Fuzzy-Decision-Making Problem of *L-Lysine* Production

M. Petrov* **and T. Ilkova**
Institute of Biophysics and Biomedical Engineering,
Bulgarian Academy of Sciences,
105 Acad. George Bonchev St., Sofia 1113, Bulgaria

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A fuzzy-decision-making procedure is applied to find the optimal feed policy of a fed-batch fermentation process for *L-lysine* production in a stirred tank bioreactor from *Brevibacterium flavum* 22LD. The policy consists of a feed flow rate, feed concentration of glucose and threonine, and fermentation time. In this paper the fermentation process is formulated as a general multiple objective optimization problem. By using an assigned membership function for each of the objectives, the general multiple objective optimization problem can be converted into a maximizing decision problem. In order to obtain a global solution, a method of fuzzy sets theory is introduced to solve the maximizing decision problem. This method allows direct determination of the optimization problem solution. The applied multiple objective optimization of the process has shown a vast increase of its productivity and decrease of the glucose and threonine concentration at the end of the process.

Key words:
fuzzy-decision-making, *L-lysine* production, multiple objective optimization, Pareto optimal solution, fuzzy sets theory

Introduction

Multiple objective optimization provides a framework for understanding the relationships between the various objective functions and allows engineers to make decisions on how to trade-off among the objectives to achieve the performance considered "the best". It is an inherently interactive algorithm, with the engineer constantly making decisions. However, the weighted sum method in a multiple objective optimization textbooks is pervasive. This is one of the most commonly used techniques for solving problems of multiple objective optimization of chemical processes. The decision making (DM) assigns a weighting factor for each of the objective functions to convert a multiple objective optimization problem into a single objective function problem. The optimal solution of the weighted sum problem is one of the Pareto solutions to the multiple objective optimization problems. However, such a solution may be a local solution due to a duality gap between the solutions of the weighted single objective and multiple objective optimization problems. Clearly, if the Pareto surface is nonconvex, the weighted sum method may yield poor designs no matter what weight or optimization method is used. Several methods have been proposed to overcome the drawback of such a nonconvex problem.[1]

Sendin *et al.*[2] have illustrated a general multiple objective optimization framework of biochemical systems and have applied it optimizing several metabolic responses involved in the ethanol production process by using *Saccharomyces cerevisiae* strain. The general multiple objective indirect optimization method (GMIOM) is based on the use of the power law formalism to obtain a linear system in logarithmic coordinates. The problem is addressed with three variants within the GMIOM: the weighted sum approach, the goal programming and the multiple objective optimization. We have compared the advantages and drawbacks of each one of the GMIOM modes. The results obtained have shown that the optimization of the biochemical systems was possible even if the underlying process model was not formulated in an S-system form, and that the systematic nature of the method has facilitated the understanding of the metabolic design and it could be of significant help in devising strategies for improving biotechnological processes.

Zhou *et al.*[3] have used a Pareto optimization technique to locate the optimal conditions for an integrated bioprocessing sequence and the benefits of reducing first the feasible space by developing a series of operation windows to provide a smaller search area for the optimization.

Many of the multiple objective optimization problems in the real world take place in an environment in which the goals, the constraints, and the consequences of possible actions are not known precisely. To deal with imprecision quantitatively, the problem in a fuzzy environment is introduced in

*Corresponding author: mpetrov@biomed.bas.bg, tanja@biomed.bas.bg

this study to handle these imprecise goals and constraints. Such fuzzy multiple objective optimal control problems are converted into a maximizing decision problem through the subjective membership functions for each of the objective functions. The optimal solution for each of the membership functions is denoted as the degree of satisfaction with the assigned threshold requirements.[4–6]

Tonnon *et al.*[7] have used interactive procedure to solve multiple objective optimization problems. A fuzzy set has been used to model the engineer's judgment on each objective function. The properties of the obtained compromise solution were investigated along with the links between the present method and those based on the fuzzy logic. An uncertainty is modelled which has been affecting the parameters by means of fuzzy relations or fuzzy numbers, whose probabilistic meaning is clarified by a random set and the possibility theory. Constraint probability bounds that satisfy 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 on a vast class of practical problems. The relations with a recent formulation are also pressured in the context of convex modelling.

Wang *et al.*[8] have used fuzzy-decision-making adding a procedure that is applied to find the optimal feed policy of a fed-batch fermentation process for fuel ethanol production using a genetically engineered *Saccharomyces* yeast 1400 (pLNH33). By using an assigned membership function for each of the objectives, the general multiple objective optimization problem can be converted into a maximizing decision problem. A hybrid search method of differential evolution is introduced in order to obtain a global solution.

L-Lysine is useful as a medicament, chemical agent, food material (food industry) and feed additive (animal food). *L-Lysine* is important for the proper growth of the human body as it plays an essential role in the production of carnitine, a nutrient responsible for converting fatty acids into energy and helping to lower cholesterol. Its demand has been steadily increasing in recent years and several hundred thousands tons of *L-lysine* (about 800 000 tons/year) are annually produced worldwide almost by microbial fermentation. The significance of research and development has increased rapidly since the discovery of the fermentative amino acid production in the fifties, leading to innovative fermentation processes, which have replaced the classical manufacturing methods of *L-lysine* like acid hydrolysis. The most effective and cheapest method for *L-lysine* biosynthesis (in biological active form) is the microbiological method by a direct fermentation.[9]

In this study, a fuzzy-decision-making procedure has been developed to determine the optimal feed policy of a fed-batch fermentation process for *L-lysine* production from *Brevibacterium flavum* 22LD. The process is formulated as a general multiple objective optimal problem (GMOOP). By using an assigned membership function for each of the objectives, the GMOOP can be converted into a maximizing decision problem. A method of fuzzy sets theory has been introduced in order to obtain a global solution to the maximizing decision problem.

Material and methods

Kinetic model of the fed-batch process

The mathematical model of the fed-batch processes includes the dependences between the concentrations of the basic process variables: cell mass concentration (bacteria *Brevibacterium flavum*), substrate concentration (glucose), *L-lysine*, *threonine* concentration and oxygen concentration in the liquid phase. The model is based on the mass balance equations. We accept that the stirred tank bioreactor has a perfect mixing. Simulation and determination of the optimal initial condition and mass transfer coefficient $k_L a$ of the batch process were redeveloped by Petrov and Ilkova.[10] The model of the fed-batch process has the following type:

$$\frac{\mathrm{d}\gamma_X}{\mathrm{d}t} = \mu\gamma_X - \frac{F}{V}\gamma_X \tag{1}$$

$$\frac{\mathrm{d}\gamma_S}{\mathrm{d}t} = \frac{F}{V}(\gamma_{S\,in} - \gamma_S) - (k_5\mu + k_6 + k_7\eta)\gamma_X \tag{2}$$

$$\frac{\mathrm{d}\gamma_{Tr}}{\mathrm{d}t} = \frac{F}{V}(\gamma_{Tr_{in}} - \gamma_{Tr}) - k_{13}\mu\gamma_X \tag{3}$$

$$\begin{aligned}\frac{\mathrm{d}\gamma_{C_L}}{\mathrm{d}t} &= k_L a(\gamma_{C^*} - \gamma_{C_L}) - \\ &- (k_{14}\mu + k_{15} + k_{16}\eta)\gamma_X - \frac{F}{V}\gamma_{C_L}\end{aligned} \tag{4}$$

$$\frac{\mathrm{d}\gamma_L}{\mathrm{d}t} = \eta\gamma_X - \frac{F}{V}\gamma_L \tag{5}$$

$$\frac{\mathrm{d}V}{\mathrm{d}t} = F \tag{6}$$

where:

$$\mu = \frac{k_1\gamma_{Tr}\gamma_{C_L}}{(k_2 + \gamma_{Tr})(k_3 + \gamma_{S_0} - \gamma_S)(k_4 + \gamma_{C_l})},$$

and

$$\eta = \frac{k_8 \gamma_S \gamma_{C_L}}{(k_9 + \gamma_S)(k_{10} + \gamma_S)(k_{11} + \gamma_{C_L})(k_{12} + \gamma_{C_L})}$$

The model for specific biomass growth rate seems unbounded (becomes unbounded when the glucose concentration is close to $k_3 + \gamma_{S0}$). At the beginning of the batch process at an increased amount of sugar there is a phenomenon named "glucose effect" or "catabolite repression". This effect is connected to the quick glucose metabolic transformation, and the products from this cannot be used in the anabolic processes and the catabolites oppress the ferment cycle of the three-carbon acid (TCA) and functions as a feedback. A small amount of sugar enters as an inductor and stimulates the productivity of the ferments of TCA. This way, the relative rate of the product is increased.

The initial condition given at $t = 0$ is $\gamma_{X(0)} = 3.4$ g L^{-1}, $\gamma_{S(0)} = \gamma_{S_0} = 120.0$ g L^{-1}, $\gamma_{Tr(0)} = \gamma_{Tr_0} = 84.0$ g L^{-1}, $\gamma_{C_L(0)} = 6.9$ mg L^{-1}, and $\gamma_{L(0)} = 0.0$ g L^{-1}.

The initial liquid volume is $V(0) = V_0 = 10$ L, the initial feed flow rate is $F(0) = F_0 = \text{const} = 0.02$ L h^{-1}, and the initial final time is $t_f = 48$ h.

The coefficients of the model (1)–(6) are $k_1 = 20.8$, $k_2 = 42.0$, $k_3 = 28.00$, $k_4 = 1.1$, $k_5 = 1.01$, $k_6 = 0.07$, $k_7 = 0.51$, $k_8 = 62.0$, $k_9 = 28.0$, $k_{10} = 37.0$, $k_{11} = 4.0$, $k_{12} = 0.12$, $k_{13} = 6.1$, $k_{14} = 448.0$, $k_{15} = 22.0$, $k_{16} = 209.0$, and $k_La = 135.0$ h^{-1}.

System constraints

Almost 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.

$$0 \le F(t) \le F_{\max} \tag{7}$$

$$g_1 = V(t) - V_f \le 0 \tag{8}$$

The concentration of glucose, threonine and oxygen must be positive all the time; otherwise, an unrealistic solution in the optimization problem would be obtained. Thus we have:

$$\begin{aligned} g_2 &= -\gamma_{S(t)} \le 0 \\ g_3 &= -\gamma_{Tr(t)} \le 0 \\ g_4 &= -\gamma_{C_L(t)} \le 0 \end{aligned} \tag{9}$$

In addition, the stoichiometry of the *L-lysine* formation from glucose, threonine and oxygen for the cell must be obeyed in the fermentation process, therefore three constraints have been introduced for each specific yield factor to obtain a realistic solution in this optimization problem. According to the definition of the yield factor, these constraints are

$$g_5 = \frac{\gamma_{L(t)} V(t)}{\gamma_{S_{in}} [V(t) - V_0] + V_0(\gamma_{S_0} + k_5 \gamma_{X_0}) - V(t)[\gamma_{S(t)} + k_5 \gamma_{X(t)}]} - \frac{1}{k_7} \le 0, \quad t > 0 \tag{10}$$

$$g_6 = \frac{\gamma_{X(t)} V(t) - \gamma_{X_0} V_0}{V(t)[\gamma_{Tr_{in}} - \gamma_{Tr(t)}]} - \frac{1}{k_{13}} \le 0, \; t > 0 \tag{11}$$

$$g_7 = \frac{\gamma_{L(t)} V(t)}{k_L a(\gamma_{C^*} - \gamma_{C_L(t)}) + \gamma_{C_0} V_0 + k_{14} \gamma_{X_0} V_0 - \gamma_{C_L(t)} V(t) - \gamma_{S_{in}}(k_{14} + k_{15})} - \frac{1}{k_{16}} \le 0, \quad t > 0 \tag{12}$$

The concentration of glucose and threonine at the end of the fermentation processes have to be limited to avoid possible adverse effects on downstream product separation. Therefore, we have

$$\begin{aligned} g_8 &= \gamma_{S(t_f)} - \gamma_{S_{\min}} \le 0 \\ g_9 &= \gamma_{Tr(t_f)} - \gamma_{Tr_{\min}} \le 0 \end{aligned} \tag{13}$$

The lower bounded levels $\gamma_{S_{F\min}}$ and $\gamma_{Tr_{F\min}}$, will help reduce the separation cost in downstream processing.

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

Formulation of the decision-making problem

The objective of the problem is to find the optimal feed flow rate – $F(t)$, feed concentration of glucose ($\gamma_{S_{in}} = \gamma_{S_0}$), threonine ($\gamma_{Tr_{in}} = \gamma_{Tr_0}$), and fermentation time – t_f such that the *L-lysine* production is greater than or equal to the threshold value, and the consumption of glucose and threonine is less than or equal to the threshold values.

According to these statements, the production planning problem becomes a multiple objective decision-making problem. Two requirements must be fulfilled in such a decision-making problem. The first requirement is to find the optimal feed flow rate, feed concentration, fermentation time, and the associated objective function values. Such an optimal solution can be obtained by using multiple objective optimization techniques. However, the second requirement is to check whether or not the optimal solution will satisfy the pre-assigned threshold values. If the optimal solution does not satisfy the threshold values, the DM has to trade-off some threshold values. The effort should be repeated to find another optimal solution.[8]

According to the above-mentioned procedures, the first requirement is thus expressed as the following multiple objective optimal control and optimal parameter selection problem. This problem is simply called the multiple objective optimization problem (MOOP) and is expressed as

$$\max_{u} J_1 = \gamma_{L(t_f)} V(t_f) \tag{14}$$

$$\min_{u} J_2 = \gamma_{S_{in}} [V(t_f) - V_0] + \gamma_{S_0} V_0 \tag{15}$$

$$\min_{u} J_3 = \gamma_{Tr_{in}} [V(t_f) - V_0] + \gamma_{Tr_0} V_0 \tag{16}$$

$$\min_{u} J_4 = t_f \tag{17}$$

The first objective function corresponds to the total price of L-*lysine* production. The second and third objective functions are the cost of the substrates. The last objective function corresponds to the operating cost.

Multiple objective optimization is a natural extension of the traditional optimization of a single objective function. If the multiple objective functions are commensurate, minimizing one objective function will minimize all criteria and the problem can be solved using traditional optimization techniques. However, 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 gives rise to the distinction between multiple objective optimization and traditional single objective optimization. The problem is further complicated by the lack of a complete order for multiple objectives.[8]

In order to concisely define the Pareto optimal solution, we introduce the following definitions:[3,8]

Definition 1. The feasible region in input space, Ω is the set of all admissible control variables and the system parameters that satisfy the system constraints

$$\Omega = \{\mathbf{u} \equiv [F(t), \gamma_{S_{in}}, \gamma_{Tr_{in}}, t_f]^T \mid \dot{\mathbf{z}} = \mathbf{f}(\mathbf{z},\mathbf{u}), \mathbf{z}(0) = \mathbf{z}_0,$$

$$0 \le F(t) \le F_{\max}; \quad g_k(\mathbf{z},\mathbf{u}) \le 0, \quad k = 1,\dots,9$$

Here the state equation, $\dot{\mathbf{z}} = \mathbf{f}(\mathbf{z},\mathbf{u})$ consists of the fed-batch model (1)–(6).

We are now in a position to define Pareto optimal solutions in respect to the combined optimal control and optimal parameter selection problem.

Definition 2. A control action $\mathbf{u}^*$ is a Pareto optimal policy if and only if $\mathbf{u} \in \Omega$ such that it does not exist there:

$$J_i(\mathbf{u}) \le J_i(\mathbf{u}^*) \quad i = 1,\dots,4;$$

$$J_k(\mathbf{u}) < J_k(\mathbf{u}^*) \text{ for some } k$$

In general, there is an infinite number of Pareto policies for a given multiple objective optimization problem. The collection of Pareto policies is the Pareto set. The image of this set is called the trade-off surface.

After the optimal solution is obtained from a multiple objective optimization technique, the second requirement in this decision-making problem is then performed to check whether or not the optimal solution satisfies the assigned threshold values. If the optimal solution does not satisfy the threshold values, the DM has to assign another threshold requirement. The problem should then be repeated to find another optimal solution. Interactive programming can be employed to solve the decision-making problem. In this study, the interactive fuzzy optimization is extended to solve the multiple objective optimal control and optimal parameter selection problem.

Fuzzy-decision-making problems

So far, we have considered the DM problem under the crisp environment; that is, the optimal solution must absolutely satisfy the assigned threshold values. An assumption that the DM has fuzzy goals for each of the objective functions is shown in (14)–(17). The fuzzy goal means an interval of the assigned threshold instead of a point value in a crisp environment. As a result, the DM considers the fuzzy objective function J_1 should be substantially greater than or equal to a threshold interval $[J_1^L, J_1^U]$. The second, third, and fourth goals should be substantially less than or equal to the assigned threshold interval $[J_k^L, J_k^U]$, $k = 2, 3, 4$.

The multiple objective optimization problem (14)–(17) is now extended to the general multiple objective optimization problem (GMOOP) given as

$$\textit{fuzzy} \max_{u} J_1 = \gamma_{L(t_f)} V(t_f) \tag{18}$$

$$\textit{fuzzy} \min_{u} J_2 = \gamma_{S_{in}} [V(t_f) - V_0] + \gamma_{S_0} V_0 \tag{19}$$

$$\textit{fuzzy} \min_{u} J_3 = \gamma_{Tr_{in}} [V(t_f) - V_0] + \gamma_{Tr_0} V_0 \tag{20}$$

$$\textit{fuzzy} \min_{u} J_4 = t_f \tag{21}$$

The fuzzy requirement for each of all objective functions can be quantified by eliciting membership functions from the DM. Maximizing the fuzzy goal stated by the DM may achieve "*substantially greater than or equal to some intervals*", and the DM is asked to determine the subjective membership function which is a strictly monotonically decreasing function with respect to J_1. The membership function of (18) has the type:

$$\nu_1(J_1) = \begin{cases} 0; & J_1 \leq J_1^L \\ \dfrac{J_1 - J_1^L}{J_1^U - J_1^L}; & J_1^L \leq J_1 \leq J_1^U \\ 1; & J_1 \geq J_1^U \end{cases} \quad (22)$$

where J_1^L or J_1^U represent the value of J_1 such that the grade of the membership function $\nu(J_1)$ is 0 or 1.

The membership functions for minimizing goals of (19)–(21) are expressed as

$$\nu_k(J_k) = \begin{cases} 1; & J_k \leq J_k^L \quad k = 2,3,4 \\ \dfrac{J_k^U - J_k}{J_k^U - J_k^L}; & J_k^L \leq J_k \leq J_k^U \\ 0; & J_k \geq J_k^U \end{cases} \quad (23)$$

where J_k^L or J_k^U represent the value of J_k such that the grade of the membership function $\nu(J_k)$ is 1 or 0.

As a result, the DM considers that the fuzzy objective function J_1 should be substantially greater than or equal to the threshold interval $[J_1^L J_1^U]$. The second and third goals should be substantially less than or equal to the assigned threshold interval $[J_k^L J_k^U]$, $k = 2, 3, 4$. As a result, the fuzzy problems (18)–(21) appeared in (14)–(17).

The membership function for each of the objective functions is described in Fig. 1.

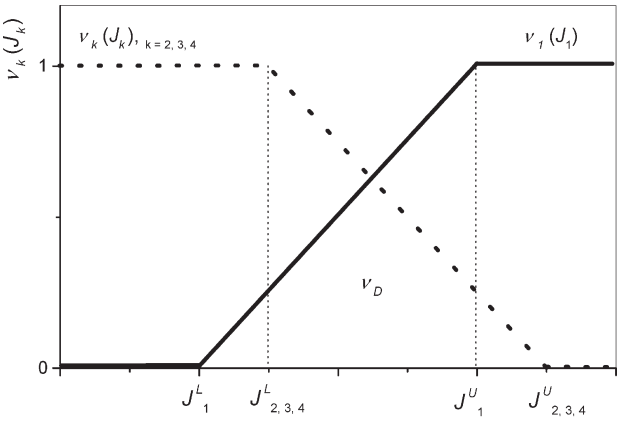

Fig. 1 – *Assigned membership function for each of the objective functions*

Having elicited the membership functions from the DM for each of the objective functions, the GMOOP (18)–(21) can be converted into the fuzzy multiple objective optimization problem (FMOOP) by an aggregation of the criteria[11]

$$\min_{\mathbf{u}\in\Omega} [\nu_1(J_1)\nu_2(J_2)\nu_3(J_3)\nu_4(J_4)]^T$$

By introducing a general aggregation function $\nu_D(J_k)$, a fuzzy multiple objective decision making problem (FMODMP) or maximizing decision problem can be defined by[11]

$$\nu_D = \max_{\mathbf{u}\in\Omega} \min_k \{\nu_k(J_k),\ k = 1,\ldots,4\} \quad (24)$$

Observe that the value of the aggregation function can be interpreted as representing an overall degree of satisfaction with the DM's multiple fuzzy goals. Let us consider the fuzzy maximizing problem. While the objective function value is greater than the assigned upper bound, such a solution absolutely satisfies the DM. On the other hand, the objective function value is less than the lower bound. It must be rejected. While the objective function value is located between the threshold interval, the DM has satisfied the solution to some degree.

Fundamental to the MOOP (14)–(17) is the Pareto optimal concept, and thus the DM must select a compromise solution among the many Pareto optimal solutions. The relationships between the optimal solutions of the (24) and the Pareto optimal concept of the MOOP can be characterized by the following theorem.[1,8]

Theorem 1. If $\mathbf{u}^*$ is a unique optimal solution to the FMODMP (24), then $\mathbf{u}^*$ is a Pareto optimal solution to the MOOP (14)–(17).

This theorem is used to guarantee that the unique optimal solution of the (24) is a Pareto solution to the crisp multiple objective optimal control problems (18)–(21). The statement of this theorem does not guarantee the unique optimal solution to (24).

Sakawa[5] has introduced the concept of fuzzy Pareto or M-Pareto optimal solutions for the general multiple objective nonlinear programming problems. Such a definition can be extended to the combined optimal control and optimal parameter selection problem in this study. This is defined in terms of membership functions instead of the objective functions.

Definition 3. If $\mathbf{u}^* \in \Omega$ is said to be an M-Pareto optimal solution to GMOOP if and only if another $\mathbf{u} \in \Omega$ does not exist there, such that $\nu_k[J_k(\mathbf{u})] \geq \nu_k[J_k(\mathbf{u}^*)]$ for all k and $\nu_j[J_j(\mathbf{u})] \neq \nu_j[J_j(\mathbf{u}^*)]$ for at least one j.

Note that the set of Pareto optimal solutions is a subset of the set of M-Pareto optimal solutions as observed from Definitions 2 and 3, and (22). Here M refers to membership. Using the concept of M-Pareto optimality, the fuzzy version of Theorem 1 can be obtained under slightly different conditions.

Theorem 2. If $\mathbf{u}^*$ is a unique optimal solution to the FMODMP (24), then $\mathbf{u}^*$ is an M-Pareto optimal solution to the GMOOP (18)–(21).

Theorem 2 is used to guarantee that the unique optimal solution of the maximizing decision problem (24) is an M-Pareto optimal solution of the fuzzy problems (18)–(21). The key point for using this theorem is to find a unique optimal solution of the problem (24). A global optimization method must be employed to determine such a unique solution.

Interactive programming techniques are tools for searching a satisfactory solution by interaction between the DM and the computer. It can be regarded as an interface between humans and computers. An interactive programming algorithm is introduced in this study to find a satisfactory solution to the GMOOP, as follows:

1. Assigning the threshold intervals $[J_k^L J_k^U]^r$.

2. Eliciting a membership function $v_k(J_k)$ from the DM for each of the objective functions.

3. Solving the maximizing decision problem (24). Let $[\mathbf{u}^r, v_k^r(J_k)]$ be the M-Pareto optimal solution to the GMOOP.

4. If the DM is satisfied with the current levels of $v_k^r(J_k)$, $k = 1,\ldots,4$, the current M-Pareto optimal solution $[\mathbf{u}^r, v_k^r(J_k)]$ is the satisfactory solution for the DM. Otherwise, to classify the objectives into three groups based on the DM's preference, including

(a) a class of the objectives that the DM wants to improve,

(b) a class of the objectives that the DM may possibly agree to relax, and

(c) a class of the objectives that the DM accepts.

The index set of each class is represented by $\mathbf{I}^r$, $\mathbf{R}^r$, and $\mathbf{A}^r$, respectively. The new threshold intervals $[J_k^L J_k^U]^{r+1}$ are reassigned in such a way that $[J_k^L J_k^U]^r \subset J_k^L J_k^{U\,r+1}$ for any $k \in \mathbf{I}^r$, $[J_k^L J_k^U]^{r+1} \subset [J_k^L J_k^U]^r$ for any $k \in \mathbf{R}^r$, and $[J_k^L J_k^U]^{r+1} = [J_k^L J_k^U]^r$ for any $k \in \mathbf{A}^r$. Then repeat Step 2.

Here, it should be stressed that any improvement for one of the objective functions can be achieved only at the expense of at least one of the other objective functions.

Results and discussion

Since the feed flow rate $F(t)$ is a time dependent variable, the optimal control problem can be considered 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.

Since the physical constraints in (10) – (12) are included in the optimization problem, the penalty function method is used to handle the system constraints in fuzzy optimization. Therefore, the function used in fuzzy optimization is defined as

$$Q \cong \underset{\mathbf{u},t}{\tilde{\max}}\, J = \nu_D - \sum_{i=1}^{7} \chi_i \int_0^{t_f} g_i(\mathbf{u})_+^2 \mathrm{d}t - \\ - \chi_8 g_8(\mathbf{u})_+^2 - \chi_9 g_9(\mathbf{u})_+^2 \tag{25}$$

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

The integration of the square penalty functions in (25) is used to cover the state variables on the whole time domain.

In this paper, the concept of Pareto optimality is employed to characterize a solution to multi-objective optimization problems.

In order to obtain a global optimal solution, a fuzzy sets theory method is introduced to solve the maximizing decision problem. A simple guideline is presented in the interactive programming procedures in order to find a satisfactory solution to the general multiple objective optimization problem.

Fuzzy sets theory allows the possibility to develop a "*flexible*" model that reflects in more details all possible values of the criterion and control variables under the model developed. The model of the fed-batch process (1)–(6) is considered the most appropriate but deviations are admissible with a small degree of acceptance. It is represented by a fuzzy set of the following type γ_X, γ_S, γ_{Tr}, γ_{C_L}, and γ_L has come into view approximately by the following relations:[11–13]

$$\beta_i(t,\mathbf{u}) = \frac{1}{1+\varepsilon_i^2}, \quad i = 1,\ldots,5 \tag{26}$$

where:

$$\varepsilon_1 = \bar{\varepsilon}_1 - \left(\mu - \frac{F}{V}\right)\gamma_X,$$

$$\varepsilon_2 = \bar{\varepsilon}_2 - \left(\frac{F}{V}(\gamma_{S_{in}} - \gamma_S) - (k_5\mu + k_6 + k_7\eta)\gamma_X\right),$$

$$\varepsilon_3 = \bar{\varepsilon}_3 - \left(\frac{F}{V}(\gamma_{Tr_{in}} - \gamma_{Tr}) - k_{13}\mu\gamma_X\right),$$

$$\varepsilon_4=\bar{\varepsilon}_4-\left(k_L a(\gamma_{C^*}-\gamma_{C_L})-(k_{14}\mu+k_{15}+k_{16}\eta)\gamma_X-\frac{F}{V}\gamma_{C_L}\right),$$
$$\varepsilon_5=\bar{\varepsilon}_5-\left(\eta\gamma_X-\frac{F}{V}\gamma_L\right)$$

The membership function $\beta_0 \equiv \nu_D$ has the form (22). The membership function of the model (26) is shown in Fig. 2.

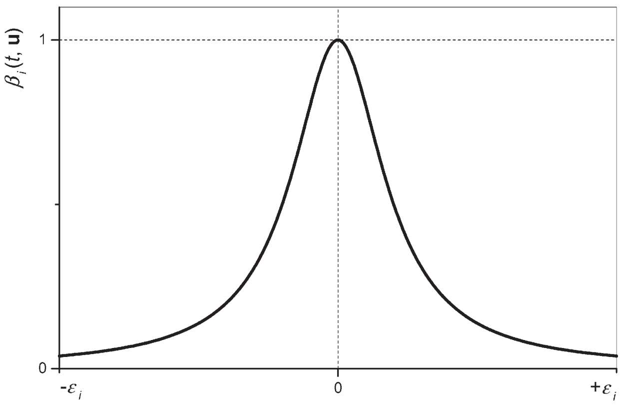

Fig. 2 – *Membership function for the model*

The prepositional "*flexible*" model of the process reflects better influence of all good values of the kinetics variables. The "*flexible*" model reflects in more details over all possible values of the criterion and control variables under the model developed. After examination, the model is considered the most acceptable.

The fuzzy set of the solution is presented with a membership function of the criteria β_0 and model β_i[13,14]

$$\beta_D(t,\mathbf{u})=(1-\xi)\prod_{i=0}^{5}\beta_i^{\theta_i}(t,\mathbf{u})+ + \xi\left\{1-\prod_{i=0}^{5}[1-\beta_i(t,\mathbf{u})]^{\theta_i}\right\} \quad (27)$$

The solution was obtained by using the common *defuzzification* method BADD:[14]

$$\mathbf{u}^0=\sum_{i=1}^{q}\frac{\beta_{D_i}^{\theta_i}(t,\mathbf{u})\,\mathbf{u}_i}{\sum_{j=1}^{p}\beta_{D_j}^{\theta_i}(t,\mathbf{u})}, \quad (28)$$
$$i=1,\dots,q; \qquad j=1,\dots,p; \qquad p=q^m$$

This method allows direct (non-iterative) determination of the optimization problem.

All programs were written using a FORTRAN 77 programming language version 5.0. All computations were performed on AMD Athlon II X2 245, 2.9 GHz computer using Windows XP operating system.

The control variables are satisfied in the following intervals: $[0.00 \le F(j) \le 0.05]$ L h^{-1}, $[90 \le \gamma_{S_{in}} \le 140]$ g L^{-1}, $[70 \le \gamma_{Tr_{in}} \le 120]$ g L^{-1}, and $[40 \le t_f \le 60]$ h. The time is discretized in 6 min (but it is fuzzy).

The values elected for the parameters that characterize the compensation degree ξ, and weights of $\beta(t, \mathbf{u})$ are $\xi = 0.95$, $\theta_0 = 1$, and θ_i (i=1, …, 5) = 0.9, respectively.

The lower bounded levels for the glucose, and threonine concentration are $\gamma_{S_{min}} = \gamma_{Tr_{min}} = 0.5$ g L^{-1}.

The lower and upper values of the objective functions are:

J_k^L = [350 g, 800 g, 800 g, 40 h] and
J_k^U = [600 g, 1500 g, 1300 g, 60 h].

By choosing 10 time partitions for the final time – t_f, and 12 time partition for the feed flow rate – $F(j)$, feed concentration of glucose – $\gamma_{S_{in}}$, and threonine – $\gamma_{Tr_{in}}$, have to be determined in the finite-dimensional optimization problem.[15]

The maximizing decision ν_D at these threshold requirements was $\nu_D = 0.6842$ after 17280 iterations. The *L-lysine* product of 521.04 g is higher than the lower bound of the threshold requirement assigned, so that its corresponding membership function value was $\nu_1^*(J_1) = 0.684$. The minimum supplied amounts of glucose and threonine were 1000.00 g and 933.33 g, respectively. The fermentation time was 44.44 h. These four minimum values were within the desired requirements. The optimal feed concentrations for glucose and threonine were 100.0 g L^{-1} and 93.33 g L^{-1}, respectively.

The DM is satisfied with the current levels of $\nu_k^r(J_k)$, $k = 1,\dots,4$, the current M-Pareto optimal solution $[\mathbf{u}^r, \nu_k^r(J_k)]$ is the satisfactory solution for the DM. Otherwise, it is necessary to change the intervals J_k^L or J_k^U, $k = 1,\dots,4$ and to determine the task (24) again.

After solving the maximizing problem (25) with fuzzy sets (26)–(28), the maximizing decision ν_D was $\nu_D = 0.7785$. The *L-lysine* product of 563.66 was such that its corresponding membership function value was $\nu_1^*(J_1) = 0.8555$. The minimum supplied amounts of glucose and threonine were 1039.11 g and 1127.46 g, respectively. The optimal feed concentrations for glucose and threonine were 97.39 g L^{-1}, and 105.67 g L^{-1}, respectively. The value of ν_D means that 77.85 % of satisfaction was achieved by each of the assigned requirements. The maximum *L-lysine* concentration of 52.84 g L^{-1} was obtained.

The optimal feed flow rate is shown in Fig. 3.

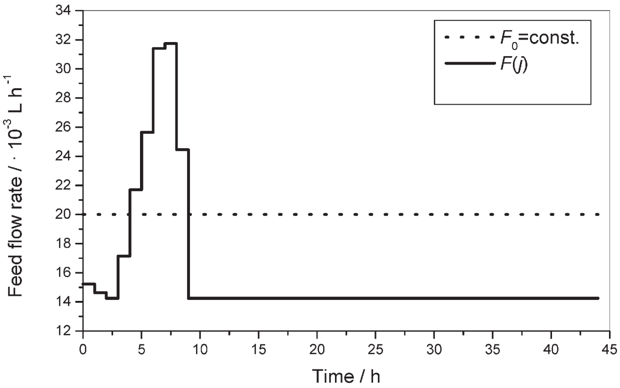

Fig. 3 – *Optimal feed flow rate*

The cell concentration profiles of *Brevibacterium flavum* 22LD before and after optimization are shown in Fig. 4.

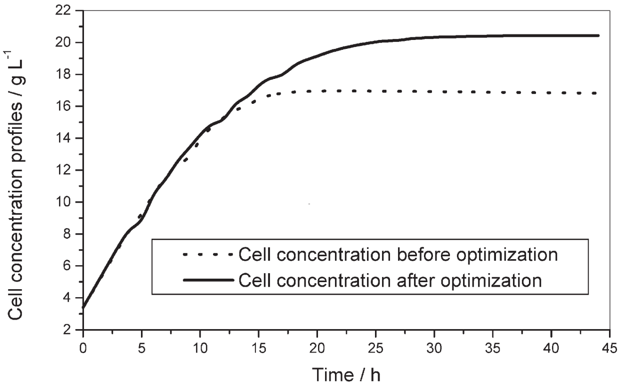

Fig. 4 – *Concentration profiles of biomass before and after optimization*

Fig. 4 notices an augmentation of the cell concentration quantity with more than 20 % at the end of the process in comparison to that without optimization and $F_0 = 20.0 \cdot 10^{-3}$ L h^{-1}.

The concentration profiles for glucose and threonine, before and after optimization, are represented in Fig. 5.

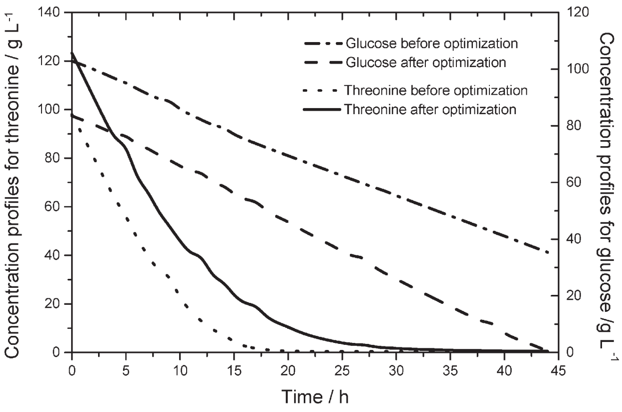

Fig. 5 – *Concentration profiles of glucose and threonine before and after optimization*

The concentration of glucose and threonine at the end of the fermentation processes have to be limited to avoid possible adverse effects on downstream product separation.

The *L-lysine* production from glucose and threonine before and after optimization is also illustrated in Fig. 6.

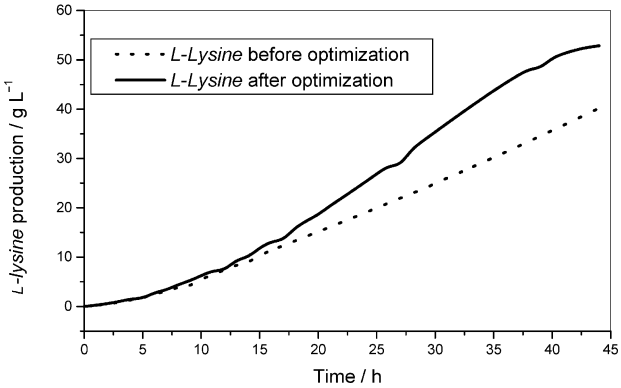

Fig. 6 – *Concentration profiles of L-lysine before and after optimization*

Fig. 6 notices an augmentation of the *L-lysine* quantity with more than 30 % at the end of the process in comparison to that without optimization.

Conclusions

1. The *L-lysine* production planning problem using a *Brevibacterium flavum* 22LD has been discussed in this study. Such a production planning problem has been formulated into a framework of the general multiple objective optimization problem. The fuzzy multiple objective optimal control problems have been converted into a maximizing decision problem through the subjective membership functions for each of the objective functions. The optimal solution for each of the membership functions is denoted as the degree of satisfaction with threshold requirements assigned. In order to obtain a global optimal solution, a method of the theory of fuzzy sets has been introduced to solve the maximizing decision problem.

2. The applied multiple objective process optimizations have shown a vast increase in their productiveness, respectively decrease in the residual glucose and threonine concentrations. These results led to a higher economic effectiveness for each of them at smaller outlay.

3. The results obtained from the study have shown that the multiple objective optimization is a more complex approach minimizing the risk in the procedure of decision-making and maximizing the objective formulated.

Nomenclature

$F(0) = F_0$ – initial feed flow rate, L h^{-1}
$F(t)$ – feed flow rate, L h^{-1}
F_{max} – maximum feed flow rate, L h^{-1}
g_i – penalty functions
J_k^L – low values of the objective function
J_k^U – upper values of the objective function
J_k – objective functions, g
k_i – coefficients in the model, (i = 1, 16)
k_La – mass transfer coefficient, h^{-1}
m – number of the control variables, m = 4
q – number of discrete values of the vector **u**
t – process time, h
t_f – final time of the process, h
u – vector of control variables, $\mathbf{u} = [\gamma_{S_{in}}, \gamma_{Tr_{in}}, F, t_f]^T$
$\mathbf{u}^0$ – optimal values of control variables
V – liquid volume, L
$V(0) = V_0$ – initial liquid volume, L
V_f – maximal liquid volume, L

Greek letters

$\beta_i(t, \mathbf{u})$ – membership function for the model, –
γ_X – biomass mass concentration, g L^{-1}
$\gamma_{X(0)}$ – biomass initial mass concentration, g L^{-1}
γ_S – glucose mass concentration, g L^{-1}
$\gamma_{S(0)} = \gamma_{S_0}$ – glucose initial mass concentration, g L^{-1}
$\gamma_{S_{in}}$ – glucose feed mass concentration, g L^{-1}
$\gamma_{S_{min}}$ – lower bounded levels for glucose mass concentration, g L^{-1}
γ_{Tr} – threonine mass concentration, g L^{-1}
$\gamma_{Tr_{min}}$ – lower bounded levels for threonine mass concentration, g L^{-1}
$\gamma_{Tr_{in}}$ – threonine feed mass concentration, g L^{-1}
$\gamma_{Tr(0)} = \gamma_{Tr_0}$ – threonine initial mass concentration, g L^{-1}
γ_{C_L} – dissolved oxygen mass concentration in liquid phase, mg L^{-1}
$\gamma_{C_L(0)}$ – dissolved oxygen initial mass concentration, mg L^{-1}
γ_{C^*} – dissolved oxygen mean mass concentration, mg L^{-1}
γ_L – L-*lysine* mass concentration, g L^{-1}
ξ – parameter characterized the compensation degree
η – specific consumption rate of cell culture from glucose and oxygen, h^{-1}
μ – specific growth rate of cell culture from glucose, threonine and oxygen, h^{-1}
ν_D – general aggregation function, –
ε_i – deviations of the basic model, i = 1,…,5
$\bar{\varepsilon}_i$ – given deviations of the basic model, i = 1,…,5
θ_i – parameter, those give weight of β(t, **u**)
χ_i – weights coefficients
$\nu_k(J_k)$ – membership function for objective functions, –

Abbreviations

DM – Decision making
FMODMP – Fuzzy multiple objective decision-making problem
FMOOP – Fuzzy multiple objective optimization problem
GMOOP – General multiple objective optimization problem
MOOP – Multiple objective optimization problem

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