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

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ABSTRACT

Optimisation of a fed-batch fermentation process is usually done by 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. In this paper, the optimal feed rate control of a secondary metabolite process was investigated under the different cost factors. A material balance model was used to describe the secondary metabolite production process, where the specific growth rate and the specific product formation rate were assumed to follow the substrate inhibition kinetic. This optimisation problem was formulated as a free final time problem in the optimal control literature where the control objective was to maximise the product at the end of the batch. It was shown mathematically that without a cost factor, the process was operated at the condition where the ratio of the specific product formation rate and the specific growth rate was maximum. With the presence of the cost factor, the operating condition was bounded by two extreme situations. One was at the maximum specific growth rate, where the cost factor is high and the operating time is at utmost important. The other was at the maximum ratio of the specific product formation rate and the specific growth rate, where the operating time was less important and the maximum product was required at the end of the batch. With the moderate cost factor, the process started with growth and gradually changed to product formation.

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

INTRODUCTION

Optimisation of fed-batch fermentation processes has been a topic of research for many years. The approaches used by many research groups to determine the substrate feed rate profile that optimizes 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). Also due to the physical constrained on the feed rates, the Pontryagin's Maximum principle is 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 the production and the length of operating time. Moreover, it was shown previously that the cost factor must be presented in formulating the objective function for a primary metabolite production process, otherwise the optimal feed rate profile can not be determined (Vanichsriratana, 1997).

In this paper, the effect of cost factor in the objective function on the optimal feed rate control of the secondary metabolite production process is investigated. This optimisation problem was for-

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mulated as a free final time problem in the optimal control literature where the control objective was to maximise the product at the end of the batch.

In the next section, the mathematical model of a fed-batch secondary metabolite process is described and the optimisation method based on the calculus of variations is introduced. In the subsequent section, the optimal feed rate profile for this process is then derived based on two cases of objective functions – with or without cost factor. The paper is then concluded is the last section.

MATERIALS AND METHODS

Mathematical model and optimal feed rate control

Based on the material balance equation, the model for a fed-batch secondary metabolite production can be written as:

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

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

$$\frac{dP}{dt} = \mu X - DP \quad (3)$$

$$\frac{dV}{dt} = F \quad (4)$$

$$D = F/V \quad (5)$$

where X, S, P are biomass, substrate and product 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 and π are specific cell growth rate and specific product formation rate respectively (1/hr.); Y_{xs} is the yield of cell mass from substrate (g cell/g substrate) and V is fermenter volume (l). Further details and analysis on the fed-batch operation can be found in (Dunn and Mor, 1975; Lim, *et al*., 1977; Yamane and Shimizu, 1984)

In this paper, the specific rates μ and π are nonlinear functions of substrate concentration and in the form of substrate inhibition kinetic.

$$\mu = \frac{\mu_{max} S}{\left(K_S + S + S^2/K_i\right)} \quad (6)$$

$$\pi = \frac{\pi_{max} S}{K_{\pi s} + S + S^2/K_{\pi i}} \quad (7)$$

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

$$0 \le F \le F_{max} \quad (8)$$

$$V(t_f) = V_f \quad (9)$$

The objective of this fermentation process is to produce as much product as possible at the end of the batch. This objective can be written in a general form of an objective function as shown in Equation (10) and can be solved using the calculus of variations (Noton, 1972; Bryson and Ho, 1975; Ramirez, 1994).

$$J(F) = f(X(t_f), P(t_f)) \quad (10)$$

The obtained open loop optimal feed rate profile consists of a sequence of maximum, minimum and singular feed rates depending on the following condition:

$$\frac{\partial H}{\partial F} = -\frac{\lambda_X X}{V} + \lambda_V + \frac{\lambda_S (S_f - S)}{V} - \frac{\lambda_P P}{V} = \Psi \quad (11)$$

where H is the Hamiltonian and λ_i is the costate variable of state i, (i = X, S, P and V)
From the Maximum principle, the optimal feed rate is determined by Ψ as follow:

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

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

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

The singular feed rate (F_{sing}) can be determined by repeatedly differentiating Ψ until feed rate (F) appears in the time derivative equation of Ψ.

$$\frac{d^k}{dt^k}\Psi = 0 \; ; \; k = 1,2,3...$$

RESULTS AND DISCUSSION

Case 1. Objective function with Cost Factor

In the first case, the objective function with time cost factor is investigated. Since the objective of the fermentation process is to produce as much product as possibly under production-time constraint, the given objective can be written into an objective function as:

$$J(F) = P(t_f) - \varepsilon \int_{t_0}^{t_f} dt \quad (12)$$

The Hamiltonian equation for this process can then be written as:

$$H = -\varepsilon + \left(\lambda_X \mu - \frac{\lambda_S}{Y_{xs}}\mu + \lambda_P \pi\right)X + \left(-\frac{\lambda_X X}{V} + \lambda_V + \frac{\lambda_S (S_f - S)}{V} - \frac{\lambda_P P}{V}\right)F \quad (13)$$

where the costate equations are:

$$\dot{\lambda}_X = -\frac{\partial H}{\partial X} = -\lambda_X(\mu - D) + \frac{1}{Y_{xs}}\lambda_S \mu - \lambda_P \pi \quad (14)$$

$$\dot{\lambda}_S = -\frac{\partial H}{\partial S} = -\lambda_X X \mu' + \frac{1}{Y_{xs}}\lambda_S X \mu' + D\lambda_S - \lambda_P X \pi' \quad (15)$$

$$\dot{\lambda}_P = -\frac{\partial H}{\partial P} = \lambda_p D \quad (16)$$

$$\dot{\lambda}_V = -\frac{\partial H}{\partial V} = -\frac{F\lambda_X X}{V^2} + \frac{F\lambda_S}{V^2}(S_f - S) - \frac{F\lambda_P P}{V^2} \quad (17)$$

The transversality or final conditions can also be written as:

$$\lambda_X(t_f) = 0 \quad (18)$$

$$\lambda_S(t_f) = 0 \quad (19)$$

$$\lambda_P(t_f) = \frac{\partial J}{\partial P_{tf}} = 1 \quad (20)$$

The optimal control sequence is then calculated from Equation (21) in which the sign of Ψ is used to indicate the period of maximum, minimum or singular feed rate.

$$\frac{\partial H}{\partial F} = -\frac{\lambda_X X}{V} + \lambda_V + \frac{\lambda_S (S_f - S)}{V} - \frac{\lambda_P P}{V} \quad (21)$$

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

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

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

During the singular period ($\Psi = 0$), the singular feed rate is determined by differentiating Equation (21) until feed rate (F) reappears in the equation. The first derivative of Ψ is:

$$\frac{d\Psi}{dt} = 0 = \frac{\lambda_S \mu' X (S_f - S)}{VY} - \frac{\lambda_X \mu' X (S_f - S)}{V} - \frac{\lambda_P \pi' X (S_f - S)}{V} \quad (22)$$

which implies that,

$$\frac{\lambda_S \mu'}{Y} - \lambda_X \mu' - \lambda_P \pi' = 0 \quad (23)$$

And the second derivative of Y is,

$$\frac{d^2\Psi}{dt^2} = 0 \quad (24)$$

The singular feed rate can then be obtained from Equation (24) using Equations (1) to (4), (14) to (17) and (23) as:

$$F_{sing} = \frac{V}{(S_f - S)}\left[\frac{\mu X}{Y_{xs}} + \frac{\mu'\left(\frac{\lambda_S}{Y_{xs}}\mu - \lambda_X \mu - \lambda_P \pi\right)}{\left(\frac{\lambda_S}{Y_{xs}}\mu'' - \lambda_X \mu'' - \lambda_P \pi''\right)}\right] \quad (25)$$

Where ´ and ˝ are the first and second derivatives with respect to the substrate concentration. Comparing Equation (25) to the mass balance equation of substrate concentration in Equation (2), the following equation is obtained:

$$\frac{dS_{sing}}{dt} = \frac{\mu'\left(\frac{\lambda_S}{Y_{xs}}\mu - \lambda_X \mu - \lambda_P \pi\right)}{\left(\frac{\lambda_S}{Y_{xs}}\mu'' - \lambda_X \mu'' - \lambda_P \pi''\right)} \quad (26)$$

Equation (26) is the singular substrate concentration trajectory during the singular period. The singular feed rate for the secondary metabolite process can therefore be seen as feed rate that maintains substrate concentration following the trajectory in Equation (26).

During the singular period, Equation (21) equals zero:

$$-\frac{\lambda_X X}{V}+\lambda_V+\frac{\lambda_S\left(S_f-S\right)}{V}-\frac{\lambda_P P}{V} = \Psi = 0 \quad (27)$$

Since this is a free final time problem (the final operating time is not fixed), the Hamiltonian (H) becomes zero and Equation (13) during the singular period (Equation (27)) then becomes;

$$H = -\varepsilon+\left(\lambda_X \mu-\frac{\lambda_S}{Y_{xs}}\mu+\lambda_P \pi\right)X = 0 \quad (28)$$

or

$$X = -\frac{\varepsilon}{\left(\frac{\lambda_S}{Y_{xs}}\mu-\lambda_X \mu-\lambda_P \pi\right)} \quad (29)$$

Substituting Equation (23), which is the condition for the singular period into Equation (29) results in;

$$X = -\frac{\mu'\varepsilon}{\left(\pi'\mu-\pi\mu'\right)} \quad (30)$$

Equation (30) shows the relationship between the substrate and biomass concentration at the different operating cost factor (ε) during the singular period. The profile of substrate concentration (Equation (26)) and the singular feed rate (Equation (25)) during the singular period then become:

$$\frac{dS_{sing}}{dt} = \frac{\mu'\left(\pi'\mu-\pi\mu'\right)}{\left(\pi'\mu''-\pi''\mu'\right)} \quad (31)$$

$$F_{sing} = \frac{V}{\left(S_f-S_{sing}\right)}\left(\frac{\mu X}{Y_{xs}}+\frac{\mu'\left(\pi'\mu-\pi\mu'\right)}{\left(\pi'\mu''-\pi''\mu'\right)}\right) \quad (32)$$

It can be seen that the singular substrate concentration is not constant as in the primary metabolite process (Vanichsriratana, 1997), but follows the profile in Equation (31). Note also that the optimal substrate concentration profile is bounded by two conditions where $dS_{sing}/dt = 0$. These conditions are:

$$\mu' = \frac{\partial\mu}{\partial S} = 0 \quad (33)$$

and

$$(\mu\pi'-\mu\pi') = 0 \text{ or } \frac{d(\pi/\mu)}{dS} = 0 \quad (34)$$

Therefore the optimal substrate concentration profile will start with the concentration that is suitable for the biomass production (Equation (33)) and gradually changes to the one that is suitable for the product formation (Equation (34)). The changing rate of the substrate concentration profile from biomass production to product formation will depend on the value of the cost factor that is used in the objective function.

Case 2. Objective function without Cost Factor

The circumstance is, however, different from the other case where the given objective function does not take the operating cost into account (ε = 0). The given objective function in this case is:

$$J(F) = P(t_f) \quad (35)$$

Following the same procedure, the Hamiltonian equation in (13) during the singular period, given the objective function (35), becomes:

$$H = \left(\lambda_X \mu-\frac{\lambda_S}{Y_{xs}}\mu+\lambda_P \pi\right)X = 0$$

or

$$\frac{\lambda_S \mu}{Y_{xs}}-\lambda_X \mu-\lambda_P \pi = 0 \quad (36)$$

And the singular feed rate in this case (from Equation (25)) becomes:

$$F_{sing} = \frac{V}{\left(S_f-S_{sing}\right)}\frac{\mu X}{Y_{xs}} \quad (37)$$

Equation (37) shows that the substrate concentration is kept constant at S_{sing} during the singular period. The singular substrate concentration (S_{sing}) can be obtained from combining Equation (23) and (36) which results in:

$$\lambda_P(\mu\pi' - \mu\pi') = 0$$

Since λ_P is not zero, this implies,

$$(\mu\pi' - \mu\pi') = 0$$

or

$$\frac{d(\pi/\mu)}{dS} = 0 \qquad (38)$$

The substrate concentration is therefore kept constant at the level which maximises the ratio of the specific product formation rate over the specific growth rate. Note that this level of substrate concentration is not necessarily the level that maximises the product formation rate (i.e. $\pi' = 0$). With the ratio of high production rate over low growth rate, the process will take long operating time due to the slow growth rate and result in high product concentration at the end of the batch. This condition is obtained from the fact that we have considered only maximising product concentration and did not put the cost of operating time into account. This can be considered as an ideal condition for maximising secondary metabolite production. However, most of the process would operate under some production-time constraint considered earlier and excessive long operating time might not be applicable in industry.

CONCLUSION

The present of cost factor (ε) in the objective function has effects on the optimisation of the secondary metabolite production process. When the cost factor (ε) is present in the objective function, the optimal substrate concentration was bounded by two conditions. One is at the maximum specific growth rate and the other is at the maximum ratio of the specific product formation rate and the specific growth rate. The fermentation process, therefore, starts with the condition that is sutiable for the biomass production and then changes to the condition that is suitable for the product formation. The changing rate from biomass production to product formation depends on the value of the cost factor that is used in the objective function.

When the cost factor (ε) is not present in the objective function, the process is operated at the condition where the ratio of the specific product formation rate and the specific growth rate is at the highest. This results in high product concentration at the end of the batch but the process will take long operating time due to the slow growth rate and may not be desirable.

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