

# A study on the control of a bioreactor for the bioethanol production process

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Presented at  
25th Polish Conference of  
Chemical and Process Engineering,  
20–23 September 2026,  
Kraków, Poland.  
Guest Editors: Katarzyna Bizon,  
Przemysław Jodłowski

## Article info:

Received: 30 May 2026  
Revised: 10 August 2026  
Accepted: 17 August 2026

## Abstract

This paper presents the results of numerical studies on the control systems of the bioethanol production process in a continuous stirred tank bioreactor. The studies included the bioreactor control by means of a nonlinear model predictive controller (NMPC) with constraints based on the process model. Particular attention was paid to the influence of the values of control signals generated by the controller on the metabolic changes taking place in biomass cells. These changes are initiated as a result of exceeding the permitted values of the process parameters. These values can be determined with the use of a developed method of numerical analysis of the mathematical model of the process. Their nature is related to the occurrence of points of change in the cell metabolic activity or the phenomenon of biomass washing out from the bioreactor. The NMPC control algorithm determines the optimal values of the control signals and searches only the given range of the control variables. As a result, the generated values of the control signals do not exceed the defined limit values, regardless of the nature and frequency of disturbances occurring in the system. This enables the process to be conducted in the area of optimal metabolic activity of microorganisms.

## Keywords

nonlinear model predictive control, nonlinear analysis, bioethanol production

## 1. INTRODUCTION

Bioprocesses are difficult to control. Due to the high sensitivity of microorganisms, a precise bioreactor control strategy is necessary. An additional difficulty is the inability to easily influence the internal environment of microbial cells by manipulating the extracellular environment (Alford, 2006; Yamuna Rani and Ramachandra Rao, 1999). Due to the complexity of basic biochemical processes, few kinetic models able to describe well the nonlinear dynamics of biomass growth are available (Yamuna Rani and Ramachandra Rao, 1999). An important aspect of the available models is the unpredictable variability of their parameters, the values of which can vary to a large extent, depending on the used strain of microorganisms (Ciesielski and Grzywacz, 2020; Harmand et al., 2008). Another drawback is a limited number of available measuring sensors dedicated to bioprocess applications on an industrial scale. It is commonly known that the basis for the proper functioning of any controller is the reliable measurement of key process variables. Standard sensors used in the fermentation process on an industrial scale measure, among others, the temperature, pH value, concentration of dissolved oxygen, stirrer speed, pressure and media flow rate (Alford, 2006; Sonnleitner, 2013). However, there are no reliable sensors measuring the metabolic activity of biomass cells, which makes it very difficult to characterize the current state of the conducted bioprocess (Carrondo et al., 2012; Luttmann et al., 2012; Mears et al., 2017; Yamuna Rani and Ramachandra Rao, 1999). As might be expected, it is possible to measure the gas phase

composition in a bioreactor using advanced spectroscopic techniques (Cervera et al., 2009). This provides some insight into the metabolic state of biomass cells (Sonnleitner, 2013), but they are not routinely used on an industrial scale. If it is not possible to directly measure a key process parameter in real time, the so-called soft sensors can be used (Luttmann et al., 2012). The principle of their operation is based on the processing of measurement data provided "online" in real time in order to calculate the value of a variable whose direct measurement is possible only in an "offline" mode. This strategy is currently the subject of intensive research as estimating the values of key process parameters will enable further automation of bioprocesses (Luttmann et al., 2012). In the case of bioprocesses, kinetic delay is also a very important issue which goes along with them. Its source are biochemical reactions that make up cellular metabolism. These reactions are catalysed by specific enzymes which must be synthesized when a given metabolic pathway is activated. The synthesis of intracellular components is very time-consuming. As a result, the reaction of biomass cells to changing process conditions in the bioreactor is delayed in time, which is a phenomenon commonly observed experimentally (Daugulis et al., 1997). A classic PID regulator, which most often controls bioreactors on an industrial scale, works in a correction mode. In order to remedy the regulation error present at a given moment of the process, it makes an appropriate adjustment of the process parameter settings (Åmand et al., 2013). However, due to the delay in adapting the cell to new extracellular conditions, it takes some time for a metabolic response to appear. This can lead to a situation



where the controller incorrectly determines control signals as it has information that is not up-to-date at the given moment of the process. As a result, biomass cells may reach a completely different metabolic state from the planned one, and the return to the original state is again associated with the time required to carry out the necessary biochemical syntheses within the cell. It clearly follows that this classical control (Ciesielski and Grzywacz, 2019b) in the case of bioprocesses and the accompanying kinetic delay are ineffective.

In order to solve the problem of effective control of nonlinear systems, a number of advanced control techniques have been developed, including:

- Adaptive Control (Åström and Wittenmark, 2008; Duan et al., 2006; Hisbullah et al., 2002; Landau et al., 2011; Oliveira et al., 2004),
- Fuzzy Logic Control (Babuška and Verbruggen, 1996),
- Artificial Neural Networks Control (Dochain, 2013; Funes et al., 2015; Petre et al., 2010; Sewsynker-Sukai et al., 2017),
- Model Predictive Control (Forbes et al., 2015; Laurí et al., 2014; Qin and Badgwell, 2003; Stanke and Hitzmann, 2012; Seborg et al., 2004).

Each of the advanced control techniques requires a specific source of process information. These sources are historical measurement data, a mathematical model of the process or the operator's experience. All of the described control techniques require a certain level of experience with the process so that the data can be interpreted properly during the synthesis of the control algorithm. This is a prerequisite for the development of appropriate control objectives and methods of implementing them. Fuzzy Logic Control algorithms are extremely valuable. They do not require a huge amount of historical measurement data for a mathematical model of the process to be directly formulated, and are able to deal well with unpredictable process dynamics and process disturbances. Their disadvantage is poor understanding of the dynamics of the controlled process, which may adversely affect the operator's interpretation of the phenomena occurring in the system. In turn, adaptive control algorithms and those based on artificial neural networks require a very large amount of historical measurement data, without which the formulation of the algorithm itself and the methods of its operation is basically impossible. Also in this case the understanding of the process is very limited as these algorithms do not include a complete process model in their structure. On the other hand, for process systems whose dynamics is described by a mathematical model, the optimal choice of their control strategy is predictive control. This algorithm does not require historical measurement data and the applied process model describes the dynamics of the system, which makes it possible to accurately understand its operation. It is in predictive control that the possibility of effective control of non-linear processes in the biotechnology and pharmaceutical industries is seen.

## 2. PROBLEM AND METHODS

Model Predictive Control (MPC) is a widely used process control technique due to its ability to handle complex linear and nonlinear multidimensional systems (Forbes et al., 2015; Qin and Badgwell, 2003). The MPC algorithm requires a robust mathematical model of the process, the accuracy of which largely determines the success of the method and its ability to deal with disturbances in the system (Laurí et al., 2014). This model is used to predict the dynamics of the controlled system over the specified time horizon, in response to the determined changes in the value of the control parameter. These values are determined based on the optimization of a properly defined cost function (Stanke and Hitzmann, 2012). The optimization issue may consist in, for example, maximizing the production, minimizing the cost or following the defined reference trajectory of a given variable. The optimization procedure is also subject to predefined process constraints which are an integral part of the optimization problem (Seborg et al., 2004). Model Predictive Control is a very effective technique as decisions on the value of the output control signals are optimal for the entire duration of the process, and the effect of system disturbances is modelled as part of the optimization problem. However, this method is considered computationally expensive compared to other control methods despite the fact that it is used in numerous branches of industry.

The fermentation of bioethanol in an aerobic environment with the yeast *Saccharomyces cerevisiae* was chosen as a model process. The process of bioethanol production by continuous fermentation is highly complex and nonlinear (Paz Astudillo and Cardona Alzate, 2011). As reported in the literature, the industrial production of bioethanol is accompanied by problems related to the stability of the conducted process (Paz Astudillo and Cardona Alzate, 2011), which is mostly managed by control systems based on classic regulators. The synthesis of a control system responsible for the supervision of optimal conditions for the growth of microorganisms inside the bioreactor is a very big challenge (Simutis and Lübbert, 2015). It boils down to developing an appropriate strategy for managing the biocatalytic environment, which is not a trivial task (Mohd Azhar et al., 2017; Ciesielski and Grzywacz, 2019a). In such a system, the desired phenomena are the growth and multiplication of biomass cells, as well as the production of the desired product. These phenomena depend on several or even over a dozen parameters, therefore modern control systems must be able to simultaneously manage many process parameters in real time (Carrondo et al., 2012). Considering the scale of world bioethanol production, the indicated problem is very serious and still remains unresolved.

### 2.1. Equations

A structured and non-segregated kinetic model developed by Jones and Kompala (1999) and well described in the literature (Ciesielski and Grzywacz, 2020; Ciesielski and Grzywacz, 2021;

(Sridhar, 2016; Sridhar, 2019) was used to describe the cell growth dynamics of *Saccharomyces cerevisiae* under aerobic conditions. It takes into account the presence of three main metabolic pathways:

- metabolic pathway of glucose fermentation (reaction  $R_1$ ),
- metabolic pathway of ethanol oxidation (reaction  $R_2$ ),
- metabolic pathway of glucose oxidation (reaction  $R_3$ ).

These three metabolic pathways make up a simplified model of cellular metabolism of yeast. The exact relationships between the mentioned metabolic pathways are presented in the metabolic diagram in our previous work (Ciesielski and Grzywacz, 2020). The mechanism of regulation of metabolic processes in the biomass cell is based on properly defined mathematical relationships which control the synthesis and activity of key enzymes, in the form of cybernetic variables  $u_i$  and  $v_i$ , given by Equations (1) and (2):

$$u_i = \frac{r_i}{\sum_j r_j} \quad (1)$$

$$v_i = \frac{r_i}{\max_j r_j} \quad (2)$$

Biomass growth rates according to a given metabolic pathway  $r_i$ , present in Equations (1) and (2), are described by Eqs. (3)–(5). They are in the form of a modified Monod kinetic equation taking into account the concentrations of intracellular enzymes  $e_i$ .

Rate of reaction  $R_1$ :

$$r_1 = \mu_1 e_1 \frac{G}{K_1 + G} \quad (3)$$

Rate of reaction  $R_2$ :

$$r_2 = \mu_2 e_2 \frac{E}{K_2 + E} \frac{O}{K_{O2} + O} \quad (4)$$

Rate of reaction  $R_3$ :

$$r_3 = \mu_3 e_3 \frac{G}{K_3 + G} \frac{O}{K_{O3} + O} \quad (5)$$

The specific growth rate  $\mu_i$  in Eqs. (3)–(5) is given by Eq. (6) and is expressed as a function of the maximum specific growth rate  $\mu_{\max,i}$ , the rate constant of enzyme synthesis  $\alpha_i$  and the rate constant of enzyme degradation  $\beta_i$ .

$$\mu_i = \mu_{i\max} \frac{\mu_{i\max} + \beta}{\alpha + \alpha^*} \quad (6)$$

Metabolic pathways  $R_1 - R_3$  are catalysed by intracellular enzymes  $e_1 - e_3$ , the formation rates of which are expressed by Eqs. (7)–(9).

Synthesis rate of enzyme  $e_1$ :

$$r_4 = \alpha \frac{G}{K_1 + G} \quad (7)$$

Synthesis rate of enzyme  $e_2$ :

$$r_5 = \alpha \frac{E}{K_2 + E} \quad (8)$$

Synthesis rate of enzyme  $e_3$ :

$$r_6 = \alpha \frac{G}{K_3 + G} \quad (9)$$

When formulating a mathematical model of the bioethanol production process taking place in a continuous stirred tank bioreactor, the following assumptions were made:

- the bioreactor operates under isothermal conditions
- the entire reaction space of the bioreactor is homogeneous, thus there are no local concentration gradients of the system components
- there are no rheological effects of the reaction mixture associated with the presence of biomass cells
- the bioreactor is fed with a sterile mass stream
- the biochemical reaction takes place only in the reaction space of the bioreactor, excluding the space of the biomass separator and the mass recirculation loop.

One of the basic process parameters of continuous bioreactors is the dilution rate. It is defined as the ratio of the volumetric flow rate  $F_v$  through the cross-section of the bioreactor to its volume  $V$ , which is represented by Eq. (10).

$$D = \frac{F_v}{V} \quad (10)$$

Using the defined process parameters (10), process assumptions, and the structured and non-segregated kinetic model, the state equations of individual system components can be represented by the following Eqs. (11)–(18). Equation (11) represents the balance of glucose concentration in the system. Equation (12) is the biomass concentration balance. Equation (13) balances the ethanol concentration in the system. Equation (14) represents the balance of dissolved oxygen in the liquid phase. The first two members describe the phenomenon of interfacial oxygen transport, under the assumption that the oxygen concentration in the gas phase does not change depending on the height of the bioreactor. Equation (15) is the balance equation of intracellular carbohydrates. Equations (16)–(18) represent the balance of concentrations of key intracellular enzymes. The values of kinetic and process model parameters used in the calculations are given in Table 1.

$$\begin{aligned} \frac{dG}{dt} = & D(G_0 - G) - X \left( \frac{r_1 v_1}{Y_1} + \frac{r_3 v_3}{Y_3} \right) - \\ & \varphi_4 \left( C \frac{dX}{dt} + X \frac{dC}{dt} \right) \end{aligned} \quad (11)$$

$$\frac{dX}{dt} = -DX + X \sum_i (r_i v_i) \quad (12)$$

$$\frac{dE}{dt} = -DE + X \left( \varphi_1 \frac{r_1 v_1}{Y_1} - \frac{r_2 v_2}{Y_2} \right) \quad (13)$$

$$\begin{aligned} \frac{dO}{dt} = & -DO + k_L a(O^* - O) - \\ & X \left( \varphi_2 \frac{r_2 v_2}{Y_2} + \varphi_3 \frac{r_3 v_3}{Y_3} \right) \end{aligned} \quad (14)$$

$$\frac{dC}{dt} = \gamma_3 r_3 v_3 - (\gamma_1 r_1 v_1 - \gamma_2 r_2 v_2) C - \sum_i (r_i v_i) C \quad (15)$$

$$\frac{de_1}{dt} = r_4 u_1 - \left( \sum_i (r_i v_i) + \beta \right) e_1 + \alpha^* \quad (16)$$

$$\frac{de_2}{dt} = r_5 u_2 - \left( \sum_i (r_i v_i) + \beta \right) e_2 + \alpha^* \quad (17)$$

$$\frac{de_3}{dt} = r_6 u_3 - \left( \sum_i (r_i v_i) + \beta \right) e_3 + \alpha^* \quad (18)$$

Table 1. Values of kinetic parameters used in numerical calculations (Zhang and Henson, 2001). Equilibrium oxygen concentration  $O^*$  was taken as 7.5 mg/L.

| Parameter             | Value | Parameter                 | Value |
|-----------------------|-------|---------------------------|-------|
| $\mu_{1\max}, h^{-1}$ | 0.44  | $K_1, g/L$                | 0.05  |
| $\mu_{2\max}, h^{-1}$ | 0.19  | $K_2, g/L$                | 0.01  |
| $\mu_{3\max}, h^{-1}$ | 0.36  | $K_3, g/L$                | 0.001 |
| $Y_1, g/g$            | 0.16  | $\varphi_1, g/g$          | 0.403 |
| $Y_2, g/g$            | 0.75  | $\varphi_2, g/g$          | 2.087 |
| $Y_3, g/g$            | 0.60  | $\varphi_3, g/g$          | 1.067 |
| $K_{O_2}, mg/L$       | 0.01  | $\varphi_4, g/g$          | 0.95  |
| $K_{O_3}, mg/L$       | 2.2   | $\alpha, g/(g \cdot h)$   | 0.3   |
| $\gamma_1, g/g$       | 10.0  | $\beta, g/(g \cdot h)$    | 0.7   |
| $\gamma_2, g/g$       | 10.0  | $\alpha^*, g/(g \cdot h)$ | 0.03  |
| $\gamma_3, g/g$       | 0.8   | $k_L a, h^{-1}$           | 225   |

## 2.2. Nonlinear model predictive controller

The standard calculation algorithm of a nonlinear predictive controller consists of two parts. The first component is an optimizer, the task of which is to solve nonlinear optimization problems formulated in real time. Commonly available numerical Sequential Quadratic Programming (SQP) algorithms are used for this purpose. The SQP techniques are considered to be effective methods for solving the constrained optimization problem (Papageorgiou et al., 2015). There are many software packages available in standard scientific programs which, depending on a project, are able to solve complex problems with up to several thousand unknown quantities (SOLNP (Ye, 1987; Ye, 1989), DYN0 (Fikar and Latifi, 2002), *fmincon* (Byrd et al., 2000; Coleman et al., 2001)). Basically, the SQP methods involve minimization of the cost function against modifications of the input variables. The second component of the algorithm is a predictor of the system response to determined changes in the value of the control signal. Kalman filters are used as standard state estimators of dynamic systems. The basic version of the Kalman filter is used to estimate the state of linear systems invariant in time, which are disturbed by white noise (Kalman, 1960). On the other hand, its extended

version (Extended Kalman Filter) is used for the estimation of nonlinear systems in which the disturbances are not always white noise (Grewal and Andrews, 2014). This filter contains a linearization procedure for a nonlinear process model. The linearization process leads to the transformation of sometimes very complex mathematical relationships into their simplified linear form, which in turn leads to significant shortening of time of numerical calculations. When the linearization of the model is carried out in close proximity to the current steady state, such approximation gives good results. However, this procedure always involves the loss of a certain amount of information provided by the nonlinear model. Therefore, the prediction of the system response to the values of control signals determined by the optimization procedure should be as accurate as possible. Possible inaccuracies in performed calculations lead directly to the error of the predicted steady states of the system, which are summed up over the entire prediction horizon. Therefore, wherever possible, unchanged forms of nonlinear equations describing the dynamics of the system should be used to predict the state of the system.

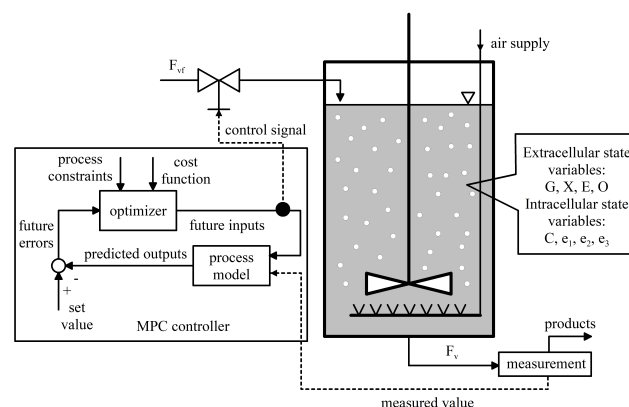


Figure 1. Schematic diagram of a continuous stirred tank bioreactor with a one-dimensional model predictive controller of the flow rate of mass stream feeding the process system.

In this work a nonlinear predictive controller was used to control the flow rate of mass stream feeding the continuous stirred tank bioreactor. The considered process system is shown schematically in Fig. 1. The algorithm of the nonlinear predictive controller was developed on the basis of the literature (Grüne and Pannek, 2017). The nonlinear cost function was defined according to Eq. (19). The trajectory of control signals is determined by the nonlinear optimization procedure by searching for the minima of the cost function, Eq. (20). The dynamic response of the controlled system is predicted on the basis of the original forms of nonlinear equations of state, Eqs. (11)–(18). When determining the prediction trajectory, the numerical method of Euler integration was used, in accordance with Eq. (21) (Kincaid and Cheney, 2002). When selecting the values of predictive controller parameters, the general guidelines described in detail in the paper (Rossiter, 2004) were applied.

$$J = \lambda_{y_i} \sum_{i=1}^{N_p} (y_{\text{zad}}(k + N|k) - y_{\text{pred}}(k + N|k))^2 + \lambda_{u_i} \sum_{i=1}^{N_c-1} (\Delta u(k + N|k))^2 \quad (19)$$

$$\min J \quad (20)$$

$$Y_i = Y_{i0} + \frac{\partial f_i}{\partial t} \Delta t, \quad \text{where } \Delta t = T_p \quad (21)$$

### 2.3. Process constraints

Our previous work (Ciesielski and Grzywacz, 2021) contains in-depth considerations on the essence of the proper formulation of process constraints in the case of bioprocess control. Therefore, the developed algorithm of the nonlinear predictive controller has been supplemented with constraints based on the nonlinear process model. In order to formulate the process constraints for the nonlinear MPC controller based on the mathematical model of the process, the diagram of the metabolic activity of biomass cells published in our previous work (Ciesielski and Grzywacz, 2021) was used. It was prepared using our original method of qualitative interpretation of bifurcation diagrams (Ciesielski and Grzywacz, 2019a; Ciesielski and Grzywacz, 2020; Ciesielski and Grzywacz, 2021).

The method described in detail in our last paper (Ciesielski and Grzywacz, 2021) was used to construct the process map. The diagram of metabolic activity of biomass cells was supplemented with a gradient of bioethanol concentrations obtained in the process system. The numerical data necessary for this purpose were obtained using a detailed analysis of the quantitative course of the steady state branches of ethanol concentration in the bioreactor. The compilation of qualitative and quantitative data allowed for the preparation of a process map, presented in Fig. 2.

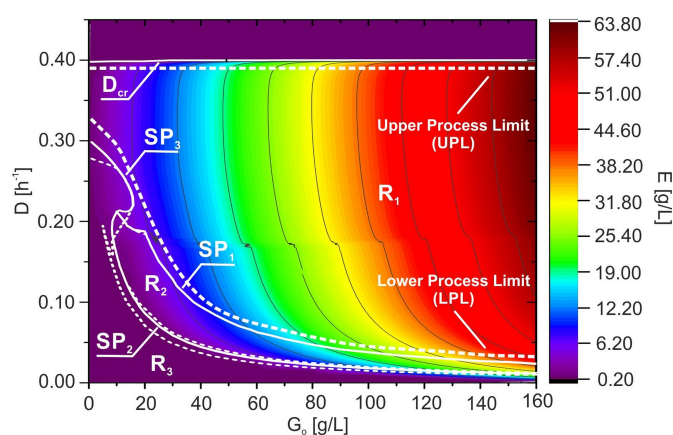


Figure 2. Process map for the bioethanol production process in a continuous stirred tank bioreactor with marked lower and upper process limitations.

The areas marked with symbols  $R_1$ ,  $R_2$  and  $R_3$  presented in Fig. 2 represent the areas of domination of glucose fermentation, ethanol oxidation, and glucose oxidation reactions, respectively. According to the assumptions of the kinetic model, the dominance of a given metabolic pathway is determined by the process conditions prevailing at a given time. Based on the proposed method of qualitative interpretation of bifurcation diagrams, the values of process parameters for which changes in the dominant pathway in the metabolic system of biomass cells are initiated were determined. The initiation points of these changes are marked in Fig. 2 with the symbol  $SP$ . Changing the process conditions in the system forces the biomass cells to change their preferred metabolic pathway according to one of three possible scenarios:

- At the point  $SP_1$  there is a change in the dominant metabolic pathway from glucose fermentation to ethanol oxidation,
- At the point  $SP_2$  there is a change in the dominant metabolic pathway from ethanol oxidation to glucose oxidation,
- At the point  $SP_3$  there is a change in the dominant metabolic pathway from glucose oxidation to glucose fermentation.

By analysing the prepared process map (Fig. 2) it is possible to formulate general conclusions concerning the optimal areas of bioreactor operation and control constraints. With the assumption of maximizing bioethanol production, the target area where the highest product concentrations are generated in the bioreactor is the area  $R_1$ . Within the area the product concentration depends strongly on the value of glucose concentration in the feed stream  $G_0$ , which should be as high as possible. The value of the dilution rate  $D$  has a much smaller influence on the bioethanol concentration obtained in the bioreactor. The line of the critical dilution rate  $D_{cr}$  and lines  $SP_1$  and  $SP_3$  are safe limits for carrying out the process. The assumption of a dilution rate value higher than  $D_{cr}$  initiates the phenomenon of washing out of biomass cells from the system. On the other hand, crossing the  $SP_1$  and  $SP_3$  lines initiates unfavourable changes in the metabolic system of biomass cells, including the transition of microorganisms from fermentative to oxidative mode of operation. Both of these the diagram (Fig. 2). It should be additionally noted that within the areas of biomass oxidative activity there is an oscillation area which is undesirable from the point of view of running the process on an industrial scale. The selection of control variable settings should exclude the bioreactor operation in this process area.

In order for the information contained in the process map to be useful during the synthesis of the model predictive controller, it was subjected to the digitization process. As a result, all process-critical boundary lines will be expressed as mathematical functions. These functions will compose a library of process constraints, which is an integral part of the optimization procedure of the model predictive controller. Due to the fact that in the analysed case the control variable is the

dilution rate  $D$ , the critical boundary curves were expressed by the function  $D = f(G_0)$ . During the digitization of the process map, a safety buffer zone was established between the boundary line determined from numerical tests and the proposed process boundaries. The mathematical forms of process boundaries are represented by Eqs. (22)–(24), while their graphical course is illustrated by the white dashed line in Fig. 2. The upper process limit is described by the simple Eq. (22). The lower process limit (LPL) consists of two curves described by Eq. (23) and Eq. (24). The former (22) describes the course of the LPL in the area of low glucose concentrations for  $G_0 < 80$  g/L, while the latter (24) defines the course of the LPL in the range of medium carbon substrate concentrations in the  $G_0$  range from 80 g/L to 160 g/L. Mathematically formulated process constraints Eqs. (22)–(24) based on a nonlinear process model were integrated with the optimization procedure of the predictive controller, making up a numerical library of process constraints. As a result of this procedure, the controller has information about the allowed ranges of the value of the dilution rate  $D$ .

$$D = 0.3900 \text{ h}^{-1} \quad (22)$$

$$D = 0.31815 + 0.00128G_0 - 6.33809 \cdot 10^{-4}G_0^2 + 1.93084 \cdot 10^{-5}G_0^3 - 2.28293 \cdot 10^{-7}G_0^4 + 9.63944 \cdot 10^{-10}G_0^5 \text{ h}^{-1} \quad (23)$$

$$D = 0.15145 - 0.00196G_0 + 1.18905 \cdot 10^{-5}G_0^2 - 2.64057 \cdot 10^{-8}G_0^3 \text{ h}^{-1} \quad (24)$$

## 2.4. Classic PI control

For comparison, simulation calculations of the control of a classic PI controller were performed for the analysed process. The nature of bioprocesses fits well with the characteristics of the PI controller, yet this type of control is often ineffective in practice, and tuning the cascade system of PI controllers is a complicated and time-consuming task. However, due to the fact that the PI controller is widely used in industrial-scale process regulation, it has been used in this paper as a reference point to illustrate real problems related to bioprocess control. In this study, the most common case from industrial practice is analysed, covering the problem of one-dimensional control of the process taking place in a continuous stirred tank bioreactor with ideal mixing by means of the flow rate of mass stream feeding the apparatus. The bioreactor is equipped with an automatic control system coupled with a valve regulating the flow rate of the feed stream  $F_v$ . The scheme of such control is a modification of Fig. 1 in which a PI controller is introduced in place of the MPC controller.

The dependence of the flow rate on time, which is the controller output signal, is shown in Eq. (25).

$$F_v(t) = F_v(0) + K_p \left( e(t) + \frac{1}{T_i} \int_0^t e(t) dt \right) \quad (25)$$

After taking into account Eq. (25), the expression for the dilution rate  $D$ , present in the balance equations of the bioreactor, takes the form of Eq. (26).

$$D = \frac{F_v(0) + K_p \left( e(t) + \frac{1}{T_i} \int_0^t e(t) dt \right)}{V} \quad (26)$$

The concentration of bioethanol ( $E$ ) was assumed as the controlled variable. Therefore, the control error present in Eqs. (25) and (26) was defined with Eq. (27).  $E_{\text{SET}}$  is the set value of bioethanol concentration in the system, and  $E(t)$  is its current value.

$$e(t) = E_{\text{SET}} - E(t) \quad (27)$$

## 2.5. Numerical methods

The research work on the bioreactor control systems was carried out in several stages, using a number of methods for solving numerical problems and a number of computational packages. The nonlinear analysis of the bioreactor steady states described by Eqs. (11)–(18) was made using the XPPAUT 8 program (Ermentrout, 2002), which is integrated with the AUTO computational package (Doedel et al., 2002) commonly used for bifurcation analysis. The program simulating the operation of the PI controller was written in the FORTRAN programming language. The calculation of time trajectories of state variables was performed using the Gear numerical integration method, which is recommended for stiff systems of ordinary differential equations (Kincaid and Cheney, 2002). On the other hand, the program simulating the operation of the nonlinear predictive controller was written using the MATLAB computing package. The ODE15s procedure was used to integrate a system of ordinary differential equations, which is recommended for stiff systems of differential equations. The MPC controller optimizer algorithm used the *fmincon* procedure (Coleman et al., 2001; Byrd et al., 2000), available in the optimization toolbox of the MATLAB package. This procedure is recommended for solving the problem of nonlinear optimization with linear or nonlinear constraints. As a predictor of the system response to the applied control signal between the sampling times of the MPC controller, the integration of original forms of nonlinear equations of state by the Euler method was used (Kincaid and Cheney, 2002).

## 3. RESULTS AND DISCUSSION

In order to check the presented MPC controller algorithm, the following process data set was selected (Mustafa et al., 2014). Feeding the bioprocess system with a stream with a concentration of  $G_0 = 20.0$  g/L was considered, which is illustrated in Fig. 3. The initial steady state was reached by the system for the dilution rate  $D_{\text{SS}} = 0.3000 \text{ h}^{-1}$ . At the steady state for this set of parameters, a product concentration of  $E_{\text{SS}} = 7.73$  g/L is formed in the bioreactor. It was assumed

that the concentration of bioethanol at the new steady state should be  $E_{SET} = 7.03$  g/L. It was stated that the adopted ethanol concentration can be achieved in the allowed process area, which is between the lower process limit (point) located for  $D_{LPL} = 0.2000$  h<sup>-1</sup> and the upper process limit (point) located for  $D_{UPL} = 0.3900$  h<sup>-1</sup>. In addition, on the basis of the available numerical data, it was found that the system can reach a new set point at two steady states for the values of dilution rate of  $D_1 = 0.2500$  h<sup>-1</sup> and  $D_2 = 0.3868$  h<sup>-1</sup>, respectively. The selected process situation is close to the line of change of metabolic activity from  $R_1$  to  $R_2$ , and the function of ethanol concentration depending on the dilution rate has a large gradient. Diagram illustrating the operation of the synthesized model predictive controller is presented in Fig. 4. The process of bioethanol production conducted at the steady state achieved for  $G_0 = 20.0$  g/L and  $D = 0.3000$  h<sup>-1</sup>, which corresponds to the concentration  $E = 7.73$  g/L of bioethanol in the bioreactor, was considered. The set value of bioethanol concentration was established at  $E_{SET} = 7.03$  g/L. The length of the prediction horizon was determined as  $N_p = 6T_p$  h, the control horizon as  $N_c = 4T_p$  h, while the values for cost function weighting factors were determined as  $\lambda_E = 1.0$  and  $\lambda_D = 300.0$ . The controller with such setting values eliminated the control error present in the system and reached the set value after 60 hours (Fig. 4A), without exceeding the lower and upper process limits (Fig. 4B). The set value of the controlled variable was achieved for the dilution rate  $D = 0.3868$  h<sup>-1</sup>. This is a very important feature of the model predictive controller, as the generated values of the control signals are always within a defined area. Moreover, it is not possible for the generated values to be outside the area, irrespective of the values of the model predictive controller parameters or the intensity and amplitude of steady state bioreactor disturbances appearing in the system. In accordance with the analysis of the steady states presented in Fig. 3, the set value of bioethanol concentration  $E_{SET} = 7.03$  g/L may also be reached by the system for the value of the dilution rate  $D = 0.2500$  h<sup>-1</sup>.

Comparative calculations using a PI controller were carried out for two different settings. In the first case the controller setting values were  $K_c = 0.5$  and  $T_i = 3.0$ . In such a situation, the controller, by eliminating the control error formed at the point 0 hours, determined the values of the control signals in the range between the upper and lower process limits, as shown in Fig. 5. In the second case for the same value of control error, the value of the controller gain factor was changed to  $K_c = 3.5$ , leaving the value of the integration time unchanged at  $T_i = 3.0$  (Fig. 6). The generated values of the control signals  $D$  exceeded the lower process limit operating point (Fig. 6B). As a result, in the first time period after the occurrence of the control error, the process system was found within the undesirable process areas characterized by oxidative metabolic activity of biomass cells. During this period covering the first 5 hours after the occurrence of the control error, the bioreactor was in the area of glucose oxidation, oscillation and ethanol oxidation (Fig. 6B). Only after 5 hours the system returned

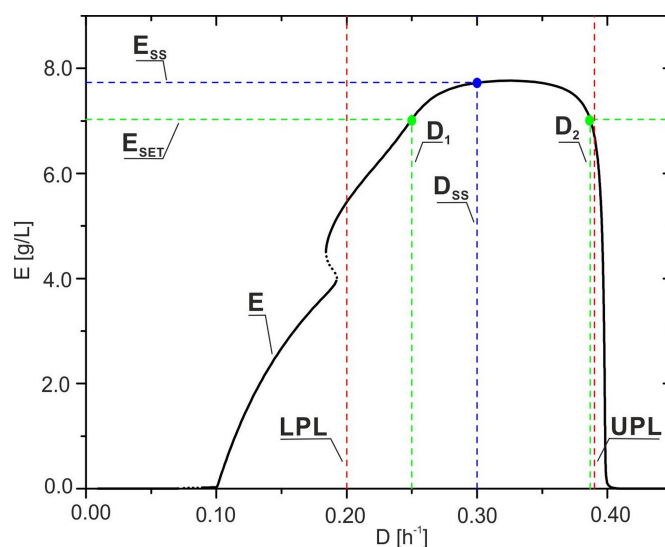


Figure 3. The steady state branch of the bioreactor, illustrating the change in bioethanol concentration  $E$  depending on the value of the dilution rate  $D$ , for glucose concentration in the feed stream  $G_0 = 20.0$  g/L.

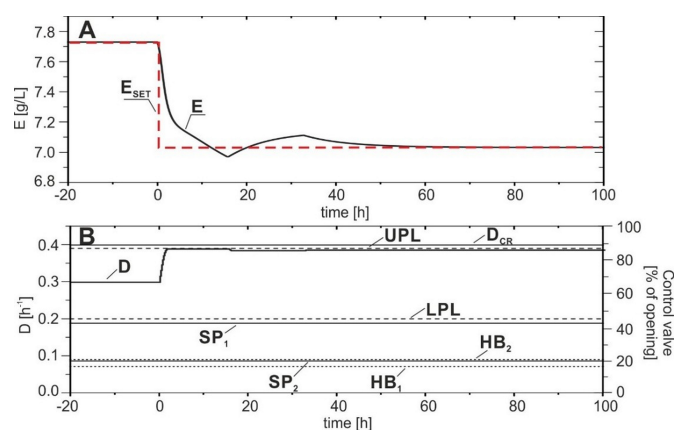


Figure 4. Numerical simulation of the response of the process system and nonlinear MPC controller to a change in the desired bioethanol concentration from 7.73 g/L to 7.03 g/L for the value of glucose concentration in the bioreactor feed stream  $G_0 = 20.0$  g/L. MPC controller setting parameters:  $T_p = 0.2$  h,  $N_p = 6T_p$  h,  $N_c = 4T_p$  h,  $\lambda_E = 1.0$ ,  $\lambda_D = 300.0$ .

to the glucose fermentation area, located between the lower and upper process limit operating points. The phenomenon of leaving the target area of glucose fermentation is undesirable as it initiates changes in the intracellular metabolism of biomass, which in turn translates directly into the product concentrations and stability of the process achieved in the system. In addition, such rapid changes in process conditions, which directly affect the metabolic state of biomass cells, may lead to the phenomenon of osmotic stress and, as a result, deterioration of bioethanol production efficiency.

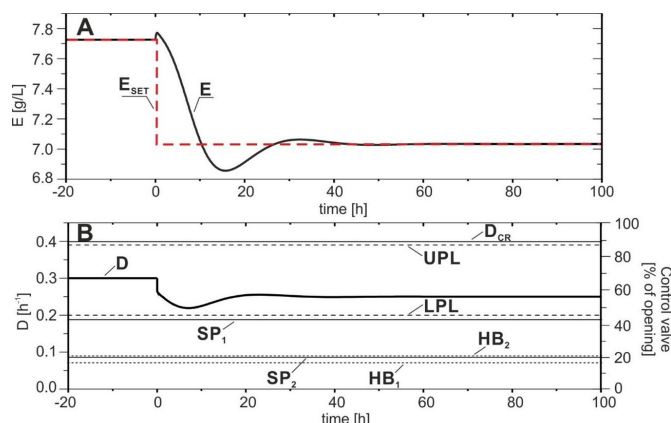


Figure 5. Numerical simulation of the response of the process system and PI controller to a change in the desired bioethanol concentration from 7.73 g/L to 7.03 g/L for the value of glucose concentration in the bioreactor feed stream  $G_0 = 20.0$  g/L. PI controller setting parameters:  $K_c = 0.5$ ,  $T_i = 3.0$ .

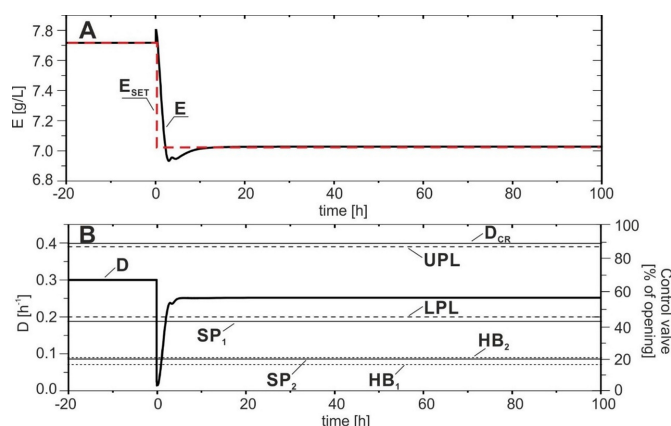


Figure 6. Numerical simulation of the response of the process system and PI controller to a change in the desired bioethanol concentration from 7.73 g/L to 7.03 g/L for the value of glucose concentration in the bioreactor feed stream  $G_0 = 20.0$  g/L. PI controller setting parameters:  $K_c = 3.5$ ,  $T_i = 3.0$ .

## 4. CONCLUSIONS

On the basis of the numerical studies carried out on the control of the bioethanol production process by means of a nonlinear MPC controller with constraints based on the model, the following conclusions can be drawn:

- The MPC algorithm determines the optimal values of the control signals by searching only the given range of the control variable.
- The generated values of the control signals do not exceed the defined limit values, independently of the intensity and amplitude of the disturbances appearing in the system.
- With the library of process constraints proposed in this work, it is possible to narrow down the search area for the optimal values of the control signal, which significantly

shortens the adjustment time of the control error present in the system.

- Already at the prediction stage, the kinetic delay effects typical of bioprocesses are taken into account in the calculations, thanks to which the determined values of control signals can be applied in advance to the process system, which significantly improves the quality of control and the stability of the conducted process.
- When there are several operating points characterized by the same value of the controlled variable, it is possible to direct the search of the allowed range of the control variable in the right direction by appropriately selecting the values of the weighting factors of the cost function or narrowing down the searched range on the basis of the data contained in the process map.

On the other hand, on the basis of the numerical studies carried out on the control of the bioethanol production process by means of a PI controller the following conclusions can be drawn:

- It is possible to choose the setting value of the PI controller parameters so that when a control error occurred, the controller determined the values of the control signals in the allowable range of the control variable  $D$ .
- Even a small change in the value of the controller gain factor may cause the generation of control variable signals from the outside of the allowed operating area and thus cause the lower and upper process limits to be exceeded.
- There is no possibility for the algorithm of the PI controller to introduce limitations on the generated control signals, thus the process system can be in an undesirable operating area for a longer period of time.

## SYMBOLS

|          |                                                                            |
|----------|----------------------------------------------------------------------------|
| $C$      | intracellular storage carbohydrate concentration, g/g <sub>biomass</sub>   |
| $D$      | dilution rate, h <sup>-1</sup>                                             |
| $D_{cr}$ | critical dilution rate, h <sup>-1</sup>                                    |
| $E$      | ethanol concentration, g/L                                                 |
| $e_i$    | $i$ -th pathway intracellular enzyme concentration, g/g <sub>biomass</sub> |
| $F_V$    | volume flow rate through bioreactor, g/L                                   |
| $F_{Vf}$ | volume flow rate of feed stream, g/L                                       |
| $G$      | glucose concentration, g/L                                                 |
| $G_o$    | feed glucose concentration, g/L                                            |
| HB       | Hopf bifurcation point                                                     |
| $J$      | cost function                                                              |
| $K_i$    | $i$ -th pathway Michaelis constant, g/L                                    |
| $k_{La}$ | oxygen mass transfer coefficient, h <sup>-1</sup>                          |
| $K_o$    | oxidative pathway oxygen saturation constant, mg/L                         |
| LPL      | lower process limit                                                        |
| $N_c$    | control horizon, h                                                         |
| $N_p$    | prediction horizon, h                                                      |

|                       |                                                                                                                                               |
|-----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| $O$                   | dissolved oxygen concentration, mg/L                                                                                                          |
| $O^*$                 | dissolved oxygen solubility limit, mg/L                                                                                                       |
| $r_i$                 | $i$ -th pathway growth rate, $h^{-1}$                                                                                                         |
| $r_{i,max}$           | maximum growth rate of all pathways at any instant, $h^{-1}$                                                                                  |
| $R_1$                 | reaction of glucose fermentation                                                                                                              |
| $R_2$                 | reaction of ethanol oxidation                                                                                                                 |
| $R_3$                 | reaction of glucose oxidation                                                                                                                 |
| $SP_1$                | the switch point of the dominant metabolic pathway from glucose fermentation to ethanol oxidation, or inversely ( $R_1 \leftrightarrow R_2$ ) |
| $SP_2$                | the switch point of the dominant metabolic pathway from ethanol oxidation to glucose oxidation, or inversely ( $R_2 \leftrightarrow R_3$ )    |
| $SP_3$                | the switch point of the dominant metabolic pathway from glucose oxidation to its fermentation, or inversely ( $R_3 \leftrightarrow R_1$ )     |
| $T_p$                 | sampling time, h                                                                                                                              |
| $u_i$                 | $i$ -th pathway cybernetic variable controlling enzyme synthesis                                                                              |
| UPL                   | upper process limit                                                                                                                           |
| $v_i$                 | $i$ -th pathway cybernetic variable controlling enzyme activity                                                                               |
| $X$                   | biomass concentration, $mg/dm^3$                                                                                                              |
| $Y_i$                 | $i$ -th pathway yield coefficient, $g_{biomass}/g_{substrate}$                                                                                |
| <b>Greek symbols:</b> |                                                                                                                                               |
| $\alpha$              | specific enzymatic synthesis rate, $g/(g \cdot h)$                                                                                            |
| $\alpha^*$            | parameter for constitutive enzyme synthesis, $g/(g \cdot h)$                                                                                  |
| $\beta$               | specific enzymatic degradation rate of intracellular enzymes, $g/(g \cdot h)$                                                                 |
| $\gamma_i$            | stoichiometric parameters, g/g                                                                                                                |
| $\lambda_i$           | weight coefficient of cost function                                                                                                           |
| $\mu_i$               | $i$ -th pathway modified specific growth rate constant, $h^{-1}$                                                                              |
| $\mu_{imax}$          | $i$ -th pathway maximum specific growth rate constant, $h^{-1}$                                                                               |
| $\varphi_i$           | stoichiometric parameters, g/g                                                                                                                |

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