Bioautomation, 2008, 10, 21-30 ISSN 1312 – 451X

Multiple Objective Optimization and Optimal Control of Fermentation Processes

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Received: February 2, 2008 **Accepted: July 15, 2008**

Published: October 21, 2008

Abstract: *A multiple objective optimization is applied for finding an optimum policy of fed-batch processes of whey fermentation and L-lysine production. The multiple objective optimization problems are transformed to a standard problem of optimization with single objective function by a general utility function with weight coefficients for each single utility coefficient criteria. A combined algorithm is applied when solving the maximizing decision problem. The algorithm includes a method for random search of finding an initial point and a method based on the fuzzy sets theory, combined in order to find the best solution of the optimization problem. The application of the combined algorithm eliminates the main disadvantage of the used fuzzy optimization method, namely it decreases the number of discrete values of the control variables. Thus, the algorithm allows problems with larger scale to be solved. After this multiple optimization, the useful product quality rises and the residual substrate concentration at the end of the process decreases. In this way, the process productivity is increased.*

Keywords: *Multiple objective optimization, Combined algorithm, Method of random search, Fuzzy sets theory, Fuzzy optimization, L-lysine, Whey fermentation.*

Introduction

Multiple objective optimization is a natural extension of the traditional optimization of a single objective function. If the multiple objective functions are commensurate, minimizing a single objective function, it is possible to minimize all criteria and the problem can be solved using traditional optimization techniques. On the other hand, if the objective functions are incommensurate, or competing, then the minimization of one objective function requires a compromise in another objective function. The competition between multiple objective functions is a key distinction between multiple objective optimization and traditional single objective optimization.

Multiple objective optimizations provide a framework for understanding the connections between the various objective functions and allow the engineer to make decisions on how to trade-off among the objectives to achieve performance considered to be “the best”. It is an inherently interactive algorithm, with the engineer constantly making decisions.

In [19] a Pareto optimization technique has been used to locate the optimal conditions for an integrated bioprocessing sequence and the benefits of first reducing the feasible space by the development of a series of operation windows to provide a smaller search area for the optimization.

In [11, 14] a general multiple objective optimization framework of biochemical systems is shown. It applies for optimizing several metabolic responses involved in the ethanol production process by using *Saccharomyces cerevisiae* strain.

In [13] a procedure for solving multiple objective optimization problems is illustrated. A fuzzy set is used to model the engineer's judgment on each objective function. The properties of the obtained compromise solution were investigated along with the connections between the present method and based fuzzy logic one. An uncertainty, which affects the parameters, is modeled by means of fuzzy relations or fuzzy numbers, whose probabilistic meaning is clarified by a random set and possibility theory. Constraint probability bounds that find a solution can be calculated and procedures that consider the lower bound as a constraint or as an objective criterion are presented. Some theorems make the computational effort particularly limited regarding a vast class of practical problems. The relations with a recent formulation in the context of convex modeling are also pressured.

In [3, 16, 17] a fuzzy-decision-making procedure is used to find the optimal feed policy of a fed-batch fermentation process for fuel ethanol production using a genetically engineered *Saccharomyces yeast 1400* as well as the fuzzy optimization of a two-stage fermentation process with cell recycling including an extractor for lactic acid production. By using an assigned membership, a function for each of the objectives, the general multiple objective optimization problems were converted into maximizing decision problems. In order to obtain a global solution, a hybrid search method of differential evolution is introduced.

In [5-9] you can see an application of dynamic and neuro-dynamic programming for single objective optimal control of fed-batch fermentation processes by strains *E. coli*, *Kluyveromyces marxianus var. lactis MC 5* and a fermentation process for *L-lysine* production. The results show that the neuro-dynamic programming lightened the computing procedure and decreased the computing time in comparison with dynamic programming. These priorities make the method suitable for *on-line* single objective optimization.

In [10] a simple combined algorithm guideline is used to find a satisfactory solution to the general multiple objective optimization problem of a fed-batch fermentation process for lactose oxidation from a natural substratum of the strain *Kluyveromyces marxianus var. lactis MC 5*. The obtained optimal control results show an increase of the process productivity and a decrease of the residual substrate concentration.

In this study multiple objective optimization of aerobic fed-batch cultivation of *Kluyveromyces marxianus var. lactis MC 5* and *L-lysine* production by strain *Brevibacterium flavum 22 LD* is developed. The single objective functions reflect the biomass process and *L-lysine* productivity, degree of the substrate utilization and the separation cost in downstream processing. The multiple objective optimization problems are transformed to problems with a single objective function. The combined algorithm applies for the optimal problem solution. The algorithm includes a method for random search of an initial point and a method based on fuzzy sets theory.

Materials and methods

The processes models

The models of the processes have the types [10, 15]:

Model of fed-batch process of whey fermentation

$$\begin{aligned}
&\frac{dX}{Dt} = \mu X - \frac{F}{V} X \\
&\frac{dS}{dt} = \frac{F}{V}(S_{in} - S) - Y_1 \mu X \\
&\frac{dC_L}{dt} = \frac{k_l a}{(1-\varepsilon_G)}(C^* - C_L) - Y_2 \mu X - \frac{F}{V} X \\
&\frac{dV}{dt} = F \\
&\mu = \mu_m \frac{S^2}{(k_S + S^2)} \frac{C_L}{(k_C + C_L + C_L^2 / k_i)};\ k_l a = 52\left(\frac{P}{V}\right)^{0,38} W_G^{0,23};
\end{aligned} \tag{1}$$

$$P = 60.9 \rho n^3 d^5 \mathrm{Re}^{-0.4}\ ;\ W_G = \frac{4\,Q_G}{\pi\ D^2};\ \varepsilon_G = 0.53\left(\frac{Q_G}{nd^3}\right)^{-0.014}.$$

Model of fed-batch process of L-lysine biosynthesis

$$\begin{aligned}
&\frac{dX}{dt} = \mu\ X - \frac{F}{V}\ X \\
&\frac{dS}{dt} = \frac{F}{V}(S_{in} - S) - k_5 \mu\ X - k_6\ X - k_7 \eta\ X \\
&\frac{dTr}{dt} = \frac{F}{V}(Tr_{in} - Tr) - k_{13}\ \mu\ X - \frac{F}{V} Tr \\
&\frac{dC_L}{dt} = k_l a(C^* - C_L) - k_{14}\ \mu\ X - k_{15}\ X - k_{16}\ \eta\ X - \frac{F}{V}\ C_L \\
&\frac{dL}{dt} = \eta\ X \\
&\frac{dV}{dt} = F \\
&\mu = \frac{k_1\ Tr\ C_L}{\left[(k_2 + Tr)(k_3 + S_0 - S)(k_4 + C_L)\right]};\ \eta = \frac{k_8\ S\ C_L}{\left[(k_9 + S)(k_{10} + S)(k_{11} + C_L)(k_{12} + C_L)\right]}.
\end{aligned} \tag{2}$$

In the models (1) and (2) the symbols are as follows:

C^* – equilibrium dissolved oxygen concentration [g·l^{-1}]; C_L – dissolved oxygen concentration [g·l^{-1}]; F – feed flow rate [l·h^{-1}]; $k_l a$ – volumetric mass transfer coefficient [h^{-1}]; S – concentration of substrate [g·l^{-1}]; S_{in} – input feed substrate concentration [g·l^{-1}]; t – process time [h]; X – biomass concentration [g·l^{-1}]; ρ – liquid density [kg·m^{-3}]; μ – specific growth rate [h^{-1}]; μ_m – maximal grown rate [h^{-1}]; V – working volume, [l]; D – bioreactor diameter [m]; d – impeller diameter [m]; n – agitation speed [s^{-1}]; P – power input [W]; Q_G – gas flow rate [m^3·s^{-1}]; Re – Reynolds number; W_G – gas velocity [m·s^{-1}]; ε_G – gas hold-up; L – concentration of *L-lysine* [g·l^{-1}]; Tr – threonine concentration [mg·l^{-1}]; Tr_{in} – input feed threonine concentration [g·l^{-1}]; η – specific rate of *L-lysine* [h^{-1}].

The initial conditions and coefficients in models are given as follows:

Model of fed-batch process of whey fermentation
$X(0) = X_0 = 0.2$, $S(0) = S_0 = S_{in} = 50$, $C(0) = C_0 = C^* = 6.0\text{x}10^{-3}$, $V(0) = V_0 = 1$, $\mu_m = 0.89$, $k_S = 1.62$, $k_C = 3.37\text{x}10^{-3}$, $k_i = 0.47$; $Y_1 = 2.25$, $Y_2 = 3.4\text{x}10^{-3}$.

Model of fed-batch process of L-lysine biosynthesis
$X(0) = X_0 = 3$, $S(0) = S_0 = S_{in} = 100$, $Tr(0) = Tr_0 = Tr_{in} = 80$, $C_L(0) = C^* = C_0 = 6.1\text{x}10^{-3}$, $L(0) = 0$, $V(0) = V_0 = 10$, $k_1 = 20.8$, $k_2 = 42$, $k_3 = 28$, $k_4 = 1.1$, $k_5 = 1.01$, $k_6 = 0.07$, $k_7 = 0.51$, $k_8 = 62$, $k_9 = 28$, $k_{10} = 37$, $k_{11} = 4$, $k_{12} = 0.12$, $k_{13} = 6.1$, $k_{14} = 448$, $k_{15} = 22$, $k_{16} = 209$, $k_la = 120$.

System constraints of the both processes

Nearly all engineering processes will have physical constraints. In this study, the flow rate is bounded and the volume of the bioreactor is constrained, i.e.

$$0 \le F(t) \le F_{\max} \tag{3}$$

$$g_1 = V(t) - V_f \le 0 \tag{4}$$

For the both processes the glucose (5), oxygen (6) and threonine (9) concentration must be positive all the time; otherwise, an unrealistic solution in the optimization problem will be obtained. Therefore we have the following:

$$g_2 = -S(t) \le 0 \tag{5}$$

$$g_3 = -C_L(t) \le 0 \tag{6}$$

In addition, here are the following constrains for stoichiometry by the processes:

$$g_4 = \frac{X(t)\,V(t) - X_0\,V_0}{\left[V(t) - V_0\right]S_{in} + S_0\,V_0 - S(t)\,V(t)} - \frac{1}{Y_1} \le 0 \tag{7}$$

$$g_5 = \frac{X(t)\,V(t) - X_0\,V_0}{\frac{k_l a}{(1-\varepsilon_G)}(C^* - C_L(t)) + C_0\,V_0 - C_L(t)\,V(t)} - \frac{1}{Y_2} \le 0 \tag{8}$$

$$g_6 = -Tr(t) \le 0 \tag{9}$$

$$g_7 = \frac{L(t)\,V(t)}{V(t)[S_{in} - S(t)] + k_5 X_0 V_0 - (k_5 + k_6)X(t)V(t)} - \frac{1}{k_7} \le 0 \tag{10}$$

$$g_8 = \frac{X(t)\,V(t) - X_0\,V_0}{V(t)[Tr_{in} - Tr(t)]} - \frac{1}{k_{13}} \le 0 \tag{11}$$

$$g_9 = \frac{L(t)\,V(t)}{k_l a(C^* - C_L(t)) + C_0 V_0 + k_{14} X_0 V_0 - C_L(t)V(t) - (k_{14} + k_{15})X(t)V(t)} - \frac{1}{k_{16}} \le 0 \tag{12}$$

If the constraints in (7)-(8) and (10)-(12) are not included in the optimization problem, unrealistic predicted values may be found.

Formulation of multiple objective optimizations

A production-planning problem is considered in this study when the decision maker designs a control policy to find the optimal feed flow rate – $F(t)$; input feed substrates concentration – S_{in} and Tr_{in}; initial substrates concentration – S_0 and Tr_0 of the both processes, and the associated objective function values. Such an optimal solution can be obtained by multiple

objective optimization techniques. This problem is simply called multiple objective optimization problem and is expressed like this:

$$\max Q_1(\mathbf{u}) = \left[X(t_f)\,V(t_f) - X_0 V_0\right] / t_f \tag{13}$$

$$\max Q_2(\mathbf{u}) = \left[S_0 - S(t_f)\right] / S_0 \tag{14}$$

$$\min Q_3(\mathbf{u}) = S_{in}\left[V(t_f) - V_0\right] + S_0 V_0 \tag{15}$$

$$\max Q_4(\mathbf{u}) = \left[L(t_f)\,V(t_f)\right] / t_f \tag{16}$$

$$\max Q_5(\mathbf{u}) = \left[Tr_0 - Tr(t_f)\right] / Tr_0 \tag{17}$$

$$\min Q_6(\mathbf{u}) = Tr_{in}\left[V(t_f) - V_0\right] + Tr_0 V_0 \tag{18}$$

The objective functions (13) and (16) correspond to the productivity of the processes – biomass production, for process (1) and *L-lysine* production for process (2). The objective functions (14) and (17) are the degree of the substrates utilizing. The objective functions (15) and (18) are the separation cost in downstream processing.

The control variables are satisfied in the following intervals:

1. For *whey fermentation*: $0 \le F(t) \le 0.02$; $40 \le S_0 \le 120$; $40 \le S_{in} \le 80$.
2. For *L-lysine* production: $0 \le F(t) \le 0.05$; $80 \le S_0 \le 120$; $80 \le S_{in} \le 120$; $60 \le Tr_0 \le 100$; $60 \le Tr_{in} \le 100$.

Since the feed rate $F(t)$ is time-dependent variable, the optimal control problem can be considered for an infinite dimensional problem. To solve this problem efficiently, the feed flow rate is represented by a finite set of control parameters in the time interval $t_{j-1} < t < t_j$ as follows $F(t) = F(j)$ for $j = 1, \ldots, K$ – number of time partitions.

The multiple objective optimization problem (13)-(18) is transformed to a problem with a single objective function by general utility function with weight coefficients for each single utility coefficients criterion. The single objective functions $Q_j(\mathbf{u})$ are transformed in the utility coefficients $\eta_j(\mathbf{u})$ by the formula [12]:

$$\eta_j(\mathbf{u}) = \frac{k\left[Q_j(\mathbf{u}) - Q_{c,j}\right]}{Q_{\max,j} - Q_{\min,j}}, \quad j = 1, 2, ..., m \tag{19}$$

where: $\kappa = \begin{Bmatrix} +1 & for & Q_j(\mathbf{u}) \to \max \\ -1 & for & Q_j(\mathbf{u}) \to \min \end{Bmatrix}$; m – number of objective functions; $Q_j(\mathbf{u})$ – current value of the criterion; $Q_{c,j}$ – more unprofitable result of criterion; $Q_{max,j}$ and $Q_{min,j}$ – utility borders, i.e. the maximal and minimal values of $Q_j(\mathbf{u})$.

After transformation, the generalized utility function is composed from the type:

$$Q_a(\mathbf{u}) = \frac{1}{m}\sum_{j=1}^{m} w_j\,\eta_j(\mathbf{u}) - \sum_{k=1}^{p} r_k \int_0^{t_f} g_k(t)\,dt, \qquad \sum_{j=1}^{m} w_j = 1 \tag{20}$$

Generalized utility function for the *whey fermentation* is composed from the type:

$$Q_a(\mathbf{u}) = \frac{1}{3}\sum_{j=1}^{3} w_j\,\eta_j(\mathbf{u}) - \sum_{k=1}^{5} r_k \int_0^{t_f} g_k(t)\,dt, \qquad \sum_{j=1}^{m} w_j = 1 \tag{21}$$

Generalized utility function for the *L-lysine* biosynthesis is composed from the type:

$$Q_a(\mathbf{u}) = \frac{1}{5}\sum_{j=2}^{6} w_j\, \eta_j(\mathbf{u}) - \sum_{k=1}^{9} r_k \int_0^{t_f} g_k(t)\, dt, \qquad \sum_{j=2}^{m} w_j = 1 \tag{22}$$

The optimal decision $\mathbf{u}^0$ maximizing the general utility function for the both processes was found by using a combined optimization algorithm. The algorithm includes two optimization methods: a method for random search of an initial point and a method based on fuzzy sets theory.

A combined algorithm for optimization

Random search with back step (RSBS) algorithm

The method of RSBS does not require a calculation of gradients, it is simple for programming; allows organizing adaptive algorithms and algorithms for searching a global extremum. RSBS is more effective when there are many control variables (more than four), because the study space is always divided in two areas – *felicitous* and *infelicitous*, and the probability for falling in the one or the other does not depend on the number of variables. RSBS algorithm is well known from the literature [12].

Fuzzy algorithm

The fuzzy sets theory (FST) has a great application in modeling, optimization, and optimal control of biotechnological processes [1-3, 16-18]. In this paper, a method based on FST is used [1, 2]. The Fuzzy algorithm includes only fuzzy criteria from type "*The optimum criterion Q_a to be possibly higher*" and it is presented by the following membership function:

$$\eta(Q_a) = \begin{cases} 0; & Q_a < Q_a^L \\ \dfrac{Q_a - Q_a^L}{Q_a^U - Q_a^L}; & Q_a^L \le Q_a \le Q_a^U \\ 1; & Q_a > Q_a^U \end{cases} \tag{23}$$

where Q_a^L and Q_a^U are *low* and *upper* values for criterion.

The following optimization problem in the class of the fuzzy mathematical programming problems can be formulated:

$$Q_a(\mathbf{u}) \cong \tilde{\max}_{\mathbf{u}}\, Q_a(\mathbf{u}) \tag{24}$$

where "$\tilde{\max}$" means "*in possibility maximum*"; "≅" means "*is come into view approximately in following relation*".

For determination of this problem, an approach generalizing the Bellman-Zadeh's method [2] is used:

$$\eta_D(Q_a) = (1-\gamma)\,\eta(Q_a)^{\theta} + \gamma\left[1 - \left(1 - \eta(Q_a)\right)^{\theta}\right] \tag{25}$$

where: γ – parameter characterized the compensation degree; θ – parameter, those give weight of $\eta(Q_a)$.

The solution is received using the common *defuzzification* method BADD [4]:

$$\mathbf{u}^0 = \sum_{i=1}^{q} \frac{\eta_{D_i}^{\theta}(Q_a)\,\mathbf{u}_i}{\sum_{j=1}^{p} \eta_{D_j}^{\theta_i}(Q_a)}, \quad i = 1,..., q;\ j = 1,2,..., p;\ p = q^m \tag{26}$$

where q is the number of discrete values of the vector **u**.

The generalized **COMBINED** algorithm scheme is:

BEGIN

1. Input number of control variables m, integer constant IY, and number of discrete values q of vector **u**.
2. Input possible area for each control variables $\mathbf{u_{min}}$, $\mathbf{u_0}$, $\mathbf{u_{max}}$, and steps **h**.
3. Input fuzzy sets parameters γ and θ.
4. Computing models before optimization from (1) and (2).
5. **CALL RSBS(m, IY, $\mathbf{u_{min}}$, $\mathbf{u_{max}}$, h, $\mathbf{u^0}$, $\mathbf{Q_a}$)**.
6. Beginning point $\mathbf{u}^0$ is accepted as equal to the one received from **RSBS**.
7. Computing models after RSBS optimization and optimal value of the each criterions Q_j and Q_a.
8. **CALL FUZZY(m, q, Gamma, Theta, $\mathbf{u^0}$, $\mathbf{Q_a}$)**.
9. Returns optimal values of control variables $\mathbf{u}^0$ after COMBINED optimization.
10. Computing models after COMBINED optimization and optimal value of the each criterions Q_j and Q_a.
11. Print results: optimal values of control variables $\mathbf{u}^0$ and criterions $Q_j(\mathbf{u})$ and $Q_a(\mathbf{u})$; time, models (1) and (2) before optimization, after COMBINED optimization; criterions $Q_j(t, \mathbf{u})$, $Q_a(t, \mathbf{u})$, and $F(t)$.

END

The generalized **FUZZY** algorithm scheme is:

BEGIN

1. Computing discrete values of each control variable:
   $\mathbf{u}_i = \left[\mathbf{u}_{\min} + k\left(\mathbf{u}_{\max} - \mathbf{u}_{\min}\right)\right] / \left(q - 1\right)$, for k = 0, 1, …, q and I = 1, 2, …, m.
2. Computing *low* and *upper* values for fuzzy criterion received from **RSBS:**
   $Q_a^L = 0.8\,Q_a(\mathbf{u}^0)$, $Q_a^U = 1.2\,Q_a(\mathbf{u}^0)$.
3. Computing of membership function $\eta_D(Q_a)$ from (23).
4. Computing of membership function of the decision $\eta_D(Q_a)$ from (25).
5. Obtaining solution $\mathbf{u}^0$ using *defuzzification* operator from (26).
6. Returns optimal values of control variables $\mathbf{u}^0$ and criterions $Q_j(\mathbf{u})$ and $Q_a(\mathbf{u})$.

END

All that is programmed using FORTRAN 77. All computations are performed on an Intel 1.8 GHz computer using Microsoft Windows XP Pro Edition operating system.

Results and discussion

Fed-batch process for whey fermentation

The obtained results after optimization are S_0 = 57.0 g·l^{-1} and S_{in} = 69.00 g·l^{-1}. The results for the basic kinetic variables, productivity and feed rate are shown from Fig. 1 to Fig. 4.

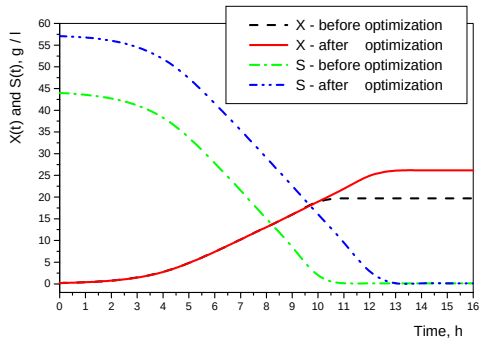

Fig. 1 Biomass and substrate concentration before and after optimization

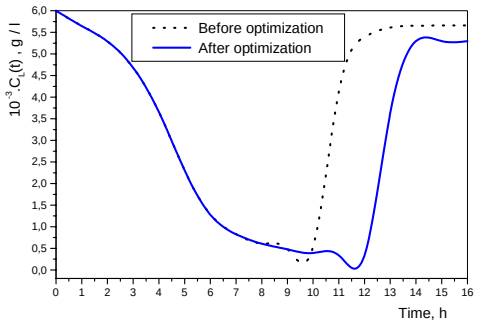

Fig. 2 Oxygen concentration before and after optimization

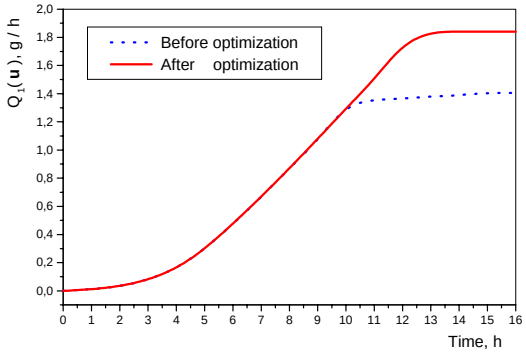

Fig. 3 Biomass productivity before and after optimization

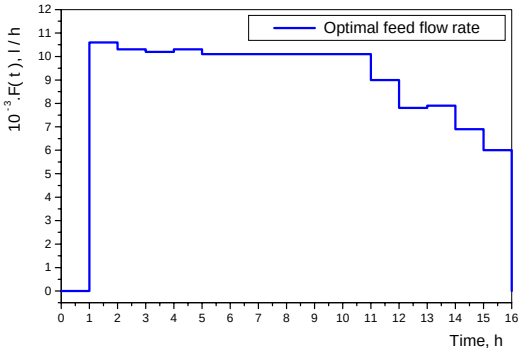

Fig. 4 Optimal profile of feed flow rate

The obtained results show that the biomass concentration increases by more than 32%, the substrate concentration decreases by 9% (Fig. 1), also the oxygen after optimization is better utilized (Fig. 2) i.e. here is a decrease with 7%. The process productivity has increased with more than 30% (Fig. 3).

Fed-batch process for L-lysine production

The obtained results after optimization for the substrate concentrations (glucose and threonine) in the feeding solution are: S_{in} = 114 g·l^{-1}and Tr_{in} = 94 g·l^{-1}, as their input values are S_0 = 89 g·l^{-1} and Tr_0 = 86 g·l^{-1}. The general kinetic variables – productivity and feed rate are shown from Fig. 5 to Fig. 8.

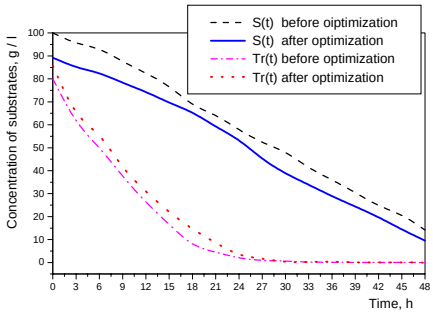

Fig. 5 Substrates (glucose and threonine) concentration before and after optimization

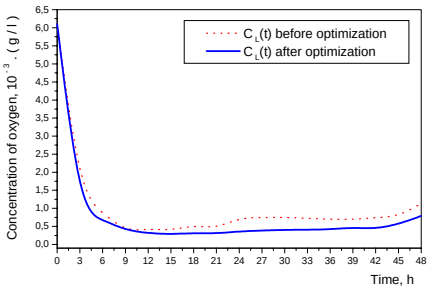

Fig. 6 Oxygen concentration before and after optimization

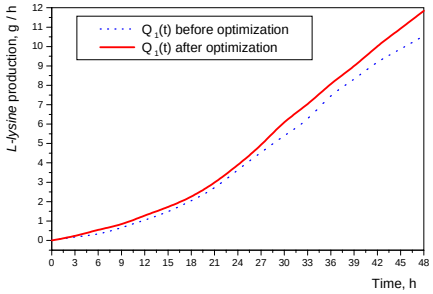

Fig. 7 *L-lysine* production (criterion Q_4) before and after optimal control

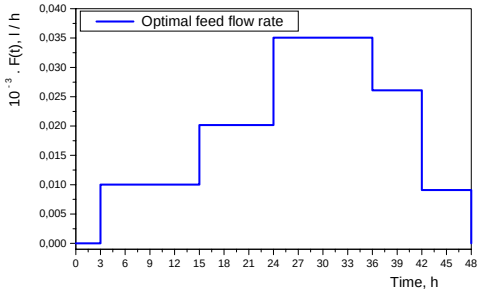

Fig. 8 Optimal profile of feed flow rate

The obtained results show that the substrates concentration decreases: for the glucose by more than 48% and for threonine by 20% (Fig. 5), the oxygen after optimization (Fig. 6), here is decreased by more than 43%. The *L-lysine* concentration increases by more than 12% and the process productivity by more than 30% (Fig. 7).

Conclusions

1. The applied multiple objective optimization of the process shows a vastly increase of their productivity, respectively decrease of the residual substrate concentration. This result leads to a higher economical effectiveness for each of them at smaller outlay.
2. The obtained results from the study show that multiple objective optimization is a more complex approach minimizing the risk in the procedure of decision making and maximizing the formulated objective.
3. Proposed combined algorithm for optimization includes a method for random search of an initial point and a method based on fuzzy sets theory, combined in order to find the best solution of the optimization problem. The application of the combined algorithm eliminates the main disadvantage of the used fuzzy optimization method, namely decreases the number of discrete values of control variables. In this way, the algorithm allows the solvattion of problems with larger scale. Developed combined algorithm can be used for the solution of other optimization problems in the area of bioprocess systems.

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