On-line Application Oriented Scheduling for Fed-batch Antibiotic Fermentation

Y. F. Xue and J. Q. Yuan

Abstract—**The great variance of cultivation periods of different antibiotic fermentation batches operated empirically results in potential loss in the economic profit and many disturbances on upstream and downstream units. With the prediction of profit function, on-line application oriented scheduling strategy for antibiotic fermentation is proposed. The scheduling intervals and the scheduling functions are introduced for fixed and flexible termination intervals. The scheduling strategies may give the optimal termination sequence of batches. The termination criterion of the optimal operation period is also presented. The scheduling strategies optimize the cultivation periods. Pseudo on-line testing using the proposed scheduling strategies is applied with the data from a Chinese pharmaceutical factory.**

I. Introduction

The batch process is one of the important parts of the process industry [1], [2]. Batch plants have greatly applied in the fields of chemical, pharmacy, food and beverages [3], [4]. Because of the complexity and variance of a bioprocess, many traditional scheduling methods have great limits in the applications of fed-batch antibiotic fermentation.

In the past, most scheduling researches on fed-batch fermentation have focused on static or off-line scheduling methods. The genetic algorithm, the iterative optimization approach and the artificial neural network (ANN) have been developed for fed-batch antibiotic fermentation [5]-[8]. These scheduling methods have applied to off-line optimization of fed-batch bioreactor systems. However, the static and off-line scheduling methods are less helpful for the optimization of the dynamic fermentation process [9]-[11]. It is of great significance to build on-line application oriented scheduling strategies for fed-batch fermentation [12]-[17].

The aim of this paper is to propose on-line application oriented scheduling strategies of cultivation periods for fed-batch antibiotic fermentation batches. These scheduling strategies aim at maximizing the total economic profit of the bioprocess. With the prediction of the economic profit function of batches [18], the scheduling strategies can on-line calculate the scheduling intervals and the scheduling functions for fixed and flexible termination intervals. The strategies also give the optimal termination sequence of batches. The termination time of batches in the flexible scheduling intervals can be deduced by the termination criterion of the scheduling strategy. Experiments with data from an industrial scale penicillin fermentation process are applied.

This paper is organized as follows. In Section II, the on-line application oriented scheduling mechanism of fed-batch fermentation is presented. In Section III, the objective function and the profit function of on-line scheduling strategies for fed-batch antibiotic fermentation is described. The scheduling strategies for fixed termination intervals and flexible termination intervals are introduced. The scheduling intervals and the scheduling functions for fixed termination intervals and flexible termination intervals are presented. In Section IV, the pseudo on-line testing using the proposed scheduling strategies are applied with the experimental data from an antibiotic pharmaceutical factory. The summary of this paper is described in Section V.

II. Scheduling Mechanism of Fed-batch Antibiotic Fermentation

The multi-reactor parallel fermentation is a widely applied production mode in antibiotic pharmaceutical factories. The scheduling operations of bioprocess usually depend on the experiences of the workers in the workshops. The cultivation periods of fermentation batches operated by experiences in an antibiotics workshop are described in Fig.1. From Fig.1, one can follow that cultivation periods of fed-batch fermentation terminated empirically are much different. The great variance of cultivation periods of batches results in potential loss in the profit of fed-batch antibiotic fermentation. To maximize the profit of the whole bioprocess, the scheduling strategies may be applied in fed-batch fermentation process.

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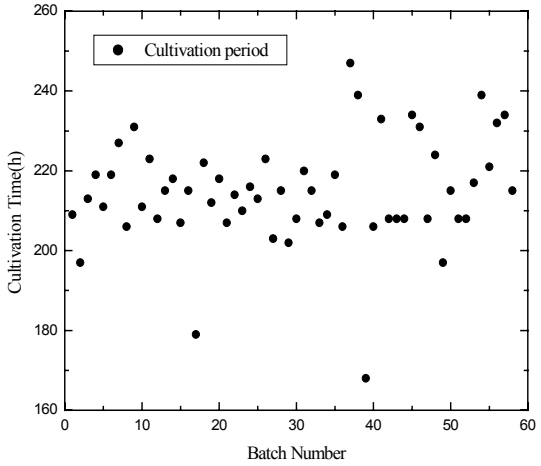

Fig.1. Cultivation periods terminated empirically

Comparing with the other bioprocess variables, the profit function $J(T_f)$ [18] can adequately reflect the economy aspect of fed-batch antibiotic fermentation better and is defined by:

$$J(T_f) = \frac{V_f - C_f}{T_f + T_p} \tag{1}$$

where V_f is the sale values of the fermentation products, C_f is the total costs of fermentation process, T_f is the cultivation time, T_p is the time interval between two successive batches in the same bioreactor.

The rolling learning-prediction approach [19] based on artificial neural networks (ANNs) has applied in the on-line prediction of profit function, which has good efficiency. The training database is composed of the variables of initial states, input variables, output variables, and data vectors of historical batches. The step length of the prediction technology is eight hours and it has five steps ahead. The time interval of maximal prediction length is 40 h. The average of the prediction errors of this approach is less than 5%.

Based on the real values and prediction values of profit function of batches, the scheduling intervals for fixed termination intervals can be calculated. The scheduling functions for fixed termination intervals of different category batches are deduced in the scheduling strategies. And the optimal termination sequence is sorted by the scheduling functions. With the permission of operation constraints, the scheduling strategy for flexible termination intervals can be applied to fed-batch antibiotic fermentation. By calculating the flexible scheduling intervals and the flexible scheduling functions, the termination time of batches is determined. With the termination criterion, the termination time can be deduced quickly and accurately. The on-line application oriented scheduling mechanism for fed-batch antibiotic fermentation is described in the Fig. 2.

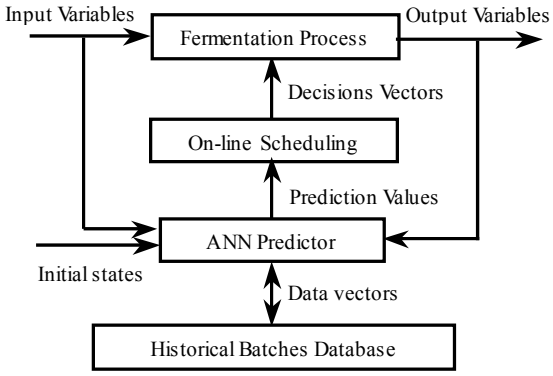

Fig.2. Schematic description of on-line optimal scheduling mechanism

III. On-line Application Oriented Scheduling for Fed-batch Antibiotic Fermentation

A. Objective Function

The objective function of the on-line scheduling strategies is to maximize the profit of the whole bioprocess. The objective function is as follows:

$$\max \sum_{i=1}^{n} J_i(T_f) T_f \tag{2}$$

where n is the total number of cultivation batches, T_f denotes the cultivation period of the i th batch, $J_i(T_f)$ is the profit function of the i th batch at T_f.

The on-line scheduling strategies not only should attain the objective function to maximize the profit of the whole bioprocess by optimizing the cultivation periods of batches, but also should cause no disturbance on upstream and downstream processing units. The principles of the scheduling strategies involve extending cultivation of good batches, stopping normal batches on time and breaking off bad batches earlier.

B. Scheduling Strategy For Fixed Termination Intervals

In practical operations, the scheduling strategies should set different upper and lower limits of cultivation periods of different category batches to maximize the profit of the whole bioprocess. In fermentation process, the termination intervals of cultivation periods of batches are usually fixed because of the constraints of the upstream and downstream processing units. The scheduling strategy for fixed termination intervals is used in the optimization of fed-batch antibiotic fermentation. The scheduling strategy for fixed termination intervals defines the fixed scheduling interval T_{fix} and the fixed scheduling function $J_{s,i}(t)$. The fixed scheduling intervals T_{fix} of batches give the upper and lower limits of Good, Normal and Bad batches:

$$T_{fix} = [T_c - mT_d, T_c + mT_d], (c = g, n, b) \quad (3)$$

$$m = \text{int}[1 + 1.28\sigma_c / T_d], (c = g, n, b) \quad (4)$$

where T_d is the time interval for cleaning up a batch, $T_c(c = g, n, b)$ denotes the average of the cultivation periods of Good, Normal or Bad batches, m is an integer, the confidence coefficient 1.28 corresponds to the confidence limit of 90%, $\sigma_c(c = g, n, b)$ is the standard deviation of classification of Good, Normal or Bad batches, the symbol int represents the function of getting the small integer nearest the real number.

If some batches go into their fixed termination intervals, at least one of the batches should be terminated in order to guarantee that the termination operations would pose no disturbance on upstream and downstream processing units. To sort the optimal termination sequence of the batches in the fixed scheduling interval, the fixed scheduling function is defined:

$$J_{s,i}(t) = J_i(t + \Delta t + kT_d)(t + \Delta t + kT_d) - J_i(t + \Delta t)(t + \Delta t) \quad (5)$$

$$k = \min\{k_i\}, (i = 1, 2, ..., n) \quad (6)$$

$$k_i = \text{int}[(1.28\sigma_{(g,n,b)} + T_{(g,n,b)} - t - \Delta t) / T_d], (i = 1, 2, ..., n) \quad (7)$$

where $J_{s,i}(t)$ denotes the profit increment of the i th batch at t in kT_d time interval, Δt is the interval between the present and the next scheduling time, n is the total number of batches in the fixed scheduling interval.

The optimal termination sequence is determined by the comparison of scheduling functions of the batches. The batch whose scheduling function is the smallest must be terminated firstly to make the least loss to the profit of the bioprocess.

C. Scheduling Strategy For Flexible Termination Intervals

The scheduling strategy for flexible termination intervals must be considered in the following conditions:

(I) In a short interval before the termination time t_{fix} in fixed scheduling interval, maintaining cultivation of a batch will result in potential loss on the profit of the whole bioprocess.

(II) At the termination time t_{fix}, the profit of a batch is on the rise and more profit will be obtained by extending cultivation of the batch.

Apparently, the principles of the scheduling strategy for flexible termination intervals are to break off a batch earlier than the scheduled termination time on condition I and to extend cultivation of a batch longer than the scheduled termination time under condition II, if the scheduling operations give no disturbance on upstream and downstream processing units.

The flexible scheduling interval is a short time interval near the termination time of fixed termination intervals. The widths of flexible termination intervals are determined by the practical operation constraints of the bioprocess. The applications of the scheduling strategy for flexible termination intervals should not pose any disturbances on the upstream and downstream processing units. The flexible scheduling interval is defined as follows:

$$T_{flex} = \left[t_{fix} + (1 - \beta)T_d, t_{fix} + (1 + \beta)T_d\right], 0 \le \beta \le 1/2 \quad (8)$$

where T_{flex} is the flexible scheduling interval, t_{fix} is the cultivation time of the batch in fixed termination intervals, β is the coefficient of T_{flex}.

When the batch goes into the flexible scheduling interval at $t_{fix} + (1 - \beta)T_d$, the decision whether to break off the batch or not must be made. At $t_{fix} + T_d$, the judgment whether to extend cultivation of the batch or not should be done. While at $t_{fix} + (1 + \beta)T_d$, the scheduled batch must be terminated immediately.

When a batch goes into its flexible scheduling interval, whether to extend cultivation or not is determined by two factors that how much profit created by the current batch at present time and in the future. The flexible scheduling function $J_{s,flex}(t)$ is defined by:

$$J_{s,flex}(t) = \left[J(t + \delta t)(t + \delta t) - J(t)t\right] - J_{ave}(t)\delta t, \; t \in T_{flex} \quad (9)$$

where t is the cultivation time of the current batch, $J(t + \delta t)$ is the profit function at $t + \delta t$, $J_{ave}(t)$ is the average of the profit functions of historical batches at t.

If a batch has been cultivated for t, the potential profit can be denoted by the slope rate $J_{slope}(t)$ of the fitting curve of profit function. The data of a fitting curve are composed of real values of profit function before t and prediction values of profit function after t. Fig. 3 is an example of a fitting curve of a fermentation batch.

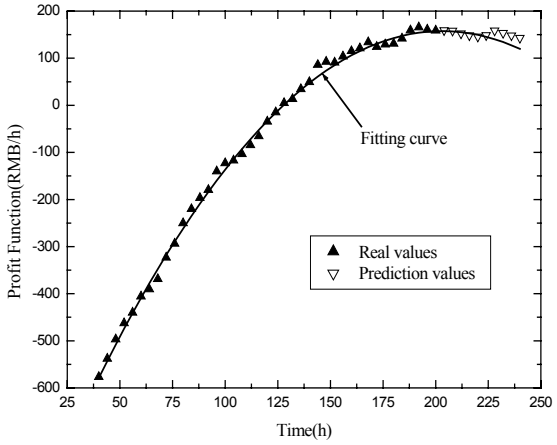

Fig. 3. Fitting curve of profit function of a batch

In the scheduling strategy for flexible termination intervals, there is a termination criterion that can deduce the termination time more easily and accurately than the flexible scheduling function.

If $J_{s,flex}(x) < 0$, it means that the potential profit of the current batch is less than that of a normal batch, thus the batch should be terminated. Rewriting Eq. (9) under this condition, it yields:

$$\frac{J(t+\delta t)-J(t)}{\delta t} < \frac{J_{ave}(t)-J(t+\delta t)}{t} \tag{11}$$

Because δt is much smaller than t, the left part of Eq. (11) is approximately equal to the slope rate $J_{slope}(t)$. Then Eq. (11) can be transformed to Eq. (10):

$$J_{slope}(t) < \frac{J_{ave}(t)-J(t+\delta t)}{t} \tag{10}$$

The termination criterion of the scheduling strategy for flexible termination intervals is determined by Eq. (10). If Eq. (10) is established, the batch in the flexible scheduling interval should be terminated immediately. If Eq. (10) is not satisfied, the batch should be maintained cultivation.

IV. Experiments

A. Experiment I

Pseudo on-line testing using these scheduling strategies is applied with the data from a penicillin fermentation production process of a Chinese pharmaceutical factory. Fig. 4 describes the curves of profit functions of the ten penicillin batches in the workshop from No.1 to No.10 in the penicillin workshop. The cultivation periods of the ten fermentation batches are listed in the Table I.

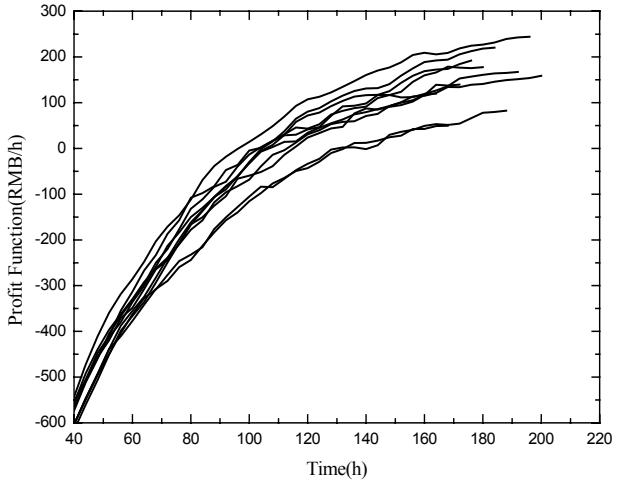

Fig. 4. Curves of profit functions of batches

With the parameters $T_d = 12$ h, $T_w = 40$ h, $T_{samp} = 4$ h and $m = 2$, the termination sequence of the ten batches in fixed termination intervals after 8 h is required to decide. With the scheduling strategy for the fixed termination intervals, the optimal termination sequence can be deduced efficiently.

TABLE I
CULTIVATION TIME OF BATCHES

Batch No.	T_f(h)	Batch No.	T_f(h)
1	176	6	180
2	188	7	168
3	200	8	184
4	164	9	196
5	172	10	192

According to the historical data of batches, $T_g = 224$ h, $T_n = 208$ h and $T_b = 176$ h. The fixed scheduling intervals T_{fix} of Good, Normal and Bad category batches are separately [200, 248], [184, 232] and [152, 200]. Comparing with T_{fix} of different categories, the four batches No.2, No.3, No.7 and No.10 are in their scheduling intervals for fixed termination intervals. By calculating the fixed scheduling functions of the four batches, the optimal termination sequence is determined and the parameters are enumerated in Table II.

TABLE II
TERMINATION SEQUENCE OF BATCHES

Batch No.	2	3	7	10
Scheduling Function	4013.1	1385.9	3941.3	2744.4
Termination Sequence	4	1	3	2

B. Experiment II

To a batch No. 11 in the penicillin workshop of the factory, $t_{fix} = 208$ h, $T_{samp} = 4$ h, $T_d = 12$ h and $\delta t = \beta T_d = 4$ h. Fig. 5 describes the fitting curve of the profit function of Batch No. 11.

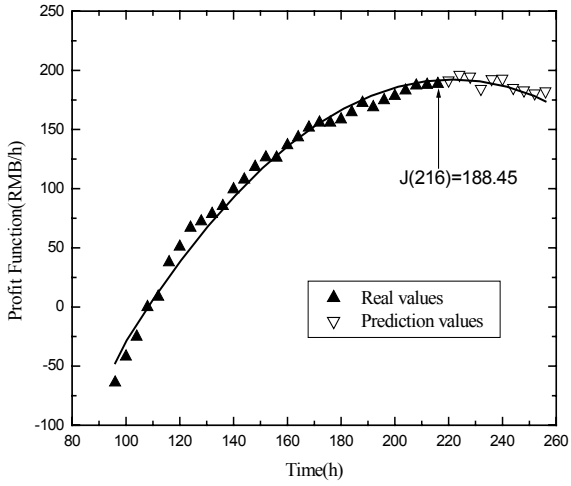

Fig. 5. Fitting curve of profit function of Batch No. 11

This batch has been cultivated for 216 h. The fitting curve of the profit function in Fig. 5 consists of the real values from 96 h to 216 h and prediction values from 220 h to 256 h.

Because $T_d > 2T_{samp}$ is satisfied and the scheduling operations cause no disturbance on the upstream and downstream processing units, the scheduling strategy for flexible termination intervals can be implemented. The decision whether Batch No. 11 should be terminated at 216 h or not is the problem to be solved.

At $t_1 = t_{fix} + (1-\beta)T_d = 216$ h, $J_{slope}(t_1) = 0.15$ and $\left[J_{ave}(t_1) - J(t_1 + \delta t)\right]/t_1 = -0.14$. Then $J_{slope}(t_1)$ is bigger than $\left[J_{ave}(t_1) - J(t_1 + \delta t)\right]/t_1$. According to the termination criterion for flexible scheduling intervals, Eq. (10) is not satisfied and Batch No. 11 should be maintained cultivation. $J(t_1) = 188.45$ RMB/h and it means that Batch No. 11 will gain profit 40705.2 RMB at 216 h. At $t_2 = t_{fix} + T_d = 220$ h, $J(t_2) = 191.54$ RMB/h and Batch No. 11 will achieve 41918.8 RMB/h at 220 h. The average increment of profit functions of batches from 216 h to 220 h is 640 RMB. Batch No. 11 will obtain profit 573.6 RMB more than a normal batch cultivated from 216 h to 220 h. Thus, Batch No. 11 will be maintained cultivation from 216 h to 220 h and the judgment of the flexible termination criterion is right. The parameters of Batch No. 11 in the flexible scheduling interval are listed in Table III.

TABLE III
PAMAMETERS OF BATCH NO. 11

Parameter	Value
$t_1 = t_{fix} + (1-\beta)T_d$ (h)	216
$J(t_1)$ (RMB/h)	188.45
Profit(t_1) (RMB)	40705.2
$t_2 = t_{fix} + T_d$ (h)	220
$J(t_2)$ (RMB/h)	191.54
Profit(t_2) (RMB)	41918.8

C. *Experiment III*

The scheduling strategies for cultivation periods of fed-batch antibiotic fermentation have been applied to 60 penicillin batches in the workshop.

TABLE IV
PROFIT COMPARISON

Parameter	Operation Empirically	Optimal Scheduling
Average Profit (RMB/h)	174.13	180.25
Increase Ratio (%)	-	3.51

Table IV shows that the average profit of the batches using the proposed scheduling strategies is 3.51% more than that operated by experience.

V. SUMMARY

In this paper, the on-line application oriented scheduling strategies are applied to optimize cultivation periods of antibiotic fermentation batches. An on-line application oriented scheduling mechanism is presented, which gives the scheduling intervals, the scheduling functions and the optimal termination sequence to optimize the cultivation periods.

The objective function of the scheduling strategies is to maximize the profit of the whole bioprocess. To attain the goal of the objective function, the cultivation periods of fermentation batches are optimized by two scheduling strategies according to different operation conditions. The fixed scheduling intervals of batches give the upper and lower limits of Good, Normal and Bad batches. With the comparison of the fixed scheduling functions of batches, the optimal termination sequence is determined. When the constraints of the practical operations are satisfied, the scheduling strategy for flexible termination intervals can be applied. With the flexible scheduling interval and flexible scheduling function, the flexible termination time can be optimized. According to the flexible termination criterion, the termination time can be easily deduced.

The pseudo on-line testing using the proposed scheduling strategies is applied with the data from a pharmaceutical factory of China. The fixed scheduling intervals, the fixed scheduling functions and the optimal termination sequence of ten fermentation batches are calculated. Under the operation constraints, the termination time is determined by the scheduling interval, the scheduling function and the termination criterion of the scheduling strategy for flexible termination intervals. The testing results using the proposed scheduling strategies are given in the paper.

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