Chemical and Process Engineering 2013, 34 (1), 175-186
DOI: 10.2478/cpe-2013-0015

OPTIMISATION OF OPERATING CONDITIONS IN FED-BATCH BAKER'S YEAST FERMENTATION

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Saccharamyces cerevisia known as baker's yeast is a product used in various food industries. Worldwide economic competition makes it a necessity that industrial processes be operated in optimum conditions, thus maximisation of biomass in production of *saccharamyces cerevisia* in fed-batch reactors has gained importance. The facts that the dynamic fermentation model must be considered as a constraint in the optimisation problem, and dynamics involved are complicated, make optimisation of fed-batch processes more difficult.

In this work, the amount of biomass in the production of baker's yeast in fed-batch fermenters was intended to be maximised while minimising unwanted alcohol formation, by regulating substrate and air feed rates. This multiobjective problem has been tackled earlier only from the point of view of finding optimum substrate rate, but no account of air feed rate profiles has been provided. Control vector parameterisation approach was applied the original dynamic optimisation problem which was converted into a NLP problem. Then SQP was used for solving the dynamic optimisation problem. The results demonstrate that optimum substrate and air feeding profiles can be obtained by the proposed optimisation algorithm to achieve the two conflicting goals of maximising biomass and minimising alcohol formation.

Keywords: fed-batch fermenters, baker's yeast, dynamic optimisation, SQP, nonlinear programming

1. INTRODUCTION

Saccharamyces cerevisia known as baker's yeast is a product obtained by fed-batch fermentation and used extensively in food industries. In virtue of tough worldwide economic competition, maximisation of biomass in production of *saccharamyces cerevisia* in fed-batch reactors bears importance. Due to problems arising in such dynamic optimisation problems, compared to steady state optimisation , the dynamic fermentation model must be considered as a constraint in the optimisation, and the dynamics are inherently complicated.

In order to solve dynamic optimisation problems, maximum principle, dynamic programming or conversion into a nonlinear programming (NLP) problem are commonly used. We consider the dynamic optimisation problem formulation of the following form:

$$\min_{u(t)} \psi\left(x(t_f), u(t)\right);\ 0 \le t \le t_f \tag{1}$$

Subject to the process dynamics

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$$\frac{dx}{dt} = f(x(t), u(t)) \tag{2}$$

$$h(x) = 0,\ g(x) < 0 \tag{3}$$

and hard constraints

$$u^{min} < u < u^{max} \tag{4}$$

with initial conditions

$$x(t_0) = 0 \tag{5}$$

where x - vector of state variables, u - control (optimisation) parameters, f - vector function, ψ, h, and g - arbitrary functions, t - time.

In this problem definition, the decision variable are the control parameters (i.e. inputs, $u(t)$) and differential-algebraic equations describing process dynamics form constraints together with hard constraints on control inputs.

Most commonly used methods for solution of dynamic optimisation problems can be divided into three classes:

- Pontryagin's Maximum Principle
- Dynamic programming
- Converting into a non-linear programming problem (NLP)

The use of maximum principle, which converts the problem into a two-point boundary value problem, poses difficulties in terms of satisfying constraints represented by differential equations. The difficulty in solution arises from the fact that boundary conditions for state variables and adjoint variables do not mach. Initial conditions are defined for the state variables, but the terminal conditions for the adjoint variables are known. In this case, the Hamiltonian (H) is formed by summing differential equations multiplied by adjoint variables such as;

$$H = J + \sum_{i=1}^{N} \lambda_i f_i \tag{6}$$

The dynamics of adjoint variables can be given by

$$\frac{d\lambda_i}{dt} = -\frac{\partial H}{\partial x_i}, \quad i = 1, 2, 3, \ldots, N \tag{7}$$

Optimal trajectories correspond to the conditions satisfying the following condition:

$$\frac{\partial H}{\partial u} = 0 \tag{8}$$

Roy et al. (2001) used the maximum principle to obtain feeding rates for three types of inhibitory fed-batch processes.

A solution by dynamic programming as was applied by Berber et al. (1999) in baker's yeast fermentation, is somewhat problem specific and requires extensive programming effort and time. Dynamic programming requires a selection of grid type interval containing minimum and maximum limits for each control variable.

Converting into a nonlinear programming problem requires the creation of a finite-end nonlinear program by discretisation of either all variables or only decision variables (Vassiliadis et al., 1994). The differential equations describing system dynamics are transformed into nonlinear algebraic equations by a discretisation method (like orthogonal collocation, finite difference, Galerkin method). This procedure converts an optimisation problem into a standard nonlinear programming (NLP) problem, which can be solved by a commercial NLP software. However, a convergence to a solution can be sometimes slow or even impossible especially when an initial guess is far from the optimal. Another difficulty arises around switching times where the optimal solution is discontinuous. As a recent example, Riascos et al. (2004) showed that discretisation of differential-algebraic equation (DAE) systems by orthogonal collocation in finite elements efficiently transforms dynamic optimisation problems into nonlinear programming (NLP) problems.

There are other methods that have been applied for finding optimal trajectories in fed-batch biochemical systems. A survey on control of fed-batch fermentation processes until mid '80s can be found in Johnson (1987). Later than the period covered by this review, for example, Parulekar (1992) employed analytical optimisation, whereas Krothapally & Palanki (1999) presented an approach for end-point optimisation of batch processes by utilising neural networks, involving training of two neural networks; one to predict switching times and the other to predict the input profile in singular region. In the above papers, optimal feed profiles were calculated for yield optimisation of alcohol in a *S. Cerevisiae* fermentation. The approach in these studies alleviated computational problems associated with the Pontryagin's maximum principle and the nonlinear approach. A hybrid modelling approach combining a mathematical model with neural networks and a fuzzy expert system was used by Schubert et al. (1994).

Valentino et al. (2003) analysed the maximisation of biomass productivity in the fed- bach fermentation of *Saccharomyces cerevisiae* by converting the problem of biomass maximisation into that of regulating the concentration of ethanol, which was achieved through allowing cells to produce a very small amount of ethanol. A novel adaptive control strategy based on internal model principle (with a single parameter to be estimated on line) was used to maintain the desired ethanol setpoint). Experimental results showed the effectiveness of the proposed algorithm.

Karakuzu et al. (2006) developed two soft sensors for the estimation of biomass concentration and specific growth rate in fed-batch baker's yeast fermentation one based on estimation of specific growth rate from process model, the other based on actual measurements. A fuzzy controller was then designed to determine the substrate and air flow rates. The controller was tested on a simulated fed-batch production scale fermenter.

Roubos et al. (1999) applied an evolutionary algorithm to calculate optimal control policies for bioreactors, and compared the results to those from two common methods; dynamic programming and Hamiltonian based gradient algorithm. (cases studied involved a hybridoma reactor and a Lee-Ramirez bioreactor.

Ronen et al. (2002) obtained the optimal feeding profile of a fed batch process by means of an evolutionary algorithm. The contribution of their work was in the sense of overcoming the problem of model mismatch, which was accomplished through updating the model by sampling the process on-line. They reported improved process performances by using the optimal profile in their experimental runs.

Peters et al. (2006) proposed a methodology for designing and implementing a real time optimising controller for nonlinear batch processes. The cost function was expressed in terms of the parameterised input trajectories and constraints were included through an interior point method with penalty function. The optimisation problem was solved by a Lyapunov based extremum seeking approach. The usefulness of the method was illustrated through simulations on a batch bioreactor.

In the present work, we used the control vector parameterisation (CVP) approach for solving the dynamic optimisation problem because the technique is easy to implement for complex models.

Control vector parameterisation was applied to several chemical engineering processes (Balku et al., 2009; Furlonge et al., 1999; Ishikawa et al., 1997; Sorensen et al., 1996; Yuceer et al., 2008). Control vector parameterisation technique is used for solution of dynamic optimisation problems by changing decision variables from time-varying process inputs $u(t)$ to parameters. In this approach only discretisation parameters, which are decision variables for optimisation, are discretised explicitly. For the parameterisation of the control profile $u(t)$, piecewise-polynomial approximations. Profiles for state variables are obtained by forward numerical integration of a model for a given input.

In this work, the amount of biomass in the production of baker's yeast in fed-batch fermenters was maximised while minimising unwanted alcohol formation, by regulating substrate and air feed rates. This multiobjective problem has been tackled before only from the point of view of finding optimum substrate rate, but no account of air feed rate profiles has been provided (Agun, 2002; Berber et al., 1999).

2. DYNAMIC MODEL

The process considered here is a production of fed-batch culture of *Saccharomyces cerevisiae*, commercially known as baker's yeast. The metabolism of yeast growth is based on the bottleneck hypothesis developed by Sonnleitner and Kappeli (1986). It assumes a limited oxygen capacity of yeast, leading to formation of ethanol under conditions of oxygen limitation and/or an excessive glucose concentration. The limited oxidation capacity, $Q_{o,lim}$, is a function of oxygen concentration in the liquid phase. If this is high enough to oxidise all glucose consumed $\left(Q_{o,lim} \geq Y_{o/s}Q_s\right)$ no ethanol is produced. In case ethanol is present in the medium as well, then the co-consumption of ethanol is possible. The amount of ethanol co-consumed is limited by oxidation capacity $\left(Q_{o,lim} \geq Y_{o/s}Q_s + Y_{o/e}Q_{e,ox}\right)$. If not, all glucose can be oxidised $\left(Q_{o,lim} \geq Y_{o/s}Q_s\right)$ then surplus glucose $\left(Q_s - Q_{o,lim} \geq Y_{o/s}\right)$ will be consumed according to reductive metabolism, resulting in ethanol fermentation (Besli et al., 1995). This implies that Monod kinetics with regard to oxygen and substrate was assumed. The model assumes furthermore that; the reactor is a single phase (liquid) isothermal system omitting the gas phase and micro organisms, and its contents are homogenous in axial and radial directions. Under these assumptions; glucose, oxygen, substrate, ethanol and cell mass balances were used to describe the liquid phase. However, the complete model which included main components of the gas phase (oxygen, carbon dioxide, nitrogen, ethanol and water) is composed of 11 differential and 16 algebraic equations and was given previously by Pertev et al. (1997).

The following algebraic equations describing kinetics and balance equations form the dynamic model (Yuzgec et al., 2009):

Glucose uptake rate:

$$Q_s = Q_{s,\max} \frac{C_s}{C_s + K_s} \tag{9}$$

Oxidation capacity:

$$Q_{o,\lim} = Q_{o,\max} \frac{C_0}{C_0 + K_0} \tag{10}$$

Specific growth rate limit:

$$Q_{s,\lim} = \frac{\mu_{cr}}{Y_{x/s}^{ox}} \tag{11}$$

Oxidative glucose metabolism:

$$Q_{s,ox} = \min\begin{pmatrix} Q_s \\ Q_{s,\lim} \\ \dfrac{Q_{o,\lim}}{Y_o / s} \end{pmatrix} \tag{12}$$

Reductive glucose metabolism:

$$Q_{s,red} = Q_s - Q_{s,ox} \tag{13}$$

Ethanol uptake rate:

$$Q_{e,up} = Q_{e,\max} \frac{C_e}{C_e + K_e} \frac{K_i}{C_e + K_i} \tag{14}$$

Oxidative ethanol metabolism:

$$Q_{e,ox} = \min\begin{bmatrix} Q_{e,up} \\ (Q_{o,\lim} - Q_{s,ox} Y_{o/s,ox} / Y_{o/e}) \end{bmatrix} \tag{15}$$

Ethanol production rate:

$$Q_{e,pr} = Y_{e/s} Q_{s,red} \tag{16}$$

Total specific growth rate:

$$\mu = \mu_{ox} + \mu_{red} + \mu_e \tag{17a}$$

or

$$\mu = Y_{x/s}^{ox} Q_{s,ox} + Y_{x/s}^{red} Q_{s,red} + Y_{x/e}^{ox} Q_{e,ox} \tag{17b}$$

Oxygen consumption rate:

$$Q_o = Y_{o/s} Q_{s,ox} + Y_{o/e} Q_{e,ox} \tag{18}$$

Unsteady state balances:

$$\frac{d(VC_s)}{dt} = FS_0 - \left(\frac{\mu}{Y_{x/s}^{ox}} + \frac{Q_{e,pr}}{Y_{e/s}} + m \right) VX \tag{19}$$

$$\frac{dV}{dt} = F \tag{20}$$

$$\frac{d(VC_e)}{dt} = (Q_{e,pr} - Q_{e,ox}) VX \tag{21}$$

$$\frac{d(VX)}{dt} = \mu VX \tag{22}$$

$$\frac{d(VC_O)}{dt} = -Q_O VX + k_L a_0 (C_O^* - C_O) V \tag{23}$$

where C_s, C_e, C_o and X denote concentrations of glucose, oxygen, ethanol and biomass respectively.

The volumetric oxygen transfer coefficient as a function of superficial gas velocity in bubble column bioreactors is given in the following equation (Karakuzu et al., 2006; Yuzgec et al., 2009).

$$K_{La} = 113 \left(\frac{F_{air}}{A_R} \right)^{0.25} \tag{24}$$

where, F_{air} [m^3/h] represents air feeding rate and A_R [m^2] denotes the cross-sectional area of reactor.

Initial conditions for simulations are given in Table 1, and values of some model parameters are listed in Table 2 as reported by Yuzgec et al. (2009). For the remaining model parameters, nominal values obtained from the literature were employed as given in Table 3.

Table 1. Initial conditions for dynamic simulation (Yuzgec et al., 2009)

State variables	For fed-batch yeast production
C_s, mol/L	4.5×10^{-3}
V, L	50000
C_e, mol/L	0.0
X, C-mol/L	0.35
C_0, mol/L	2.41×10^{-4}

Table 2. Model parameters for fed-batch reactor (Yuzgec et al., 2009)

Parameter	Value
m	0.00417 mol/(C-mol/h)
K_e	0.022 mol/L
K_l	0.00056 mol/L
K_s	0.0034 mol/L
K_0	0.000003 mol/L
$Q_{e,max}$	0.13 mol/(C-mol/h)
$Q_{s,max}$	0.41 mol/(C-mol/h)
μ_{cr}	0.21 h^{-1}
$Y_{x/e}$	1.32 mol/mol
$Y_{x/s}^{ox}$	3.65 mol/mol
$Y_{x/s}^{red}$	0.36 mol/mol

Table 3. Model parameters taken from literature (Besli et. al., 1995; Sonnleitner and Kappeli, 1986)

Parameter	Value
$Q_{o,max}$	0.20 mol/(C-mol/h)
$Y_{o/e}$	1.28 mol/mol
$Y_{e/s}$	1.9 mol/mol
$Y_{o/s}$	2.17 mol/mol
C_o^*	2.41×10^{-4} mol/L

Note: 1 C-mol of biomass has the composition $CH_{1.79}N_{0.15}O_{0.57}$

3. PROBLEM FORMULATION AND OPTIMISATION

The amount of biomass (X_{bio} (t_f)) produced at the final time of batch needs to be maximised while the total ethanol formation ($\int_0^{t_f} C_E$) needs to be minimised during the production time. Therefore, the objective function is as follows (Eq.25);

$$\max_F J = X_{bio}(t_f) - \int_0^{t_f} C_E \tag{25}$$

Subject to the process dynamics, Eqs. 5-19 and hard constraints 0 < u < 2000 L/h with initial conditions $x(t_0) = x_0$. SQP methods represent the state of the art in nonlinear programming methods. At each major iteration, an approximation is made to the Hessian of the Lagrangian function using a quasi-Newton updating method. This is then used to generate a QP sub-problem whose solution is used to form a search direction for a line search procedure. An overview of SQP can be found in optimisation books such as (Gill et al., 1998; Fletcher, 1987; Nocedal and Wright, 1999). The logic flow diagram for optimisation strategy is shown in Figure 1.

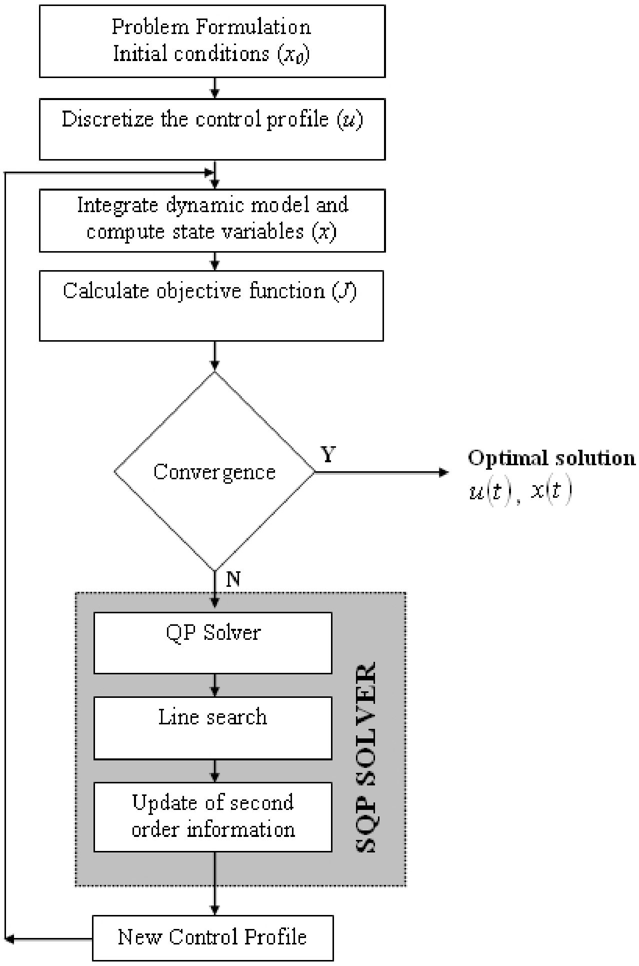

Fig. 1. Basic iteration routine for optimisation (Balku et al., 2009)

4. RESULTS AND DISCUSSION

The optimisation problem was at first expressed in discrete time domain by dividing batch time into hourly time intervals (a total of 17) each with a constant substrate and air feed rate, conforming to the initial values of the control vector. Starting from the beginning of initial values of optimisation variables, the dynamic model (Eqs. 9-23) was integrated with decision variables. Meanwhile, the state variables computed at the end of each time interval were taken as initial values for the subsequent time interval for integration. When the end of overall time domain was reached, the objective function was evaluated. We made use of a constrained multivariable optimisation function in MATLAB® Optimisation Toolbox, which uses the SQP method. This strategy revealed the substrate, i.e. glucose, feed profile to the reactor. Substrate feeding values obtained for each time interval by optimisation were used to determine oxygen uptake rate required by microorganisms at that time interval.

Gas-liquid interface mass transfer coefficient was computed with this oxygen uptake rate. An empirical mass transfer coefficient equation for gas-liquid interface for air bubble column reactors (Karakuzu et al., 2006; Yuzgec et al., 2009) was used to get the aeration rate. Consequently, substrate and air feed rates were found for each time interval as shown in Figures 2 and 3. Substrate feeding as well as aeration profile linearly increased during the first eight hours of fermentation. The subsequent substrate feeding stayed fixed till the end of the fermentation whereas aeration profile started to decrease.

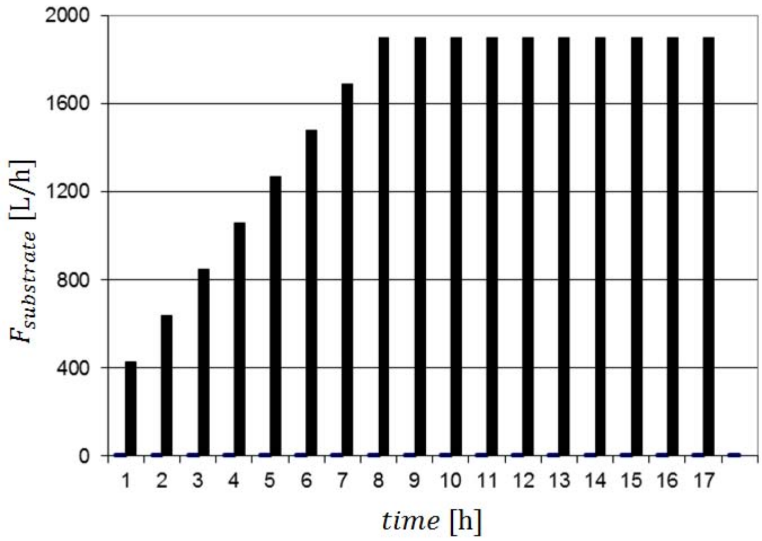

Fig. 2. Optimum substrate feeding profile

The reason for this decline was the fact that the amount of oxygen consumed by microorganisms at a constant substrate feeding period would be the same, the oxygen concentration in the reactor started to increase because of unused oxygen so that lesser aeration needed to be fed to the reactor.

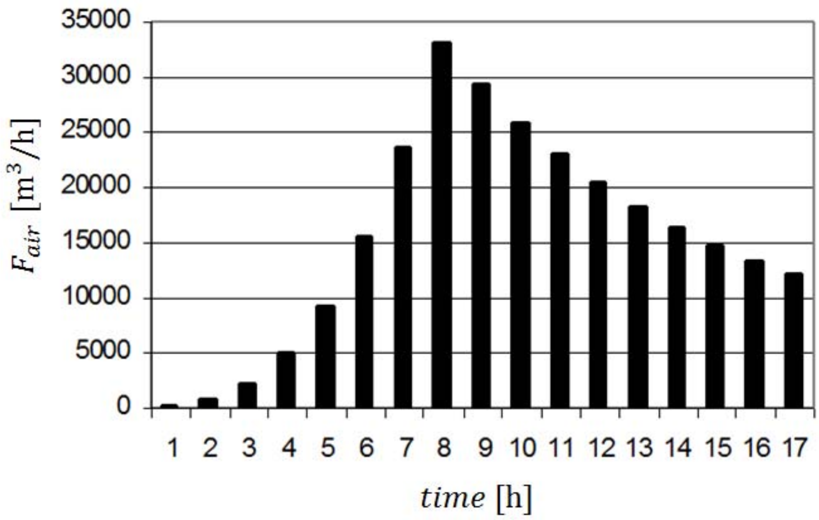

Fig. 3. Optimum aeration profile

When the fermentation process was simulated with the optimum aeration and substrate feeding profiles, the amount of biomass concentration was found to be continuously increasing (Figure 4). A part of the substrate that was fed to reactor was consumed for the formation of alcohol at the early stages of reaction.

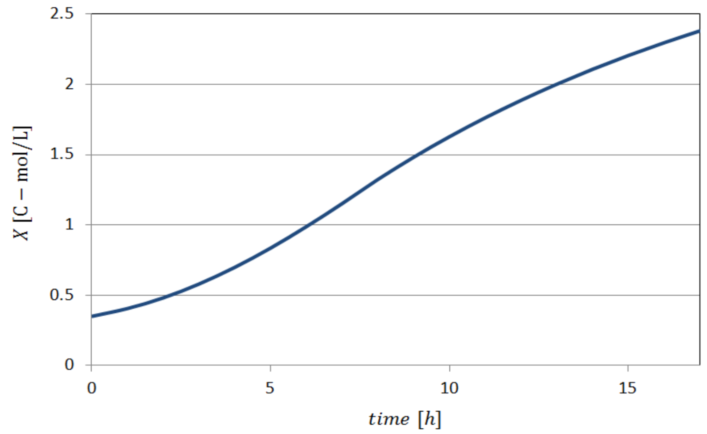

Fig. 4. Changes in biomass concentration

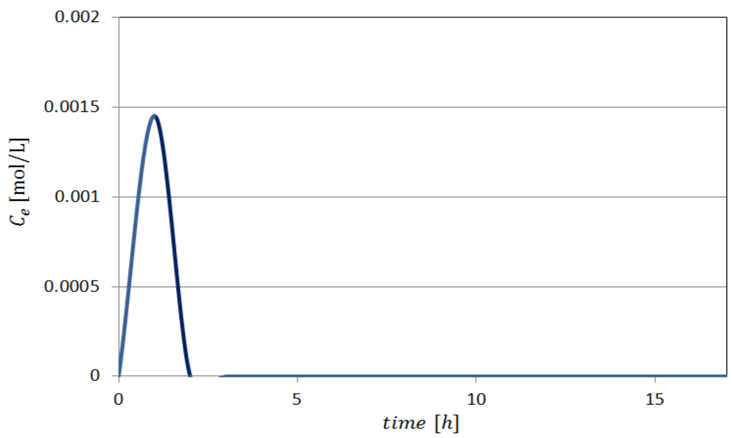

Fig. 5. Changes in ethanol concentration

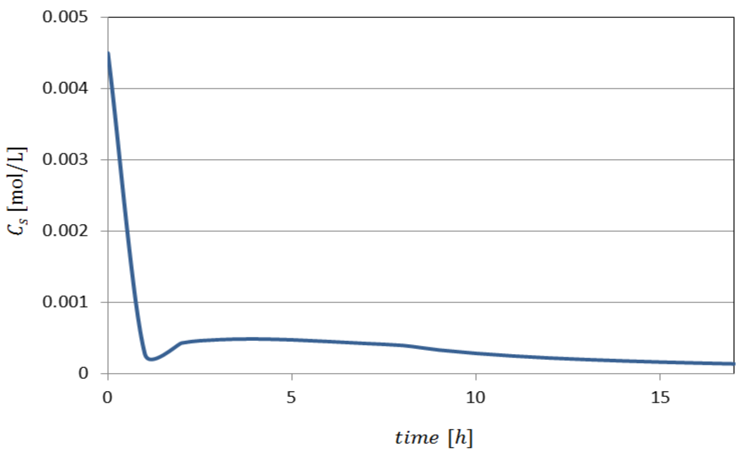

Fig. 6. Changes in glucose concentration

The absence of alcohol when the reaction was proceeding indicated that the oxygen concentration in the reactor was sufficient. For this reason, cells using oxygen could not produce alcohol hence they continued to grow up as reflected in Figure 5. Glucose concentration in the reactor initially decreased and then increased for during the first 4 hours. After this point, glucose concentration started to decrease monotonically when it reached approximately zero concentration at the end of the process (Figure 6). This was because of increasing cell concentration that required further glucose to be consumed, and led to decrease in glucose concentration.

5. CONCLUSIONS

The results demonstrate that optimum substrate and air feeding profiles can be obtained by an effective optimisation algorithm to achieve the two conflicting goals of maximising biomass and minimising alcohol formation. In conclusion, it can be claimed that, the solution method holds promise for on-line implementation in fermentation industry, provided that it is coupled with a nonlinear state estimator. State estimation will help provide compensation for uncertainties in the model and the effect of unmeasured disturbances that may come from unknown sources.

SYMBOLS

C_i	concentration of component i, mol/L
F	feeding rate, L/h
K_i	saturation constant, mol/L
k_La	total volumetric mass transfer coefficient, 1/h
m	glucose consumption rate for maintenance energy, mol/(C-mol/h)
Q_i	specific consumption or production rate, mol/(C-mol/h)
S_0	concentration of feed, mol/L
T	temperature, K
t	time, h
V	volume, L
X	concentration of biomass, C-mol/L
x_i	mole fraction of component i
$Y_{i/j}$	yield of component i on j, mol/mol

Greek symbols

μ - specific growth rate, 1/h

Superscripts

(*)	interface
(ox)	oxidative
(pr)	production

Subscripts

cr	critic
e	ethanol
i	inlet
L	liquid
lim	limitation
o	oxygen
ox	oxidative
pr	production
red	reductive
s	substrate
sat	saturate
up	uptake
x	biomass

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Received 07 July 2012
Received in revised form 07 February 2013
Accepted 14 February 2013