1985)

20. Short,J.F. and P.Eaglesfield, Trans. Inst. Chem. Eng. 30,

109-124 (1952)

21. Luedeking,R., and E.L.Piret, J. Biochem. Microbiol. Tech. Eng., 1(4), 393 (1959)

22. Bar,R., and J.L.Gainer, Biotech. Prog., 3,109 (1987)

23. Yabannavar,V.M., and D.I.C.Wang, Biotech. Bioeng., 37, 716 (1992)

LAWRENCE BERKELEY LABORATORY
UNIVERSITY OF CALIFORNIA
TECHNICAL AND ELECTRONIC
  INFORMATION DEPARTMENT
BERKELEY, CALIFORNIA 94720