

Optimization of a Primary Metabolite Fermentation Process: Effect of Cost Factor on the Optimal Feed Rate Control

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ABSTRACT

Optimization of a fed-batch fermentation process is usually done using the calculus of variations to determine an optimal feed rate profile. The obtained optimal feed rate profile consists of sequences of maximum, minimum and singular feed rates. The optimal feed rate control of a primary metabolite process was studied and a biomass production was used as an example. A simple material balance model was used to describe the chosen fermentation process. The problem was then formulated as a free final time problem in the optimal control literature where the control objective was to maximise biomass at the end of the batch. It was shown mathematically that a cost factor per unit of operating time is needed in formulating the objective function. Otherwise the optimal feed rate can not be specified. This is explained by the fact that without cost factor, the optimization algorithm does not take the importance of operating time into account and might result in longer operating time than necessary. This also indicates the essential of using fermentation model on the optimal control problem.

Key words: optimization, fermentation process, optimal control, calculus of variations, primary metabolite

INTRODUCTION

Fermentation processes are used for producing many fine chemical substances such as amino acids, antibiotics, biomass, enzymes, etc. From modes of operation, (batch, fed-batch and continuous), fed-batch operation is often used in industry due to its ability to overcome catabolite repression or glucose effect which usually occur during production of these fine chemicals (Yamane and Shimizu, 1984; Parulekar and Lim, 1985). Moreover, it also gives the operator the freedom of manipulating the process via substrate feed rate. This gives the challenge to the control and optimization of the fed-batch fermentation processes.

Optimization of fed-batch fermentation processes has been a topic of research for many years. To determine an optimal feed rate profile in the fed-batch fermentation, the other environment variables such as temperature and pH which affect bioreaction rates in the processes are assumed constant at some levels. The approaches used by many research groups to determine the substrate feed rate profile that optimises a desired objective function are usually based on the calculus of variations (Weigand, *et al.*, 1979; San and Stephanopoulos, 1984; Takamatsu, *et al.*, 1985; Lim, *et al.*, 1986; Modak, *et al.*, 1986; Cazzador, 1988; Shimizu, *et al.*, 1991). And since there are physical constraints in the minimum and maximum feed rates, the Pontryagin's Maximum principle is

also applied. In establishing the objective function, the cost of operating time so called cost factor, is usually included. This is to make a trade off between production and the length of operating time.

In this paper, the effect of cost factor in the objective function on the optimal control of the primary metabolite fermentation process is investigated. A biomass production is used as an example for the primary metabolite production process and the objective function was, therefore, to maximise biomass concentration at the end of the batch.

In the next section, the mathematical representation of a fed-batch fermentation process is described and the optimal feed rate sequences that optimise this process is then formulated. It is then shown in subsequent section that without the presence of cost factor, the optimal feed rate can not be specified.

MATERIALS AND METHODS

Optimal feed rate control

Biomass production process is used here as an example of primary metabolite production process. The fed-batch fermentation of this process can be represented by the following dynamic mass balance equations.

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

$$\frac{dS}{dt} = -\frac{1}{Y_{xs}}\mu X + D(S_f - S) \quad (2)$$

$$\frac{dV}{dt} = F \quad (3)$$

$$D = F/V \quad (4)$$

where X , S are biomass and substrate concentration (g/l) in the reactor, respectively; F is the substrate feed rate (l/hr.); S_f is the concentration of substrate in the feed stream (g/l); D is dilution rate (1/hr.); μ is the specific cell growth rate (1/hr.);

Y_{xs} is the yield of cell mass from substrate (g cell/g substrate) and V is fermenter volume (l). The specific rates μ is a function of substrate concentration.

The fed-batch fermentation is constrained by conditions on final volume, and minimum and maximum of substrate feed rates:

$$0 \leq F \leq F_{\max} \quad (5)$$

$$V(t_f) = V_f \quad (6)$$

The aim for this primary metabolite (biomass) production is to maximise the biomass concentration (X) at the final operating time using substrate feed rate (F). This aim can be transformed into an objective function as:

$$J(F) = X(t_f) - \epsilon \int_{t_0}^t dt \quad (7)$$

Where ϵ is the cost factor per unit of operating time.

This optimization problem can be solved using the calculus of variation (Noton, 1972; Bryson and Ho, 1975; Ramirez, 1994) in which the Hamiltonian equation for this process can then be written as:

$$H = -\epsilon + \lambda_x(\mu X - DX) + \lambda_s \left(-\frac{1}{Y_{xs}}\mu X + D(S_f - S) \right) + \lambda_v F \quad (8)$$

and the costate equations:

$$\dot{\lambda}_x = -\frac{\partial H}{\partial X} = -\lambda_x(\mu - D) + \frac{1}{Y_{xs}}\lambda_s\mu \quad (9)$$

$$\dot{\lambda}_s = -\frac{\partial H}{\partial S} = -\lambda_x X \mu' + \frac{1}{Y_{xs}}\lambda_s X \mu' + D \lambda_s \quad (10)$$

$$\dot{\lambda}_v = -\frac{\partial H}{\partial V} = -\frac{F \lambda_x X}{V^2} + \frac{F \lambda_s}{V^2}(S_f - S) \quad (11)$$

The transversality or final conditions can also be written as:

$$\lambda_x(t_f) = \frac{\partial J}{\partial X_{tf}} = 1$$

and

$$\lambda_s(t_f) = 0$$

The optimal feed rate sequences are then calculated from Equation (12) in which the sign of Ψ is used to indicate the period of maximum, minimum or singular feed rate.

$$\frac{\partial H}{\partial F} = -\frac{\lambda_x X}{V} + \lambda_v + \frac{\lambda_s (S_f - S)}{V} = \Psi \quad (12)$$

if $\Psi < 0$ then $F = 0$

if $\Psi > 0$ then $F = F_{\max}$

if $\Psi = 0$ then $F = F_{\text{sing}}$

The singular feed rate (F_{sing}) can be determined by differentiating Equation (12) until feed rate (F) reappears in the equation.

RESULTS AND DISCUSSION

Effect of cost factor

To determine the singular feed rate, Equation (12) is differentiated until feed rate (F) reappears in the equation. The first derivative of (12) is shown as:

$$\frac{d\Psi}{dt} = 0 = \frac{\lambda_s \mu' X (S_f - S)}{V Y_{xs}} - \frac{\lambda_x \mu' X (S_f - S)}{V} \quad (13)$$

which implies that

$$\mu' = \frac{\partial \mu}{\partial S} = 0 \quad (14)$$

or

$$\frac{\lambda_s}{Y_{xs}} - \lambda_x = 0 \quad (15)$$

It can be proved by contradiction that Equation (15) is not satisfied during the singular period. To illustrate this, it is assumed first that Equation (15) is satisfied during the singular period. The Hamiltonian (Equation (8)) during the singular

period is:

$$H = -\varepsilon + \lambda_x \mu X - \lambda_s \frac{1}{Y_{xs}} \mu X \quad (16)$$

Since the final operating time for this process is not fixed (free final time problem), the Hamiltonian is constant and equals to zero. This condition is not valid if Equation (15) is satisfied. Therefore, Equation (14) is the only necessary condition for singular period to happen in this process.

To determine the singular feed rate, Equation (12) is differentiated again. The second derivative of Y is:

$$\frac{d^2 \Psi}{dt^2} = 0 \quad (17)$$

Using Equation (1) to (3), (9), (10) and (14), the singular feed rate can be derived from Equation (17) as:

$$F_{\text{sing}} = \frac{\mu X V}{Y_{xs} (S_f - S)} \quad (18)$$

The substrate concentration (S) during the singular period will be called “singular substrate concentration (S_{sing})” and can be obtained by solving Equation (14). Note that singular substrate concentration is the substrate concentration that corresponds to the maximum specific growth rate. Equation (18) can then be written as:

$$F_{\text{sing}} = \frac{\mu X V}{Y_{xs} (S_f - S_{\text{sing}})} \quad (19)$$

The singular feed rate can be interpreted as a regulator control law which maintains the substrate concentration constant at value S_{sing} . In the above equation, $(\mu X V / Y_{xs})$ is the amount of substrate that is needed to produce biomass, and $(S_f - S_{\text{sing}})$ is the amount of substrate that is provided to produce biomass after keeping substrate concentration constant at S_{sing} . The ratio of these two values results in a desired feed rate that will control

substrate concentration at this singular level (S_{sing}). It can also be compared with the material balance of substrate concentration in Equation (2) in which Equation (19) can be obtained under a condition that substrate concentration is to be kept constant ($dS/dt = 0$) at a singular level.

In developing a singular feed rate earlier, it is noticed that without the presence of cost factor, the necessary condition for the singular period can not be specified and, therefore, singular feed rate can not be derived. Since the condition for a singular period is to keep substrate concentration at the level where specific growth rate is maximised (Equation (14)), the biomass therefore reaches the maximum at the shortest operating time. This is, however, independent of the value of cost factor as long as the cost factor exists in objective function.

In case of no cost factor, the conditions for singular period (Equation (14) and (15)) can not be uniquely specified. In this case, substrate concentration is not necessary to be kept at optimal level where specific growth rate is maximum. Singular feed rate is also not necessary to control the substrate concentration at optimal level. This would result in longer operating time than necessary and, therefore, not desirable. It is noting, however, that the final biomass concentration is also maximum at the end of the batch. This can be seen from the process model, where substrate concentration is finally all converted into biomass. Since singular feed rate is not necessary to provide substrate at optimal level for growth, the path for this operation is not the shortest one. Comparing to the cost factor case, the operating time is the shortest operating time as biomass has been produced at the maximum specific growth rate.

In real life, substrate is also used by micro-organisms for cell maintenance. Therefore, with the same amount of substrate provided, longer operating time ($\epsilon=0$) can not produce the same amount of biomass as in the shorter operating time

($\epsilon\neq0$). This points to a better selection of process model for used in process optimization. For a simple example, an addition of a maintenance term (mX) in substrate utilisation model (Equation (2)) might do the work. Equation (2) then becomes:

$$\frac{dS}{dt} = -\frac{1}{Y_{xs}} \mu X - mX + D(S_f - S) \quad (2-1)$$

where m is maintenance coefficient (g substrate/g cell·hr)

In this case, maintenance term can be used with similar role as cost factor to specified the only necessary singular condition (Equation (14)) as previously described. The singular feed rate that provides the optimal substrate concentration can then be obtained. Optimization from this model, therefore, provides the same result in both cases of objective functions - with or without cost factor. This is due to the fact that the maintenance term has already implied the cost of operating time into the process and hence, cost factor is not necessary to be included explicitly in objective function.

CONCLUSION

In optimising biomass production in fed-batch process, cost factor per unit of operating time is needed. Otherwise, the necessary condition for singular period can not be uniquely specified and singular feed rate can not provide the optimal substrate concentration level for growth. By considering the process model, this problem can be overcome by proper selection of the model employing in process optimization.

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