Fuzzy Techniques vs. Multicriteria Optimization Method in Bioprocess Control

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The aim of this paper is to elaborate an in-silico test of advanced intelligent control and optimization algorithms based on the concepts of multicriteria decision for productive bioprocesses in the medical biotechnologies domain. In the framework of this study it has been designed an intelligent control system based on fuzzy logic. The design of the fuzzy control system arises from the human expert knowledge organization necessity. In terms of multicriteria optimization strategy this paper presents a study in order to determine the optimal operating region for the production of an immunomodulator. The objective criteria include the production maximization in relation with the total bioprocess length and the oxygen transfer. The simulation results indicate that the fuzzy control system is able to evaluate the substrate amount necessary for cell growth according to biomass evolution. Moreover, the software application used for multicriteria optimization was able to determine an optimal domain for operating region. Hence, the final results show that the management of bioprocess final duration and oxygen transfer increases the cellular growth rate and (global) productivity.

Keywords: intelligent control, fuzzy model, decision-making, bioprocess optimization

The aim of this paper is to elaborate an *in-silico* test of advanced intelligent control and optimization algorithms based on the concepts of multicriteria decision for productive bioprocesses in the medical biotechnologies domain. In the framework of this study, it has been designed an intelligent control system, based on fuzzy logic.

The bioprocess control has numerous objectives function of bioprocess characteristics.

Due to the complexity of the bioprocess systems, basic models are not able to reflect the real situations.

Bioprocess reproducibility from run to run is to be carefully studied. In industry, bioprocesses are subject to a number of local control structures.

The design of the fuzzy control system arises from the human expert knowledge organization necessity [1, 2]. In terms of multicriteria optimization strategy, this paper presents a study in order to determine the optimal operating region for the production of an immunomodulator. The objective criteria include the production maximization in relation with the total bioprocess length and the oxygen transfer [3].

The information obtained from this study can be used by experts to understand better the relationship between the process inputs, the objective criteria and the zone of possible solutions than that of traditional optimization algoritms.

Experimental part

The aerobic bioprocess optimization with *Pseudomonas aeruginosa sp.* is to be performed in case of a bacterial immunomodulator preparation. As the formation of the immunomodulator product is (generally) growth-associated, the main research objective was to get high cellular concentration. Hence, the experiments were done in a bottom driven and aerated 100 L Bioengineering® bioreactor with 42 L aqueous Organotech® peptone solution as main culture substrate. The reactor was equipped with pH, temperature, dissolved oxygen, air flow, foam, and agitation controllers. The controlled parameters of the bioprocess are the following: temperature: 37 °C; impeller speed: 250-300 rpm; air flow rate: 15-40 L/min; *p*H: 7.3. The cellular growth is determined by a standard dry-weight method (usual procedure at drying at 105 °C) and by off-line determining of the optical density (OD) at λ = 570 nm. The substrate consumption was determined by analyzing the aminic nitrogen (Sörensen method) [4].

Bioprocess control using Artificial Intelligence (AI)

The limitations of the bioprocess control systems do not concern only the measurements or models, but in the mean time they are due to the fact that much valuable human knowledge is only available in a qualitative and heuristic form. Hence, it has been found that the knowledge based control structures using the human decisional factor (i.e. a subjective element) offer sometimes better results rather than the optimal control algorithms based on specific models. Intelligent techniques (i.e. neural nets, fuzzy structures, genetic algorithms or expert systems) are able to simulate human expert reasoning and decision making, dealing with uncertainties and imprecise information [5].

For this study it has been designed an intelligent control system, based on fuzzy logic. The design of a fuzzy control system arises from organization necessity of the human expert knowledge. The decisional matrix of the control system is determined by the transition from the objective level of information to the subjective one. Thus, the interest is focused on human expert experience (outlined through fuzzy rules) rather than information algorithmic process [6, 7].

The basic idea of a fuzzy inference system is to integrate the human's knowledge into a set of fuzzy IF-THEN rules, which involve operations of four components: as shown in figure 1.

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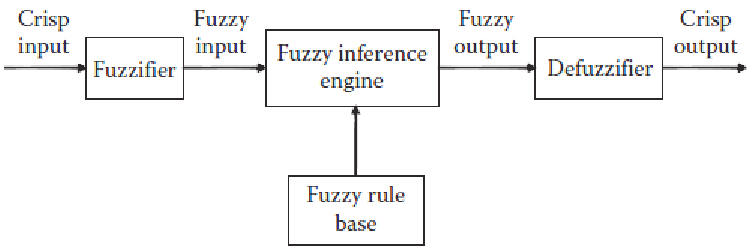

Fig. 1. General structure of a fuzzy inference system

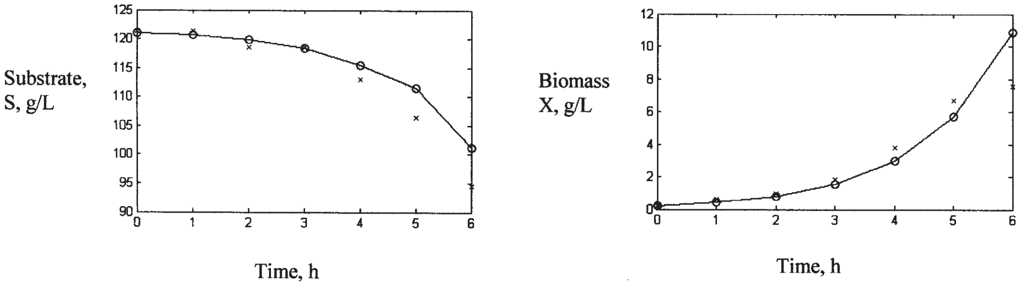

Fig. 2. Simulation results of the substrate and biomass ("x" – experimental data, "o" – simulation), Monod model

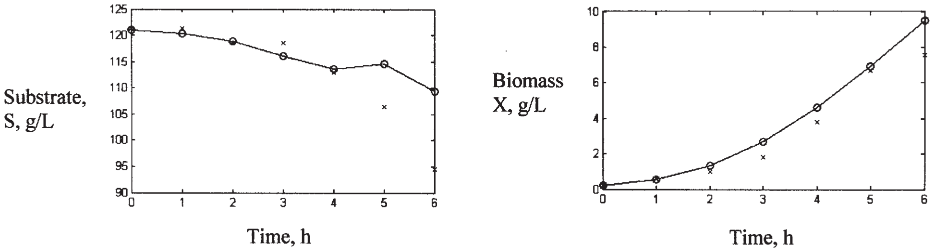

Fig. 3. Simulation results of the substrate and biomas ("x" – experimental data, "o" – simulation), Contois model

BIOSIM is an original developed software package which implements a developed control structure and has a fuzzy controller at its core. The objective is to prove that superior results can be obtained from closed-loop fuzzy control vs. the open-loop (classic) control [8]. The software uses in the background Matlab (version R2010a).

Multicriterial decision-making – a general approach

Usually, a decision is the result of conscious choice by an individual or group of individuals (decision maker), of an alternative (options) to solve, a situation or problem from those that are identified.

In common technical cases, the decision is made based on a single criterion of choice. Setting and using of at least two criteria simultaneously is a complex case in which the decision maker usually encounter difficulties in establishing the optimum alternative (solution) that best meet criteria involved in the decision system [9].

Multicriteria decision (MD) helps in this context, because is conditioned only by the existence of a mathematical model on which any alternative can be simulated. MD is a problem where several objective functions must be optimized simultaneously. Usually, the optimal criteria are (quasi-) opposing and make difficult to establish a significant problem-solving techniques of this kind. A simple approach allows converting criteria into one objective function, reducing the problem to a classical optimization problem with a single objective. Each criterion will make contribution in this function by a well-defined influence. The choice of weights that define a single objective function often knows a subjective solution that would affect the final result [10, 11]. For multicriterial analyses we used a software application named D-Sight.

D-Sight is a dedicated software solution to support decision-making processes. It provides a framework allowing decision makers to evaluate different alternatives against several criteria and identify the best solution. The used methodology provides the decision maker with additional information about how the different alternatives can be compared together and how the different criteria are discriminating the alternatives. The graphical representation of the result is called the GAIA plane (Global Visual Analysis).

In the framework of these experiments, the production of immunomodulator product is associated with cell growth rate. Therefore the objective for this research was to simulate the bioprocess evolution and to obtain large biomass quantities.

For the experiment discussed in this paper cell growth was followed over 6 hours of development and air flow rate was 40 L/min.

BIOSIM – software application

Biosim, the software application used for this part of the paper implements a control structure based on fuzzy logic. Tanase et al. presented the detailed description of the application therefore it will not be repeated here [8].

The formation of immunomodulator product is associated with cell growth rate. The substrate (S) and biomass (X) concentrations are considered the inputs of the proposed fuzzy control system - BIOSIM. The output of the fuzzy system is the correction [+/-] to be applied on the substrate flow. In a fuzzy rule-based system, using the IF-THEN-ELSE rules, the output values will be computed. Basically, fuzzy control rules provide a convenient way for expressing control policy and domain knowledge, based on an uncertain human reasoning. Hence, in the established model, different membership functions were designed for the symbolic description of inputs and output.

According to figure 2, the substrate consumption decreases towards the end of the bioprocess period, but a larger amount of biomass can be obtained in the last hour of the bioprocess.

In figure 3 it can be seen that even in the early hours of bioprocess the simulation results are similar to the experimental data, in the last hours substrate consumption is lower. The amount of biomass is increasing slowly.

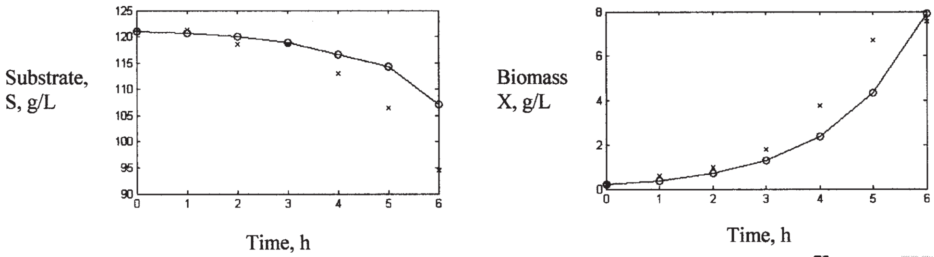

Fig. 4. Simulation results of the substrate and biomas (“x” – experimental data, “o” – simulation), Tessier model

Finally, as shown in figure 4, substrate consumption decreases towards the end of the bioprocess period, as in previous cases. Simulation results for the cellular concentration follow closely the experimental data in the first hours, but the amount of biomass decreases toward the end of the bioprocess.

Hence, for control loop simulation, several kinetic models were tested in order to obtain the most performing values and the simulation results were compared with the experimental data. The selection of kinetic model was done by applying different analysis criteria such as: the model-data error (i.e. the model adequacy test), and the convergence of the estimation rule.

The simulation results show that the fuzzy control system is able to calculate the amount of substrate necessary for cell growth in line with increasing the biomass amount. As can be seen, data obtained by simulation for biomass increasing follow closely the experimental data.

Finally, it can be proved that the fuzzy logic introduces the qualitative experience of human expert and provides an alternative solution to non-linear control as it is closer to the real world. Non-linearity is handled by rules, membership functions, and the inference process which results in improved performance, simpler implementation, and reduced design costs.

D-Sight – software application

In previous studies it was found that the bacterium *Pseudomonas aeruginosa* needs a large amount of oxygen in the early cellular growth period, but excess air is still necessary to delay the entrance into the microaerophilic growth, the microaerobic trend being characteristic for this bacterium [13].

Based on this studies we have identified optimal operating regions and we have established the objectives for multicriteria optimization.

Hence, the aim of the research study was to maximize the production in relation with the bioprocess final duration of, the final biomass concentration and to maximize the oxygen transfer. Figure 5 represents the inputs and outputs of the optimization strategy used in this investigation in order to determine the optimum process inputs for them.

As it can be seen in figure 5, the initial inputs are: the duration of the fermentation process ($3.5 \leq t_f \leq 6$ h), the initial biomass concentration ($1.7 \leq X \leq 3$ g/L), the

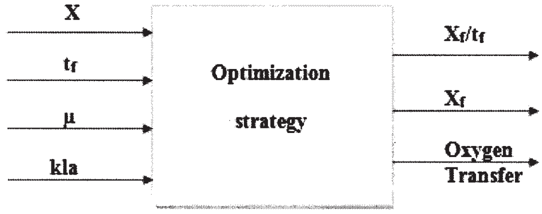

Fig. 5. Optimization strategy

specific growth rate ($0.4 \leq \mu \leq 0.65$ h^{-1}), oxygen mass transfer coefficient ($0.018 \leq l_a \leq 0{,}032$ s^{-1}).

The first step for the optimization procedure is to define the problem alternatives further, to define the evaluation criteria as shown in table 1.

For this study there were considered three cases, according to weights changes for each criteria. The weight represents the criteria importance. The global sum must be 100%. Table 2 shows the criteria weights for the selected three cases.

For the 1st case, the weights for biomass and specific growth rate are equal, while to oxygen mass transfer coefficient was given the smaller importance.

In figure 6, the criteria “X”, “t_f” and ”μ” are close to each other, while criterion “kl_a” can be consider ed in opposition with the other three. The red stick indicates the current best direction for the compromise solution. In this case “Production” is the current best alternatives.

Because bacterium used for this bioprocess needs a large amount of oxygen throughout the entire period of the bioprocess, we studied the sensitivity of the decision axis when criteria kl_a has a bigger importance.

Thus, in the 2nd case the same weight for criteria “X” (35%) and “t_f” (20%), were maintained but the weight of specific growth rate decreases (from 35% to 20%) and “kl_a” increase (from 10 to 25%).

The red stick is smaller in this case than in the previous one, as shown in figure 7. Taking into account that the bar stick is closely linked to changes made in values of weights, it can be concluded that the weights established in the first case are better than here.

The ranking of alternatives are similar in both cases, “Production” has been the best response to the preferences of the decision-maker due to the fact that its value is closest to 1.

For the last case, compared to 1st scenario, the weight for criteria “μ” (35%) and “t_f” (20%) are preserved. In order

Table 1
DEFINE ALTERNATIVES AND CRITERIA

ALTERNATIVES	CRITERIA			
	X (g/L)	t_f (h)	μ (h^{-1})	kl_a (s^{-1})
Production (g/L)	3.000	6.00	0.65	0.032
Final biomass (g/L)	2.250	4.50	0.50	0.024
Oxygen transfer (s^{-1})	1.700	3.50	0.40	0.018

Table 2
CRITERIA HIERARCHY

Weight	CRITERIA			
	X (g/L)	t_f (h)	μ (h^{-1})	kl_a (s^{-1})
1st Case	35 %	20 %	35 %	10 %
2nd Case	35 %	20 %	20 %	25 %
3rd Case	20 %	20 %	35 %	25 %

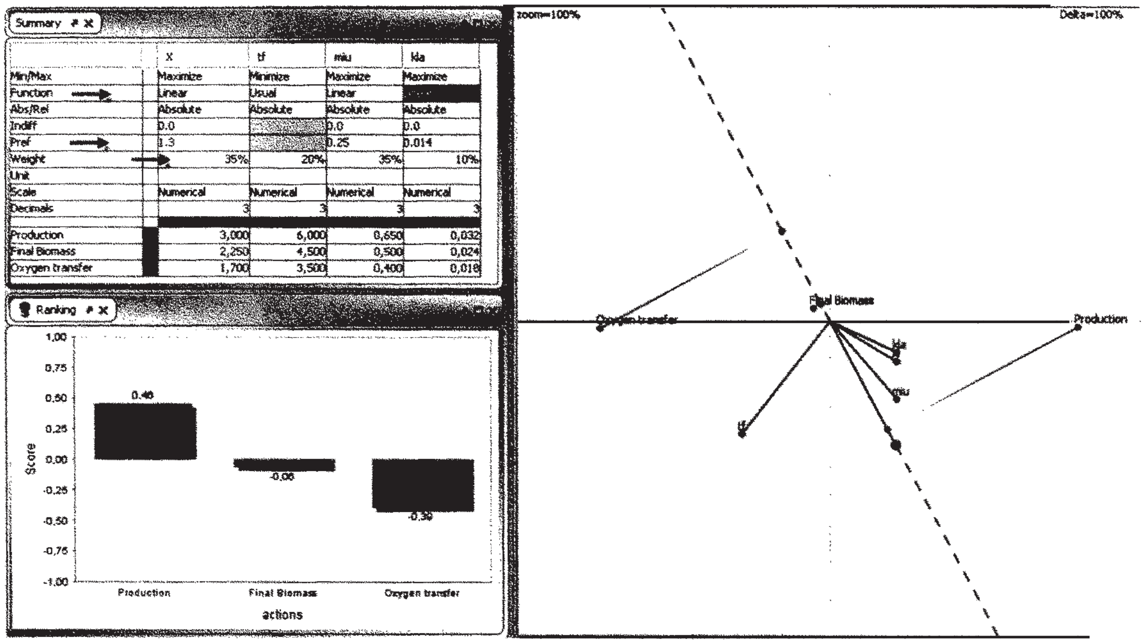

Fig. 6. Alternatives ranking and their projections in GAIA plan, 1st Case

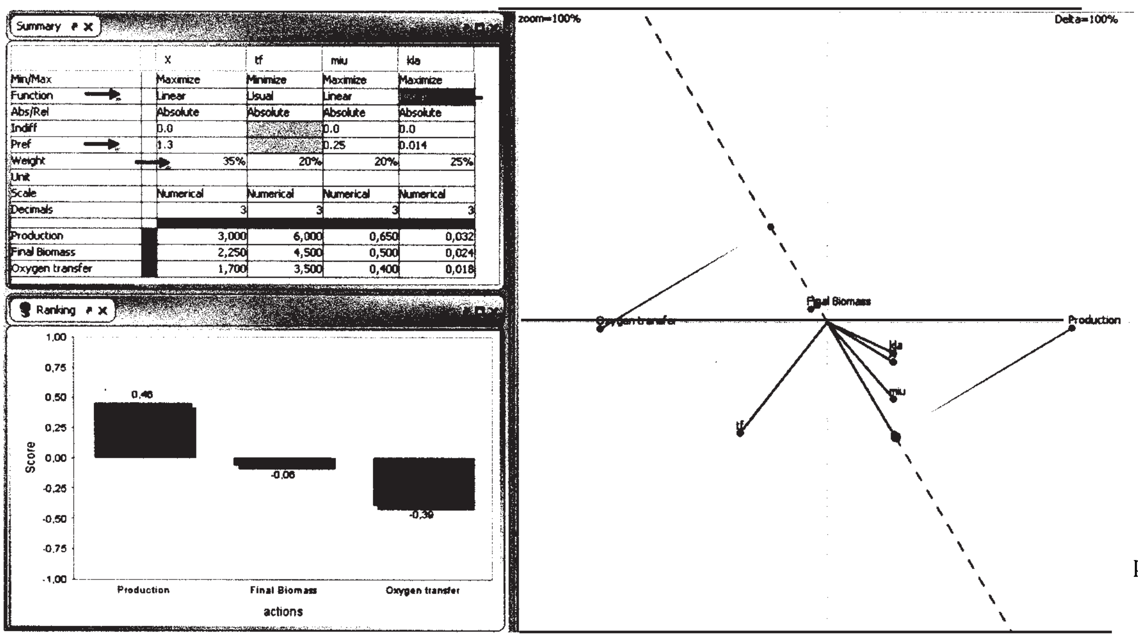

Fig. 7. Alternatives ranking and their projections in GAIA plan, 2nd Case

to increase the importance of criterion "kl_a" to 25%, the weight of "X" was decreased from 35 to 20%.

The three alternatives set when the optimization strategy was defined had kept the same score in relation with rankings. The alternative "Production" has the score closest to value 1.

As in previous cases, the criteria "X", "μ" and "kl_a" are similar to each other. This means that an alternative that will be "good" for "kl_a" criterion will be "good" for "X" and "μ" also, considering the preferences of the decision maker.

Hence, whether the optimization strategy is defined at the optimization process start and looking to all cases, in terms of alternatives and criteria projections in GAIA plan and position of the decision stick, it can be concluded that the best compromise is the case 3.

Conclusions

The first part of this study has demonstrated that intelligent control, describing the complexity of the

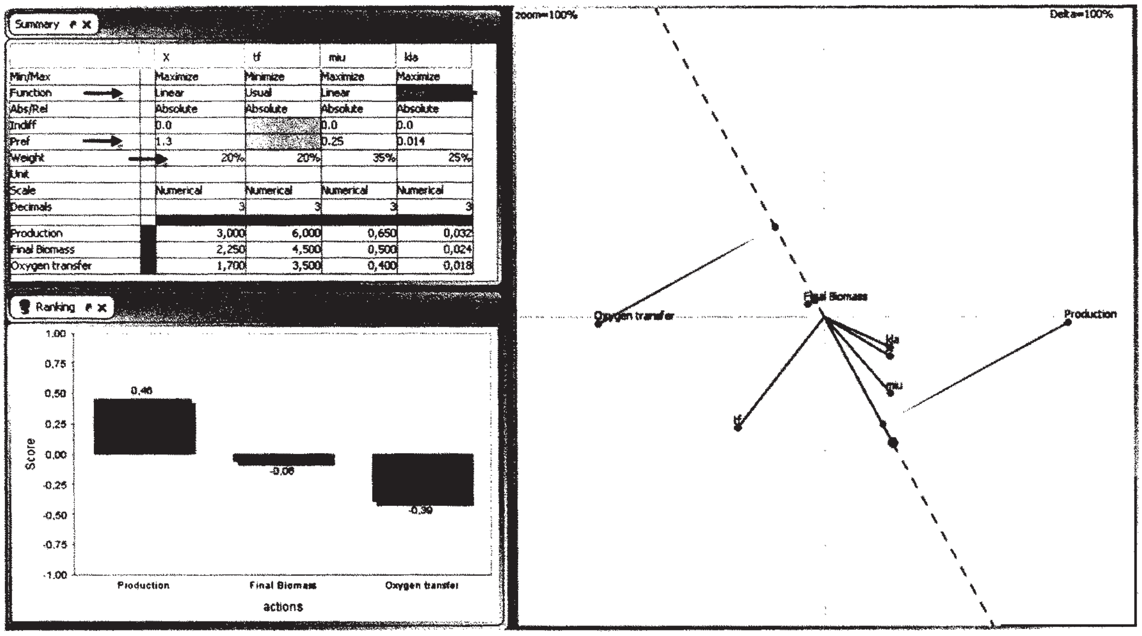

Fig. 8. Alternatives ranking and their projections in GAIA plan, 3rd Case

biological process in a qualitative and subjective manner as perceived by human operator, is an efficient control strategy for this kind of bioprocesses. The simulation results show that fuzzy control system is able to calculate the amount of substrate necessary for cell growth in line with increasing the biomass amount.

The success of such a control implementation is critically dependent upon the technical bioprocess operating conditions.

The second part of this paper was focused on a possible optimization strategy based on multicriteria method. Three cases were presented to determine the optimum operating region. The results show that controlling the final duration of the bioprocess and the oxygen transfer increases the cellular growth rate and productivity.

Although the multicriteria optimization technique used is suboptimal, it was capable to identify an acceptable domain for operating conditions.

Further, the information obtained from this study can be used by experts to understand better the relationship between the process inputs, the objective criteria and the zone of possible solutions than that of traditional optimization algoritms.

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Manuscript received: 9.07.2013