An Application of Different Mixing Systems for Batch Cultivation of *Saccharomyces cerevisiae*. Part II: Multiple Objective Optimization and Model Predictive Control

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Abstract: *Multiple objective optimization of the initial conditions, maximal rotation speed and amplitude for a batch Saccharomyces cerevisiae cultivation using impulse and vibromixing systems is developed in this paper. The single objective function corresponds to the process productiveness and the residual glucose concentration. The multiple objective optimization problems are transformed to a single objective function with weight coefficients. A combined algorithm is applied for solving the single optimization. After this optimization the useful process productiveness increases and the residual glucose concentration at the end of the process decreases. The developed optimization and obtained results have shown that the impulse mixing systems have a better productiveness and better glucose assimilation. In addition, this system is easier for realization. The combined algorithm does not have a feedback and it does not guarantee robustness to process disturbances. For that purpose model predictive control for guarantee robustness to process disturbances is developed. The developed control algorithm – combined multiple objective optimization problem and model predictive control ensures maximal production at the end of the process and guarantees a feedback on disturbance as well as robustness to process disturbances.*

Keywords: *Multiple objective optimization, Combined algorithm, Random search with back steps, Fuzzy sets theory, Model predictive control.*

Introduction

Multiple objective optimization is a natural extension of the traditional optimization of a single objective function. On one hand, if the multiple objective functions are commensurate, minimizing 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 the multiple objective optimization and traditional single objective optimization [10].

Zhou *et al.* [16] have used of a Pareto optimization technique 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 windows of operation to provide a smaller search area for the optimization.

Vera *et al.* [13] have illustrated a general multi objective optimization framework of biochemical systems and they 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 multi-objective optimization. We have compared the advantages and drawbacks of each of the GMIOM modes. The results obtained have shown that the optimization of biochemical systems was possible even if the underlying process model was not formulated in 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 improvement of biotechnological processes.

Tonnon *et al.* [12] have used interactive procedure to solve multi 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 fuzzy logic. An uncertainty, which has been affecting the parameters, is modelled by means of fuzzy relations or fuzzy numbers, whose probabilistic meaning is clarified by random set and 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 in the context of convex modelling are also pressured.

In the papers [3, 15] a fuzzy procedure 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* and the fuzzy optimization of a two-stage fermentation process with cell recycling including an extractor for lactic acid production. 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 hybrid search method of differential evolution is introduced.

Model predictive control (MPC) is a general methodology for solving control problems in the time domain [6]. More than 25 years after MPC appeared a theoretical basis for this technique has started to emerge in the industry as an effective means to deal with variable constrained control problems. In fact, that method for optimal control gives the necessary optimal profile, but it does not give the robustness of the optimization systems. Therefore the MPC can be used for ensuring maximal quality concentration at the end of the process and it guarantees a feedback on disturbance and thus – the robustness to process disturbances [7].

In the second part of the work multiple objective optimization problem (MOOP) of a batch cultivation process using the strain *Saccharomyces cerevisiae* has been developed. The single

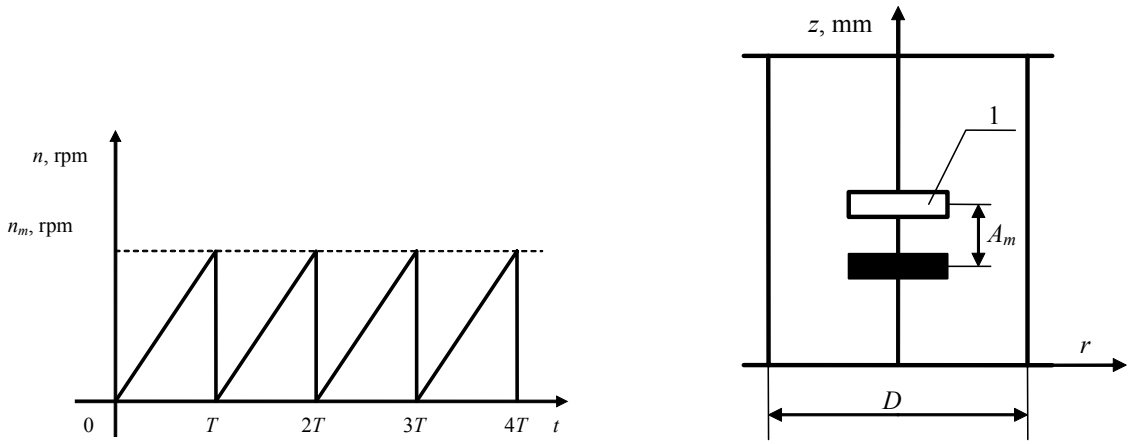
objective functions reflect the process productiveness and residual glucose concentration. A combined algorithm has been used for the determination of MOOP and MPC has been used for process control of the different mixing systems.

Materials and methods

The experimental investigations for the different mixing systems were carried out in a bioreactor with total volume 5 litres and working volume V_0 = 3 litres. The impulse mixing system included a double Rushton turbine with baffles. Maximum rotation speed of the stirrer is n_m = 260 rpm with frequency f_1 = 0.5 s^{-1} and period T = 2 s (Fig. 1a). The vibromixing was realised by replacing the turbine stirrer with vibrator plate 1 (Fig. 1b), where D is the bioreactor diameter. The maximum amplitude is A_m = 10 mm, frequency f_2 = 10 s^{-1}, and period T = 0.1 s [14].

The parameter identification of the batch models of *Saccharomyces cerevisiae* is examined in [14], using the different mixing systems. The models were developed based on the functional state approach [8] and they are shown in Table 1, where $X_{1,2}$, $S_{1,2}$ – cell and glucose concentration for different mixing systems, g·l^{-1}; $K_1 \div K_9$ and $k_1 \div k_{10}$ – the parameters of the models for different mixing systems; t – time, h.

The process is in Phase I, when $S_1 \geq 9.6$, in Phase II – when $S_1 < 9.6$ for the impulse mixing and in Phase I, when $S_2 \geq 12.81$, in Phase II – when $S_2 < 12.81$ for the vibromixing.



a) impulse mixing b) vibromixing

Fig. 1 Impulse and vibromixing realised

The maximal values of the rotation speed n_m and amplitude A_m influence the specific grown rate by the Monod constants – coefficients $K_2^{'}$, $K_5^{'}$, $k_2^{'}$, and $k_7^{'}$ (Table 1). They have been recalculated by the following dependences:

$$K_2^{'} = K_2 / n_m,\ K_5^{'} = K_5 / n_m,\ k_2^{'} = k_2 / A_m, \text{ and } k_7^{'} = k_7 / A_m.$$

The experimental investigations have shown a decrease of the biomass concentration at the end of the process. This is because there is an insufficient mass exchange in the so-called dead zones of the bioreactor [14]. This is reflected in the models (1) – (4) by a coefficient K_6. Now we will specify the coefficient and we will made the model validation at K_6 = 0. The obtained parameter values of the models (1) – (4) are:

$K_1 = 0.238$, $K_2^{'} = 1158.3$, $K_3 = 0.122$, $K_4 = 0.641$, $K_5^{'} = 621.14$,
$K_6 = 0.0$, $K_7 = 0.778$, $K_8 = 4.286$ and $K_9 = 0.106$.

These values are not significantly different from the values shown in Table 1. The model at $K_6 = 0$ showed good statistical indexes. The statistic λ value [14] is $\lambda = 1739$ at a theoretical value $F_T^{'} = 6.9$, i.e. the model is adequate and the coefficient K_6 can be removed from the model, and this will not significantly influence the simulation results.

Table 1. Models of the different mixing systems

Mixing systems	Phase I	Phase II
Impulse mixing	$\frac{dX_1}{dt} = \frac{K_1 S_1^2}{K_2^{'} + S_1^2} X_1$ (1) $\frac{dS_1}{dt} = -\frac{1}{K_3} \frac{K_1 S_1^2}{K_2^{'} + S_1^2} X_1$ (2)	$\frac{dX_1}{dt} = \frac{K_4 S_1}{K_5^{'} + S_1} X_1 - K_6 X_1^2$ (3) $\frac{dS_1}{dt} = -\frac{1}{K_8} \frac{K_7 S_1}{K_9 X_1 + S_1} X_1$ (4)
Initial conditions	$X_1(0) = 0.89$, $S_1(0) = 13.80$.	
Parameters	$K_1 = 0.254$, $K_2^{'} = 1160.9$, $K_3 = 0.161$, $K_4 = 0.714$, $K_5^{'} = 638.51$, $K_6 = 0.035$, $K_7 = 0.907$, $K_8 = 0.113$, $K_9 = 5.200$.	
Vibromixing	$\frac{dX_2}{dt} = \frac{k_1 S_2^2}{k_2^{'} + S_2^2} X_2$ (5) $\frac{dS_2}{dt} = -\frac{1}{k_4} \frac{k_3 S_2}{k_5 X_2 + S_2} X_2$ (6)	$\frac{dX_2}{dt} = \frac{k_6 S_2}{k_7^{'} + S_2} X_2$ (7) $\frac{dS_2}{dt} = -\frac{1}{k_9} \frac{k_8 S_2}{k_{10} X_2 + S_2} X_2$ (8)
Initial conditions:	$X_2(0) = 1.20$, and $S_2(0) = 15.75$.	
Parameters	$k_1 = 0.161$, $k_2^{'} = 132.76$, $k_3 = 0.312$, $k_4 = 0.161$, $k_5 = 9.280$, $k_6 = 0.367$, $k_7^{'} = 9.19$, $k_8 = 0.339$, $k_9 = 0.113$, $k_{10} = 1.521$.	

Formulation of the multiple objective optimization problem

Selection of the control variables

Control variables were used in the initial condition of the different mixing systems for solving optimization problems, such as $X_1(0)$, $X_2(0)$, $S_1(0)$, $S_2(0)$, two time dependent variables rotation speed $n_m(t)$ for impulse mixing, and maximal amplitude $A_m(t)$ for vibromixing.

The control variables intervals for the different mixing systems are:
$0.5 \le X_{1,2}(0) \le 1.5$ g·l^{-1}, $12 \le S_{1,2}(0) \le 17$ g·l^{-1}, $100 \le n_m \le 500$ rpm, and $5.0 \le A_m \le 15$ mm.

The vector of the control variables has the type:

for impulse mixing: $\mathbf{u} = [X_1(0), S_1(0), n_m(t)]^T$
for vibromixing: $\mathbf{u} = [X_2(0), S_2(0), A_m(t)]^T$

Criterion for optimization

The objective of the problem is to find optimal initial conditions of the biomass, glucose concentration, maximal rotation speed, and amplitude for the different mixing systems in which the following objective functions have maximum values:

$$\max_{\mathbf{u}} \mathbf{Q}_1 = \frac{V_0 \left(\mathbf{X}(t_f) - \mathbf{X}_0\right)}{t_f} \tag{9}$$

$$\max_{\mathbf{u}} \mathbf{Q}_2 = \frac{\mathbf{S}(0) - \mathbf{S}(t_f)}{\mathbf{S}(0)} \tag{10}$$

where $\mathbf{Q}_1$, $\mathbf{Q}_2$, $\mathbf{X}_0$, $\mathbf{S}_0$, $\mathbf{X}(t_f)$, and $\mathbf{S}(t_f)$ – vectors of the objective functions, initial conditions, and kinetics variables for the different mixing systems; t_f – final time.

The first objective function corresponds to the process productiveness. The second objective function corresponds to the residual glucose concentration.

The aggregate optimization criterion has an additive type [5]:

$$\max_{\mathbf{u}} \mathbf{J}_S = w_1 \mathbf{Q}_1 + w_2 \mathbf{Q}_2 \tag{11}$$

where $\mathbf{J}_S$ – vectors of aggregate criteria; w_1, w_2 – weight coefficients, $w_1 = w_2 = 0.5$.

Combined algorithm for optimization

Random search with back step algorithm

The random search algorithm is well-known from the literature [11]. Its rate of congruence, which is also valid for other algorithms, depends on the selection of a starting point. For augmentation of the congruence rate, a preliminary choice of a random set is used in the following scheme:

A starting point in the admissible space is generated in an accidental method:

$$\mathbf{u}_{0,i} = \mathbf{u}_{\min,i} + \xi_i \left(\mathbf{u}_{\max,i} - \mathbf{u}_{\min,i}\right), \quad i = 1, 2, ..., M; \; M = \begin{cases} 2^m + 4 & \text{at} \quad m \le 3 \\ 2m + 4 & \text{at} \quad m > 3 \end{cases}$$

where $\xi_i = URAND(IY)$. $URAND(IY)$ is a random generator of random numbers [0 ÷ 1].

The point with the best result concerning some criterion $\mathbf{J}_S$ is chosen as a starting point. After that a random search with back step algorithm is applied.

Fuzzy algorithm

Fuzzy sets theory [2] allows the possibility to develop a "*flexible*" model that reflects possible values of the criterion in more details all , as well as the control variables under the developed model. The model of the batch process (1) - (8) for different mixing systems is considered the most appropriate but deviations (ε_i) are admissible with small degree of acceptance. It is represented by fuzzy set of the following type X and S come into view approximately by the following relations:

$$\eta_i = \left(1 + \varepsilon_i^2\right)^{-1} \tag{12}$$

where $i = 1, 2$; ε_i – deviation from the models.

The prepositional "*flexible*" model of the process reflects better influence of all values of the kinetics variables.

A fuzzy criterion from the following type: "$\mathbf{J}_S$ *to be in possibility higher*" is formulated and presented with the subsequent membership function:

$$\eta_0 = \begin{cases} 1 & \text{for } \mathbf{J}_S < \mathbf{J}_{S_{\min}} \\ \dfrac{\mathbf{J}_S - \mathbf{J}_{S_{\min}}}{\mathbf{J}_{S_{\max}} - \mathbf{J}_{S_{\min}}} & \text{for } \mathbf{J}_{S_{\min}} \le \mathbf{J}_S \le \mathbf{J}_{S_{\max}} \\ 0 & \text{for } \mathbf{J}_S > \mathbf{J}_{S_{\max}} \end{cases} \tag{13}$$

where $\mathbf{J}_{S_{\min}}$ and $\mathbf{J}_{S_{\max}}$ – minimal and maximal values of criteria.

The fuzzy set of the solution is presented by a membership function of the criterion η_0 and model η_i [1]:

$$\eta_{\mathrm{D}} = (1-\gamma)\prod_{i=0}^{2} \eta_i^{\theta_i} + \gamma\left\{1 - \prod_{i=0}^{2}(1-\eta_i)^{\theta_i}\right\} \tag{14}$$

where γ – parameter characterized the compensation degree; θ_i – the weights of η_i.

The solution was obtained by using the common *defuzzification* method BADD [4]:

$$\mathbf{u}^0 = \sum_{i=1}^{q} \mathbf{u}_i \frac{\eta_{D_i}^{\theta_i}}{\sum_{j=1}^{p} \eta_{D_j}^{\theta_i}}, \; i = 1, \ldots, q; \quad j = 1, \ldots, q^m \tag{15}$$

where q – number of discrete values of control variables; m – number of control variables.

An effective algorithm for process optimization is synthesized by using the random search and fuzzy sets [9]. The combined algorithm includes a method of random search for finding an initial point and a method based on fuzzy sets theory which are combined in order to find the best solution of the optimization problem.

All programs were written using a FORTRAN 77 programming language version 5.0. All computations were performed on a Pentium IV 1.8 GHz computer using Windows XP operating system.

Results after fuzzy optimizations and optimal control

Since the maximal rotation speed $n_m(t)$ and amplitude $A_m(t)$ are time dependent variables, the optimal control problem can be considered for an infinite dimensional problem. To solve this problem efficiently, the two control variables are represented by a finite set of control parameters in the time interval $t_{j-1} < t < t_j$ as follows $n_m(t) = n_m(j)$ and $A_m(t) = A_m(j)$ for $j = 1 \div K$, where K – number of time partitions.

The optimization problem (12) - (15) is determined in two stages – a static problem for determination of the optimal values of the initial conditions $X_1(0)$, $S_1(0)$, $X_2(0)$, $S_2(0)$, $n_m(1)$, and $A_m(1)$ for different mixing systems is defined on the first stage. A dynamic problem for determination of the optimal profiles of $n_m(j)$ and $A_m(j)$, ($j > 1$) is defined on the second stage.

The obtained results of the control variables, kinetics variables, and criteria before and after optimization are shown in Table 2.

Table 2. Optimal values of control variable, kinetics variables and criteria

Mixing systems	Variables	$X_1(0)$	$S_1(0)$	$n_m(1)$	$X_1(t_f)$	$S_1(t_f)$	$Q_{1,1}$	$Q_{2,1}$
Impulse mixing	Before	0.890	13.800	260	3.267	0.162	1.426	0.988
	After	1.359	13.398	332	4.885	0.038	2.115	0.997
	Variables	$X_2(0)$	$S_2(0)$	$A_m(1)$	$X_2(t_f)$	$S_2(t_f)$	$Q_{1,2}$	$Q_{2,2}$
Vibomixing	Before	1.200	15.750	10.0	3.968	0.957	1.661	0.939
	After	1.212	12.918	10.4	4.011	0.049	1.679	0.996

The optimization results have shown (Table 2) that the biomass concentration increases by more than 49% in the impulse mixing and only by 1% for the vibromixing. Respectively, the process productiveness (criterion Q_1) increases by more than 48% in the impulse mixing and only by 1% in the vibromixing. The glucose concentration decreases more than 4 times in the impulse mixing and more than 19 times in the vibromixing. The residual glucose concentrations (criterion Q_2) are insignificant in the impulse mixing and decrease by more than 6% in the vibromixing. These results indicate the process impulse mixing productivity is better than the vibromixing and the residual glucose concentration is better in the vibromixing.

The optimal initial values of biomass and glucose concentration (Table 2) for the different mixing systems are distinguished materially for biomass > 12% and glucose > 3.5%. The optimization problem is now decided in the intervals, determined by the optimal values (shown in Table 2): $1.212 \leq X_{1,2}(0) \leq 1.359$ and $12.918 \leq S_{1,2}(0) \leq 13.398$ with the purpose to validate the optimal initial values for both mixing systems in order to choose t. The intervals of change n_m and A_m are not changed. This will allow a comparative analysis to be made. The results are presented as follows: $X_1(0) = 1.334$ and $S_1(0) = 13.122$; $X_2(0) = 1.304$ and $S_2(0) = 13.049$.

The differences between the new optimal values are insignificant (for the initial biomass concentration it is < 2.5%, for the initial glucose concentration it is < 0.7%). And for general initial condition $\boldsymbol{X(0) = 1.3}$ g·l^{-1} and $\boldsymbol{S(0) = 13.0}$ g·l^{-1} are chosen. With these initial conditions a fuzzy optimal control is made for determining $n_m(j)$ and $A_m(j)$ ($j > 1$). The obtained results for the kinetics variables and criteria are shown in Table 3.

Table 3. Optimal values of kinetics variables and criteria

Mixing systems	Variables	$n_m(1)$	$X_1(t_f)$	$S_1(t_f)$	$Q_{1,1}$	$Q_{2,1}$
Impulse mixing	Before	488	3.899	0.037	1.56	0.9972
	After	428	4.837	0.035	2.21	0.9973
	Variables	$A_m(1)$	$X_2(t_f)$	$S_2(t_f)$	$Q_{1,2}$	$Q_{2,2}$
Vibromixing	Before	14	4.025	0.044	1.64	0.9966
	After	13	4.332	0.043	1.82	0.9967

The optimization results with identical initial conditions (Table 3) have shown that the biomass concentration increases by more than 24% in the impulse mixing and by more than 7% in the vibromixing. Respectively, the process productiveness (criterion Q_1) increases by more than 38% in the impulse mixing and by more than 12% in the vibromixing. The glucose concentrations decrease by more than 6% in the impulse mixing, and by more than 4% in the vibromixing.

The results for the biomass concentrations for different mixing systems before and after optimization are shown in Fig. 2.

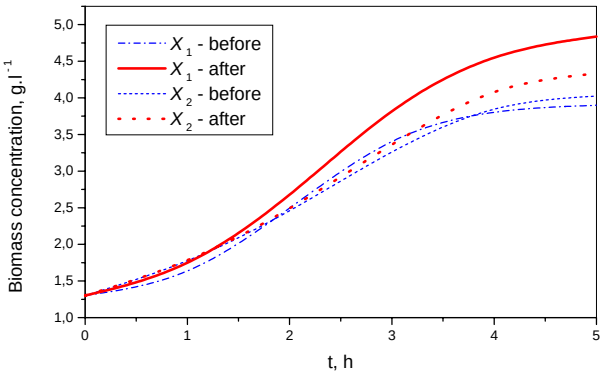
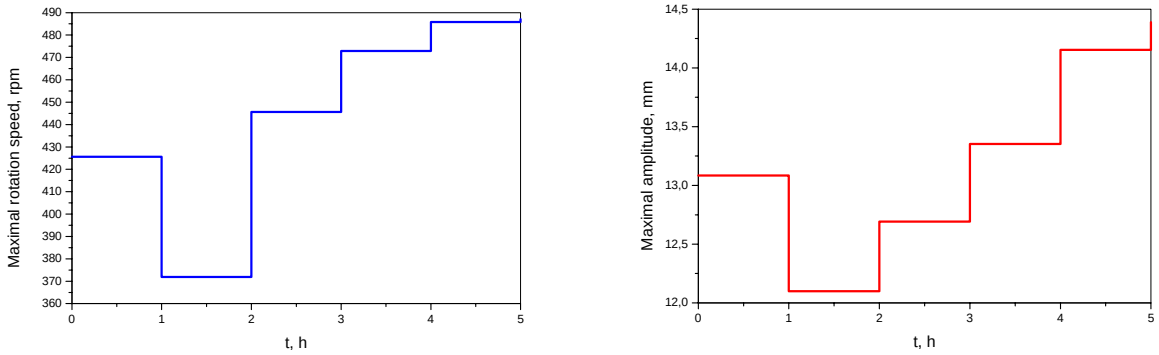


Fig. 2 Biomass concentration before and after optimization

The optimal profiles of maximal rotation speed and amplitude are shown in Fig. 3.



a) impulse mixing b) vibromixing

Fig. 3 Optimal profile of rotation speed and amplitude

The obtained results show the impulse mixing is preferable to vibromixing. Another advantage is that expensive special equipment is not required. It can be realized easily in each bioreactor which has control systems equipped with a generator for a saw impulse.

Model predictive control

In order to understand MPC algorithm see Fig. 4. The figure and the notation used in the description are adapted from [6, 7]. The first part of the MPC algorithm is the specification of the reference trajectory which may be as simple as a step change to a new set point or as it is common for batch processes – a trajectory that the system must follow. At the present time k, the reference trajectory has a value $r(k)$.

Also at k, consider the predicted process output over a future prediction horizon p. A suitable controller model of the process is used to obtain the projected behavior of the output over the prediction horizon by simulating the effects of the past inputs applied to the actual process (value $\hat{y}(k)$ at the current time) [7].

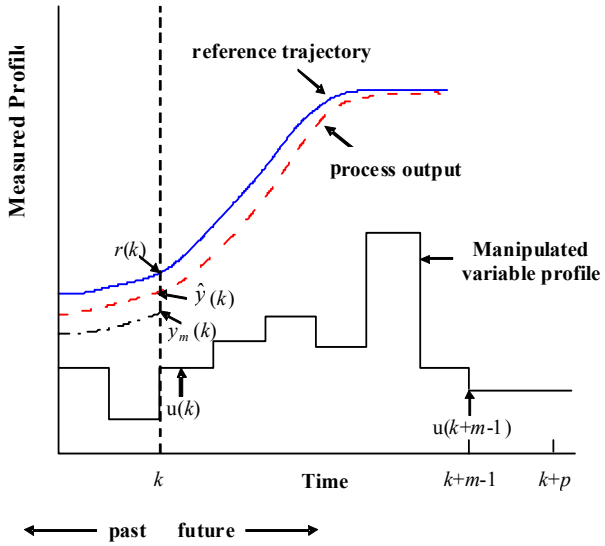


Fig. 4 MPC algorithm scheme

However, due to unmodeled disturbances and modelling errors there might be some deviations between the actual observed output $y_m(k)$ and the predicted output behaviour. Due to these deviations, the computed future manipulated variable moves are no longer appropriate and hence only the first of the computed manipulated variable moves $\Delta\mathbf{u}(k)$ is implemented on the actual process. The error $d(k) = y_m(k) - \hat{y}(k)$ is calculated and it is used to update the future measurements.

The optimization is carried out again based on this new horizon and using the updated system information and the process continues. Since the horizon recedes at the next time step, this is also known as a receding horizon control problem. However, in the case of batch systems where the final time of the process operation is specified the available prediction horizon and the window of opportunity for control shrink as the batch is close to completion. Consequently, the value of the prediction horizon in the control algorithm successively decreases as the end of batch is near [7].

At the next time instant $k + 1$, the process measurement is taken again and the horizon is shifted forward by one step. The optimization is carried out again based on this new horizon and using the updated systems information and the process continues. Since the horizon recedes at the next time step it is also known as a receding horizon control problem.

The 2nd hour is chosen as a first control point. As it may be noted that there is a diversion from the reference profile, accordingly the optimal profile is changed. The second point is at 3rd hour. The third point is at 4th hour. The obtained control guarantees the robustness and stability of the optimization criterion. The optimization criterion is criterion (11). This is represented in Fig. 5.

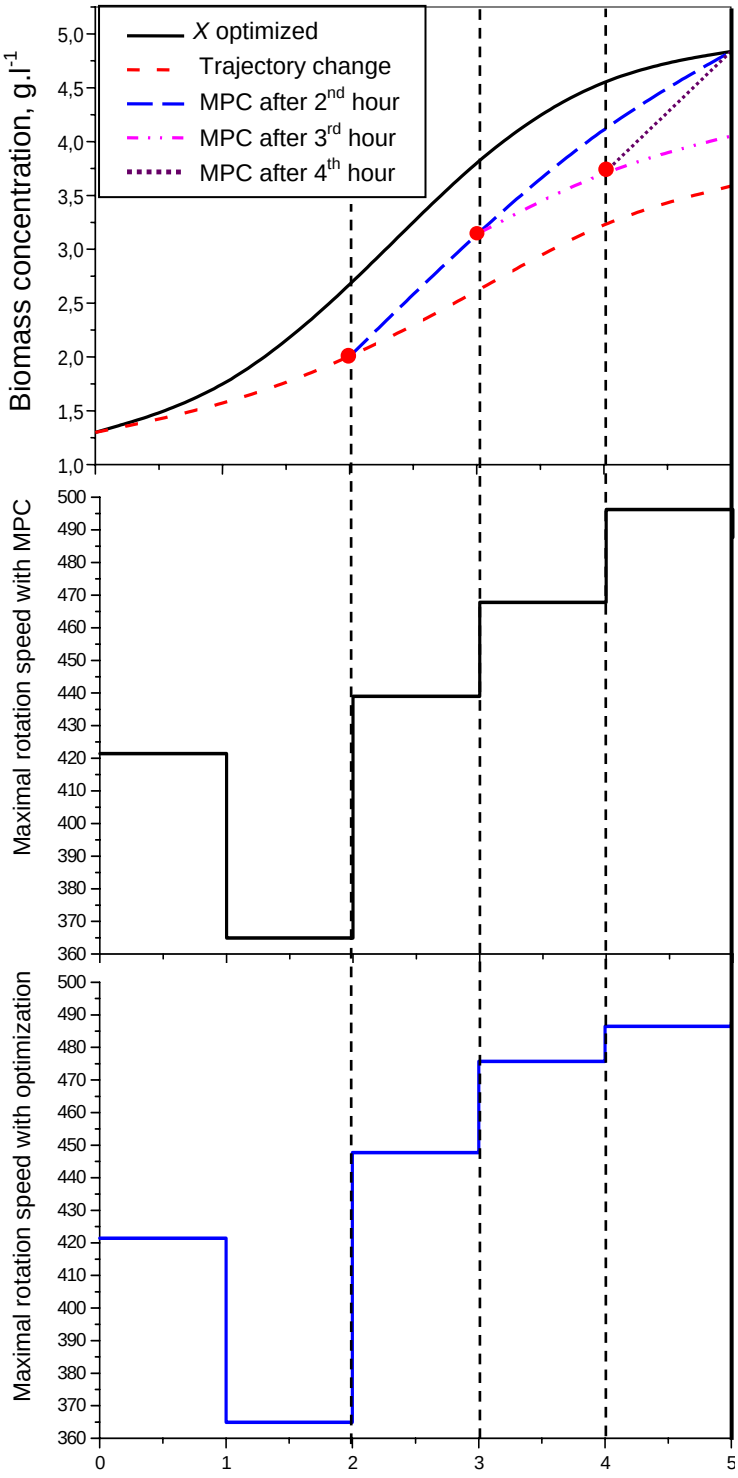


Fig. 5 MPC to *Saccharomyces cerevisiae* cultivation

Conclusions

1. The multiple optimization results with identical initial conditions have shown that the process productiveness increases by more than 38% for the impulse mixing and by more than 12% for the vibromixing. The glucose concentration decreases by more than 6% for the impulse mixing, and by more than 4% for the vibromixing. These results have shown that the impulse mixing is preferable to the vibromixing.
2. The different initial conditions have shown the biomass concentration increases by more than 49% for the impulse mixing, and only by 1% for the vibromixing. Respectively, the process productiveness (criterion Q_1) increases by more than 48% in the impulse mixing and only by 1% in the vibromixing. The glucose concentration decreases by more than four times in the impulse mixing, and more than 19 times in the vibromixing. The residual glucose concentration change (criterion Q_2) is insignificant in the impulse mixing and increases by more than 6% in the vibromixing. These results have indicated the process impulse mixing productivity is better than the vibromixing and residual glucose concentration is better in the vibromixing.
3. The applied multiple objective optimization of the process has shown a vast increase of their productivity, respectively decrease in the residual substrate concentration. This result leads to a higher economical effectiveness for each of them at a smaller outlay. The 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 solution of problems having a larger scale. The developed combined algorithm can be used for the solution of other optimization problems in the area of bioprocess systems.
4. Combined algorithm does not have a feedback and it does not guarantee robustness to process disturbances. MPC is developed to guarantee robustness of the process disturbances. The method is carried out with the purpose to control disturbance of the optimal control variables. The developed control algorithm – combined CA and MPC ensures maximum criterion at the end of the process and guarantees a feedback on disturbance as well as robustness to process disturbances.

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