Genetic Algorithm Tuning of PID Controller in Smith Predictor for Glucose Concentration Control

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Abstract: *This paper focuses on design of a glucose concentration control system based on nonlinear model plant of E. coli MC4110 fed-batch cultivation process. Due to significant time delay in real time glucose concentration measurement, a correction is proposed in glucose concentration measurement and a Smith predictor (SP) control structure based on universal PID controller is designed. To reduce the influence of model error in SP structure the estimate of measured glucose concentration is used. For the aim an extended Kalman filter (EKF) is designed. To achieve good closed-loop system performance genetic algorithm (GA) based optimal controller tuning procedure is applied. A standard binary encoding GA is applied. The GA parameters and operators are specified for the considered here problem. As a result the optimal PID controller settings are obtained. The simulation experiments of the control systems based on SP with EKF and without EKF are performed. The results show that the control system based on SP with EKF has a better performance than the one without EKF. For a short time the controller sets the control variable and maintains it at the desired set point during the cultivation process. As a result, a high biomass concentration of 48.3 $g \cdot l^{-1}$ is obtained at the end of the process.*

Keywords: *E. coli cultivation, Smith predictor, PID controller tuning, Genetic algorithm, Extended Kalman filter.*

Introduction

Cultivation of recombinant microorganisms e.g. *Escherichia coli*, in many cases is the only economic way to produce pharmaceutical biochemicals such as interleukins, insulin, interferons, enzymes and growth factors. To maximize the volumetric productivities of bacterial cultures it is important to grow *E. coli* to high cell concentration. From different modes of operation, (batch, fed-batch and continuous), fed-batch operation is often used in industry due to its ability to overcome catabolite repression or glucose effect which usually occur during production of these fine chemicals. Moreover, fed-batch operation also gives the operator the freedom of manipulating the process via substrate feed rate.

Control opportunities in fed-batch operated cultivations have been reviewed in detail in a number of articles. It is well known that the design of high performance model based control algorithms for biotechnological processes is hampered by some major problems which call for adequate engineering solutions. Different control loops are realized for control of temperature, pH, and dissolved oxygen as well as for the control of volume and anti foam considering

cultivation processes. Whereas, commercially available controllers exist only for such well established measurement systems, for substrate feed rate (i.e. glucose concentration) control there is a lack of control systems. The main reason for this is the difficulties in on-line measuring of the substrate concentration in a fast and reliable way during the cultivation process. Moreover in principle the substrate concentration measurement systems are characterized with significant time delay which sets the challenge to control considered processes.

The control strartegy for substrate feed rate can be summarized in three groups: open (feedforward)-, closed-loop (feedback) control and mixed (feedforward-feedback). Widely used in feedback control of industrial cultivation processes is the proportional-integral-derivative (PID) controller. When the object is characterized with significant time delay the conventional PID controller can not ensure the control system performance. A tool approved in the practice for time delay compensation is the Smith predictor (SP) [20]. In this predictor scheme, the mathematical model of the process is implemented in an internal feedback loop around a conventional controller. The distinctive scheme was proposed by O. J. M. Smith approximately 50 years ago, and is still attracting much attention for its usefulness. The major advantage of the SP is that delay issues can be ignored when designing the controller. The main disadvantage is that the performance of the SP control strategy is affected by the model unaccuracy. There are many applications of the SP based on linear (linearized) model plant [2-4, 12, 21] and a few based on nonlinear models [6, 9]. Considering cultivation processes there is a lack of such studies.

The another significant challenge of control design of such high nonlinear processes is controller tuning. Tuning a PID controller appears to be conceptually intuitive but can be hard in practice, if complex systems, as cultivation processes are considered. For the controller tuning in a real plant a higher degree of experience and technology are required. Usually the PID controller is poorly tuned due to highly changing dynamics of cultivation processes, which is caused by the non-linear growth of the cells, the metabolic changes as well as changes in the overall metabolism. In control design of continuous cultivation processes the controller tuning could be done with traditional methodology [13]. The models of these processes can be linearized in an equilibrium point. In contrast, considering fed-batch cultivation processes such methodologies are inapplicable (impracticable). In these cases as an alternative for the quality controller tuning optimization methods could be applied. The tuning procedure is a big challenge for the conventional optimization methods. As an alternative various metaheuristics could be used.

Heuristics can obtain suboptimal solution in ordinary situations and optimal solution in particular. Since the considered problem has been known to be NP-complete, using heuristic techniques can solve this problem more efficiently. Three most well-known heuristics are the iterative improvement algorithms, the probabilistic optimization algorithms, and the constructive heuristics. In the probabilistic optimization group, genetic algorithms (GA) based methods and simulated annealing are considerable which extensively have been proposed in the literature. The GA are highly relevant for industrial applications, because they are capable of handling problems with non-linear constraints, multiple objectives, and dynamic components – properties that frequently appear in the real-world problems [13]. Since its introduction and subsequent popularization [8], the GA has been frequently utilized as an alternative optimization tool to the conventional methods [15].

This paper focuses on the design of a glucose concentration control system based on nonlinear model plant of *E. coli MC4110* fed-batch cultivation process. Due to significant time delay in real-time glucose concentration measurement system a correction in measurement glucose concentration is proposed and the modified SP control structure based on universal PID controller is proposed. In this structure the estimate of measured glucose concentration is used to reduce the influence of model error. An extended Kalman filter (EKF) is designed to obtain this estimate. To achieve good closed-loop system performance GA based optimal controller tuning procedure is applied.

Mathematical model of *E. coli MC4110* fed-batch cultivation

The mathematical model (1) – (5) is based on real fed-batch cultivation process of *E. coli MC4110*. The cultivation process is carried out in the Institute of Technical Chemistry, Hannover University, Germany. The cultivation conditions and data measurements are discussed in [1, 18]. The model is presented as:

$$\begin{cases} \dot{\mathbf{x}}(t) = f(\mathbf{x}, F) + \boldsymbol{\eta}(t) \\ S(t) = \mathbf{H}\mathbf{x}(t) + \xi(t) \end{cases}, \tag{1}$$

$$\mathbf{x}(t) = \left[X(t) \quad S(t) \quad V(t) \quad \mu_{\max}(t) \right]^{\mathrm{T}}, \tag{2}$$

$$f(\mathbf{x}, F) = \begin{bmatrix} \mu_{\max}(t)\dfrac{S(t)}{k_S + S(t)} X(t) - \dfrac{F(t)}{V(t)} X(t) \\ -\dfrac{1}{Y_{S/X}} \mu_{\max}(t)\dfrac{S(t)}{k_S + S(t)} X(t) + \dfrac{F(t)}{V(t)}\left(S_{in} - S(t)\right) \\ F(t) \\ 0 \end{bmatrix}, \tag{3}$$

$$\mathbf{H} = \begin{bmatrix} 0 & 1 & 0 & 0 \end{bmatrix}, \tag{4}$$

$$\boldsymbol{\eta}(t) = \left[\eta_X(t) \quad \eta_S(t) \quad 0 \quad \eta_{\mu_{\max}}(t) \right]^{\mathrm{T}}, \tag{5}$$

where: X is the concentration of biomass, [g·l^{-1}]; S – concentration of substrate (glucose), [g·l^{-1}]; F – feed rate, [l·h^{-1}]; V – bioreactor volume, [l]; S_{in} – substrate concentration of the feeding solution, [g·l^{-1}]; $\mu_{\max}$ – maximum growth rate, [h^{-1}]; k_S – saturation constant, [g·l^{-1}]; $Y_{S/X}$ – yield coefficient, [-]; η_X – biomass concentration process noises, [g·l^{-1}]; η_S – substrate concentration process noise, [g·l^{-1}]; $\eta_{\mu_{\max}}$ – maximum growth rate process noise, [h^{-1}]; $\xi(t)$ – measurement noise, [g·l^{-1}].

Based on real experimental data (feeding rate data and off-line measurements of biomass and on-line data of substrate (glucose) measurements) and GA identification procedure the following numerical values of the model parameters are obtained [18]:

k_S = 0.012 g·l^{-1}, $Y_{S/X}$ = 0.5.

The initial process conditions are [1]:

t_0 = 6.68 h, $X(t_0)$ = 1.25 g·l^{-1}, $S(t_0)$ = 0.8 g·l^{-1}, S_{in} = 100 g·l^{-1}.

The model inaccuracy is modeled via zero mean white Gausian noise. The corresponding variances are [1]: η_X = 0.001 g^2·l^{-2}·h^{-1}, η_S = 0.001 g^2·l^{-2}·h^{-1} and $\eta_{\mu_{\max}}$ = 0.05 l·h^{-3}.

The glucose measurement system [1] used during the process has time delay $\Delta t = 60$ s, which is acceptable. But during this time the cells in the samples continue glucose consuming. In the beginning of the cultivation, consumed amount of glucose is neglectable at lower biomass concentration. When the biomass concentration is higher this amount is not neglectable (as could be seen in Fig. 1). This process significantly affected the control of system performance. To overcome this problem the following correction of glucose measurements is proposed:

$$S_{COR}(t) = S(t) + \frac{\mu(t) X(t)}{Y_{S/X}} \Delta t \,. \tag{6}$$

Specific grow rate $\mu(t)$ is described by Monod kinetics as:

$$\mu(t) = \mu_{\max}(t) \frac{S(t)}{k_S + S(t)}. \tag{7}$$

Control algorithm

A conventional PID control is a generic control algorithm widely used in control systems. More of 90% of control loops in industrial control system are based on PI(D) controllers. During *E. coli MC4110* fed-batch cultivation process a time delay is observed due to particularities of on-line glucose measurement system. This contributes to the significant error in glucose concentration measurement. In this case the conventional PID controller can not ensure satisfactory performance of the control system. To overcome this problem a SP is used. It is a well-known control structure based on the linear plant model. The basic idea is to use the process model to obtain an estimate of non-delayed system output. This output is used in an inner feedback loop, combined with an outer feedback loop based on the delayed estimation error.

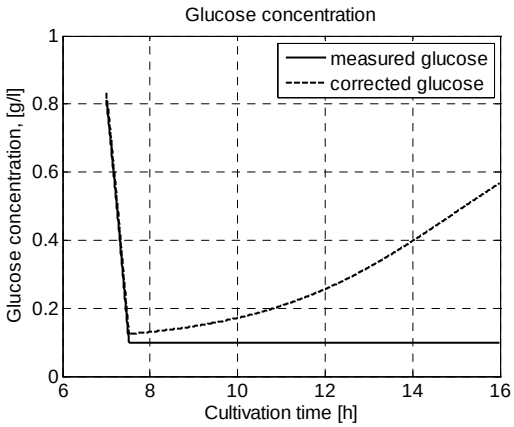

Fig. 1 Measured glucose concentration and the corrected one

In this paper a modified SP structure based on nonlinear plant model is proposed. The structure of the control system is shown in Fig. 2. In conventional case of SP only the plant output is used to form the inner feedback. Here to form the feedback term of control signal a universal PID controller is used [2-4, 7]. In addition, the predicted by nonlinear model process variables are used to form the feedforward term of control signal. This term is utilized to hold the nonlinear plant at the actual equilibrium point. It is proposed to use the estimate $\hat{S}$ obtained by EKF to reduce the influence of measurement noise ξ on the model error e_m.

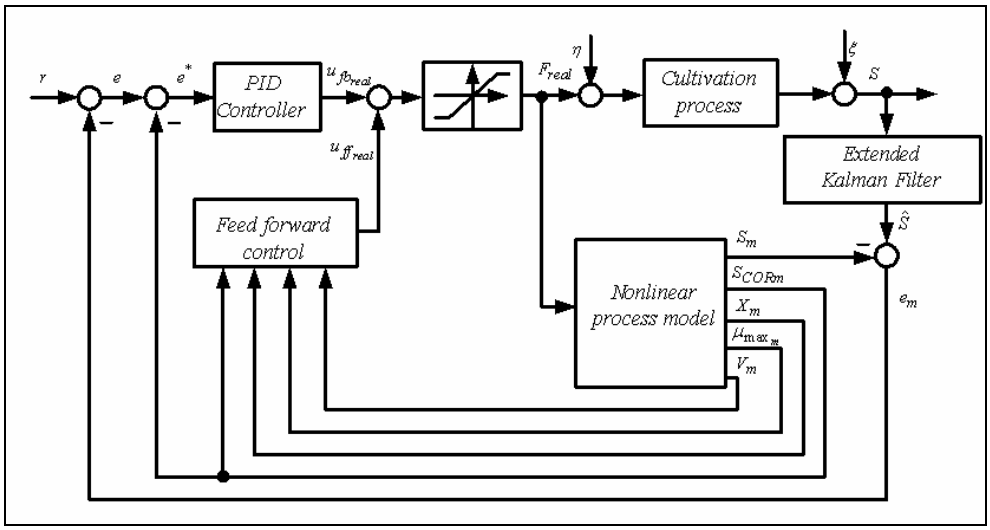

Fig. 2 Structure of the designed control system

The block named "Nonlinear process model" predicts the non-delayed model output by equations:

$$\begin{cases} \dot{\mathbf{x}}_m(t) = f_m(\mathbf{x}_m, F) \\ S_m(t) = \mathbf{H}\mathbf{x}_m(t) \\ S_{CORm}(t) = S_m(t) + \dfrac{\mu_m(t) X_m(t)}{Y_{S/X}} \Delta t, \quad \mu_m(t) = \mu_{\max_m} \dfrac{S_m(t)}{k_S + S_m(t)} \end{cases}, \tag{8}$$

$$\mathbf{x}_m(t) = \left[X_m(t) \quad S_m(t) \quad V_m(t) \right]^{\mathrm{T}}, \tag{9}$$

$$f_m(\mathbf{x}_m, F) = \begin{bmatrix} \mu_{\max_m} \dfrac{S_m(t)}{k_S + S_m(t)} X_m(t) - \dfrac{F(t)}{V_m(t)} X_m(t) \\ -\dfrac{1}{Y_{S/X}} \mu_{\max_m} \dfrac{S_m(t)}{k_S + S_m(t)} X_m(t) + \dfrac{F(t)}{V_m(t)} \left(S_{in} - S_m(t) \right) \\ F(t) \end{bmatrix}, \tag{10}$$

where: X_m is the evaluated by model concentration of biomass, [g·l^{-1}]; S_m – evaluated by model delayed concentration of substrate (glucose), [g·l^{-1}]; V_m – evaluated by model bioreactor volume, [l]; $\mu_{\max_m}$ – model maximum growth rate, [h^{-1}]; S_{CORm} – predicted by model non-delayed concentration of substrate, [g·l^{-1}]. Here $\mu_{\max_m} = 0.5$ h^{-1}.

The PID controller algorithm is described as follows:

$$u_{fb}(s) = K_p \left(be(s) - S_{CORm}(s) \right) + \frac{K_p}{T_i} e^*(s) + \frac{T_d s}{1 + \dfrac{T_d s}{N}} \left(ce(s) - S_{CORm}(s) \right), \tag{11}$$

where: $u_{fb}(s)$ is the feedback term of control variable, [l·h^{-1}]; $r(s)$ – reference signal, [g·l^{-1}]; K_p – proportional gain, [-]; T_i – integral time, [h] T_d – derivative time, [h]; b, c – set-point weight coefficients, [-]; $\dfrac{T_d}{N}$ – low-pass first order filter of D-term time-constant, [h].

The coefficients b and c are used to weight out the $r(s)$ respectively in the proportional and in the derivative term of the controller. Typically the coefficients are chosen as: $0 \le b \le 1,\ 0 \le c \le 1$. In industrial applications b and c are chosen to be equal to 0 or 1 [2-4].

The control error $e^*(s)$ is the difference between the error $e(s)$ (difference between set-point (reference signal) $r(s)$ and the model error $e_m(s)$) and the corrected glucose concentration $S_{CORm}(s)$ (Eq. (6)); the model error $e_m(s)$ is the difference between the measured glucose concentration $S(s)$ and the evaluated by process model one $S_m(s)$.

$$\begin{aligned} e^*(s) &= e(s) - S_{CORm}(s), \\ e(s) &= r(s) - e_m(s), \\ e_m(s) &= S(s) - S_m(s). \end{aligned} \tag{12}$$

For considered here *E. coli MC4110* cultivation process desired set-point is at S_{SP} = 0.1 g·l^{-1} glucose concentration [1]. Concentrations above this value lead to a substrate inhibition of the process, i.e. to a negative effect on the productivity and yield of a desired cultivation product.

Considering real applications usually digital PID controller is implemented. There are many techniques for discretization. Here for discretization of the PID controller (Eq. (11)) backward Euler method [10] is used. The mathematical description of the designed digital PID controller is:

$$u_{fb}(k) = u_p(k) + u_i(k) + u_d(k), \tag{13}$$

$$u_p(k) = K_p\left(be(k) - S_{CORm}(k)\right), \tag{14}$$

$$u_i(k) = u_i(k-1) + b_{i1}\left(e(k) - S_{CORm}(k)\right) + b_{i2}\left(e(k-1) - S_{CORm}(k-1)\right), \tag{15}$$

$$u_d(k) = a_d u_d(k-1) + b_d\left(ce(k) - ce(k-1) - S_{CORm}(k) + S_{CORm}(k-1)\right), \tag{16}$$

where

$$b_{i1} = K_p\frac{T_0}{T_i},\ b_{i2} = 0,\ a_d = \frac{T_d}{T_d + NT_0},\ b_d = K_p\frac{T_d N}{T_d + NT_0}. \tag{17}$$

The control variable used to control the feed rate has the following form:

$$F(k) = u_{fb}(k) + u_{ff}(k), \tag{18}$$

where

$$u_{ff}(k) = \frac{1}{Y_{S/X}}\frac{V_m(k)\mu_m(k)X_m(k)}{S_{in} - S_{CORm}} \tag{19}$$

is feedforward term obtained from the steady state conditions.

To reduce the influence of measurement noise $\xi(k)$ on the measured glucose concentration and the model error $e_m(k)$, the estimate $\hat{S}(k)$ instead $S(k)$ is proposed to form the error:

$$e_m(k) = \hat{S}(k) - S_m(k). \tag{20}$$

To obtain the glucose concentration estimate an EKF is designed. Based on discretization of process model (Eqs. (1) – (5)) the following EKF is obtained (see Appendix):

$$\begin{cases} \hat{\mathbf{x}}(k+1) = \mathbf{f_d}\left(\hat{\mathbf{x}}(k)\right) + \mathbf{K_{EKF}}(k+1)\left(S(k+1) - \mathbf{H}\mathbf{f_d}\left(\hat{\mathbf{x}}(k)\right)\right), \\ \hat{S}(k+1) = \mathbf{H}\hat{\mathbf{x}}(k+1), \end{cases} \tag{21}$$

$$\hat{\mathbf{x}}(0) = \begin{bmatrix} 1.25 & 0.8 & 1.35 & 0.5 \end{bmatrix}^{\mathrm{T}},$$

$$\mathbf{f_d}\left(\hat{\mathbf{x}}(k)\right) = \hat{\mathbf{x}}(k) + T_0\mathbf{f}\left(\hat{\mathbf{x}}(k)\right), \tag{22}$$

where: $\hat{\mathbf{x}}(\cdot)$ and $\hat{S}(\cdot)$ are the estimates of $\mathbf{x}(\cdot)$ and $S(\cdot)$; $\mathbf{K_{EKF}}(\cdot)$ – the EKF gain.

Finally, the real control variable has the following form:

$$F_{real}(k) = u_{fb_{real}}(k) + u_{ff}(k), \tag{23}$$

where

$$u_{fb_{real}}(k) = u_{p_{real}}(k) + u_{i_{real}}(k) + u_{d_{real}}(k). \tag{24}$$

The variables $u_{p_{real}}(k)$, $u_{i_{real}}(k)$ and $u_{d_{real}}(k)$ are formed using Eqs. (14) – (16). The error is:

$$e(s) = r(s) - e_m(s),$$

where $e_m(s)$ is according Eq. (20).

To provide control action designed for specific process requirements tuning the PID controller parameters is required. The controller parameters are: K_p, T_i, T_d, b, c and $\frac{T_d}{N}$.

Considering control system based on linear plant models there are many classical and novel or modified approaches for PID controller parameters tuning [2-4, 7, 11]. These methods are inapplicable to the considered here non-linear control system. The regarded fed-batch cultivation process can not be linearized around an equilibrium point. If a linear approximation is found, the resulting model will be valid only for a small range around the linearization point. The controller tuned by the linear model will work properly only for this limited range and for a very small time interval. Therefore, to achieve the best overall PID control it is necessary to use non-classical tuning methods for the entire operating envelope of the given system. In this work GA are applied for PID controller parameters tuning, based on control system presented in Fig. 2.

Background of the genetic algorithm

Genetic algorithm is guided largely by the mechanisms of three operators: reproduction, crossover and mutation [8] (Fig. 3). To derive a solution to a problem, the GA initializes a single population of *n* randomly encoded chromosomes (individuals). Each chromosome corresponds to one different objective function value. The objective functions (cost values) of generated population are then evaluated. In the next step individuals represented by their associated cost are ranked and the corresponding individual fitness is received. The selection algorithm chooses individuals for reproduction on the basis of their relative fitness. Thus solutions from one population are taken and used to form a new population. Through reproduction, chromosomes representing better possible solutions (most fitted individuals) are chosen from the population. Certain function is used performing selection concordant with generation gap. Selected individuals are then recombined. To form new offspring (children),

the parents are crossed over with a crossover probability. Mutation is then applied with determinate probability. The mutation is intended to prevent falling of all solutions in the population into a local optimum of the solved problem. The crossover and mutation operators are realized to yield improved off-springs for successive generations. For the new individuals the objective function and fitness function values are again calculated. The new offspring are inserted in the population. The new generated population is used for a further run of the algorithm.

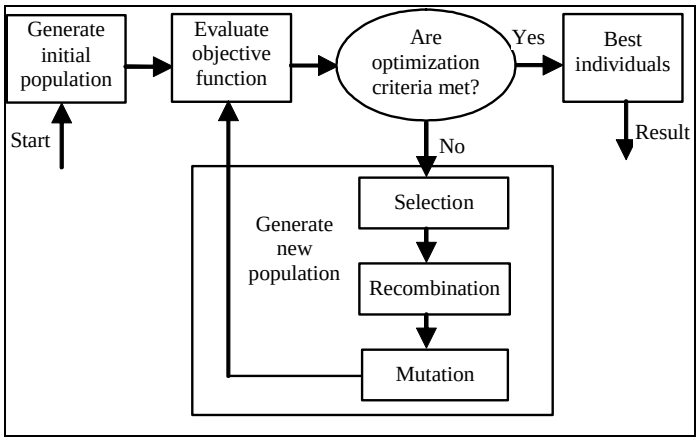

Fig. 3 Outline of the genetic algorithm

In the used here GA a binary 20 bit representation is considered Binary representation is the most common one, mainly because of its relative simplicity [5, 14]. The selection method used here is the roulette wheel selection. Crossover can be quite complicated and depends (as well as the technique of mutation) mainly on the encoding of chromosomes. A double point crossover is used here. In the accepted encoding a bit inversion mutation is used.

There are two basic parameters of genetic algorithms – crossover probability and mutation probability. Crossover rate should be high generally, about 65% – 95%. Mutation is randomly applied with low probability, typically in the range 0.01 and 0.1. The rate of individuals to be selected (generation gap) should be defined as well. Very big generation gap value does not improve performance of GA, especially regarding how fast the solution will be found. Particularly important parameters of GA are the population size and number of generations. If there are too low number of chromosomes, GA has a few possibilities to perform crossover and only a small part of search space is explored. On the other hand, if there are too many chromosomes, GA slows down. Based on results in [16, 17, 19], genetic algorithm operators and parameters for considered here PID controller parameters tuning are summarized in Table 1.

Table 1. Genetic algorithm operators and parameters

Operator	Type	Parameter	Value
encoding	binary	generation gap	0.97
crossover	double point	crossover rate	0.70
mutation	bit inversion	mutation rate	0.05
selection	roulette wheel selection	precision of binary representation	20
fitness function	linear ranking	number of individuals	200
		number of generations	200

Representation of chromosomes is a critical part of the GA application. In order to use the GA to identify controller parameters, it is necessary to encode the parameters in accordance with the method of concatenated, multiparameter, mapped, fixed-point coding [8]. Here, a chromosome is a sequence of *k*- parts each of them with **n** (encoding precision) genes. In this case the chromosome is a sequence of six parts – K_p, T_i, T_d, *b*, *c* and *N*.

The range of PID values is rationally chosen and it is true that the limitation will influence the results of the GA search; it is intended to obtain more stable, efficient and accurate solutions. For regarded problem the range of the tuning parameters is considered as follows:

K_p, T_i, T_d $\in$ [0, *inf*]; *b*, *c* $\in$ [0, 5] and *N* $\in$ [5, 1000].

Following a random initial choice, entire generation of such strings is readily processed in accordance with the basic genetic operators of selection, crossover and mutation. In particular, the selection process ensures that the successive generations of PID controller parameters produced by the GA exhibit progressively improving behavior in respect to some fitness measure.

The GA is terminated when some criteria are satisfied. To evaluate the significance of the tuning procedure and controller performance the integrated square error (I_{ISE}) criteria is used:

$$I_{ISE} = \int_0^T e^*(t)^2 \, dt \,, \tag{25}$$

where *t* is time, h; *T* – end time of the cultivation, h.

Results and discussion

On the base of the control system shown on Fig. 2 the parameters of a PID controller are tuned. For the tuning procedure a GA is applied. Using the considered objective function (Eq. (25)) a series of tuning tests are performed based on non-linear model (Eqs. (1) – (5)). For prediction of non delayed system output the model Eqs. (8) – (10) are used. Resulting optimal PID controller settings are presented in Table 2.

Table 2. Optimal controller parameters

PID controller		**Digital PID controller**	
Parameter	**Value**	**Parameter**	**Value**
K_p	0.0200	b_{i1}	0.0030
T_i	0.0368	b_d	0.0992
T_d	0.0558	a_d	0.5007
b	0.7980	*b*	0.7980
c	0.9998	*c*	0.9998
N	9.9305	*N*	9.9305
I_{ISE}	16.6943		

The results about the system performance are graphically presented in the next figures.

In Fig. 4 resulting dynamics of glucose concentration during the cultivation process is presented. As it can be seen the controller sets fast the control variable to the desire set-point of 0.1 g·l^{-1} and keep it to the end of the process. The maximum deviation from the set-point is 0.02 g·l^{-1} at time 15.8 h. Before the 14 h of cultivation the maximum deviation is 0.012 g·l^{-1}.

In Fig. 5 the control signal is presented. The control signal has not reached the actuator limitations and has not undesired oscillations with significant amplitude for the feed rate pump.

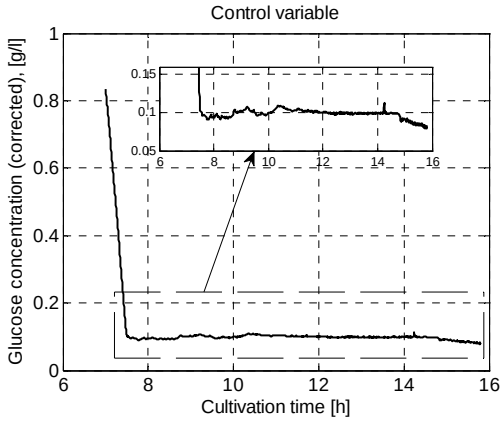

Fig. 4 Dynamics of corrected glucose concentration

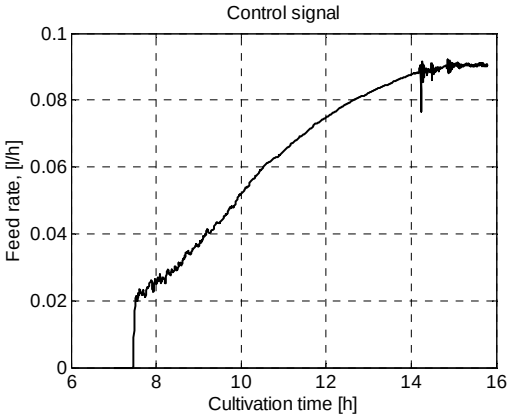

Fig. 5 Control signal

In comparison a control system based on the SP structure with universal PID controller without EKF is designed. The main deference between this system and the system on Fig. 2 is the formation of a model error. In case of the control systems with EKF (Fig. 2) the model error is formed as Eq. (20). In the case of a system without EKF the model error is formed as Eq. (12).

In Fig. 6 and Fig. 7 the resulting glucose concentration and control signal of the two control systems (with EKF and without EKF) are presented.

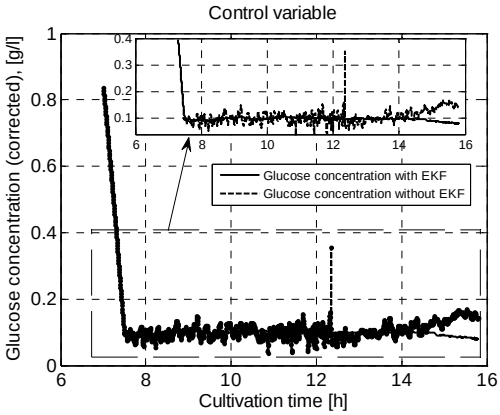

Fig. 6 Glucose concentrations for the control systems with EKF and without EKF

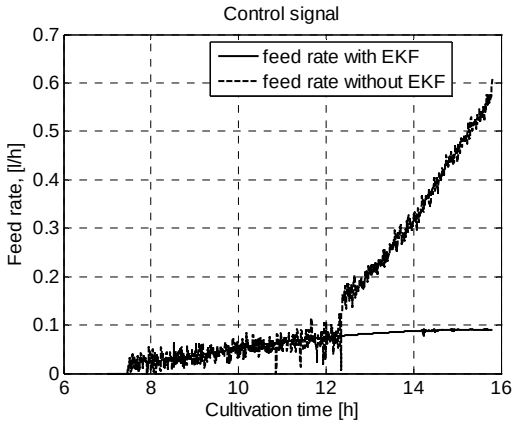

Fig. 7 Control signals for the systems with EKF and without EKF

The results show the advantages of the control system with EKF. For the system with EKF the maximum deviation from the set-point is 0.02 $g \cdot l^{-1}$ and for the system without EKF is 0.08 $g \cdot l^{-1}$. In Fig. 6 it could be seen a single peak of the maximum deviation 0.25 $g \cdot l^{-1}$for the system without EKF. Moreover, for this system oscillations of the glucose concentration for whole time are observed. In result the oscillations of the control signal are observed too (Fig. 7). After 12 h both measured and delayed glucose concentration evaluated using process model (Eqs. (8) – (10)) are decreased. It result, the ratio noise/signal in the measured glucose is increased leading to a significant increase of the model error. Thus, significant increase of

the control signal after 12 h is observed (Fig. 7). Applying the control system with EKF such effect can not be obtained.

In Fig. 8 resulting dynamics of biomass concentration for both control systems are presented. In Fig. 9 the same results for bioreactor volume are shown.

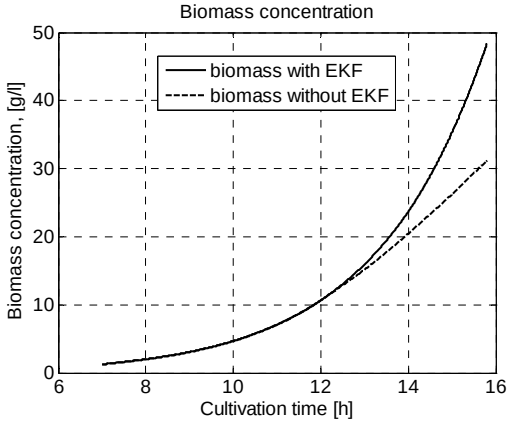

Fig. 8 Biomass concentration for the systems with EKF and without EKF

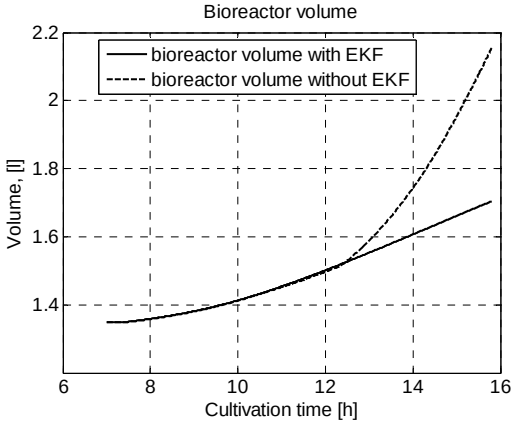

Fig. 9 Bioreactor volume for the systems with EKF and without EKF

Presented results confirmed the advantages of the control system with EKF. In this case good controller performance allows the cultivation process to be carried out for almost 16 h. At time 15.8 h the bioreactor volume is 1.7 l (for the cultivation a 2 l bioreactor is used [1]. Whereas the control system without EKF must be stopped at time 15.194 h. At this time the bioreactor volume reached the limitation of 2 l.

Based on the control system with EKF the biomass concentration at the end of the process is 48.3 $g \cdot l^{-1}$. In case without EKF the final biomass concentration is 27.4 $g \cdot l^{-1}$ (at time 15.194 h).

For the comparison of the two systems, standard deviations (σ_S) are evaluated. The resulting values are:

- for the system with EKF: σ_S = 0.0057 $g \cdot l^{-1}$;
- for the system without EKF: σ_S = 0.0246 $g \cdot l^{-1}$.

For the system with EKF four times smaller σ_S than the one for the system without EKF is obtained.

Conclusions

In this article the results of a designed feedforward feedback control systems for an *E. coli MC4110* fed-batch cultivation process are presented. The controller is used to control the glucose concentration at a desired set-point via feed rate. To reflect on time delay of glucose measurement system the SP structure with universal digital PID controller is designed. To model the time delay a correction in measurement glucose concentration is proposed. To reduce the influence of measurement noise on the glucose concentration and on the model error in SP, evaluation of model error by estimated glucose concentration instead measured one is proposed. This estimate is obtained by the designed EKF. For PID controller parameters tuning GA are applied. As a result optimal PID controller settings are obtained and good closed-loop system performance is achieved. The designed control system is

compared to the same system without EKF. The results show the advantages of the control system with EKF. For a short time the genetic algorithm tuned PID controller sets the glucose concentration (control variable) and maintains it at the desired set-point during the cultivation process. Furthermore, the control system with EKF allows carrying out the *E. coli* fed-batch cultivation process for a time 15.8 h. As a result, a high biomass concentration of 48.3 $g \cdot l^{-1}$ is obtained at the end of the process. The obtained values for the standard deviations of control variable are sufficiently small. Finally, it is demonstrated that the GA provide a simple, efficient and accurate approach of tuning the Smith predictor structure based on PID controller. Moreover, obtained results show that GA tuning can be considered as an effective methodology for achievement of high quality and better performance of the designed control system.

Appendix

The EKF gain is presented as:

$$\begin{aligned}\mathbf{K}_{\mathbf{EKF}}(k+1) &= \left[\left(\mathbf{F}(k)\mathbf{P}(k)\mathbf{F}(k)^{\mathrm{T}} + \mathbf{D}_{\boldsymbol{\eta}_\mathbf{d}}\right)\mathbf{H}^{\mathrm{T}}\right]\times \\ &\times\left[\mathbf{H}\left(\mathbf{F}(k)\mathbf{P}(k)\mathbf{F}(k)^{\mathrm{T}} + \mathbf{D}_{\boldsymbol{\eta}_\mathbf{d}}\right)\mathbf{H}^{\mathrm{T}} + D_{\xi}\right]^{-1},\end{aligned} \tag{A-1}$$

where: $\mathbf{P}(\cdot)$ is the covariance matrix; $\mathbf{F}(k)$ – the Jacobian of nonlinear function $\mathbf{f}_\mathbf{d}\left(\mathbf{x}(k)\right)\big|_{\mathbf{x}(k)=\hat{\mathbf{x}}(k)}$.

The noise covariance matrixes have the following forms:

$$\mathbf{D}_{\boldsymbol{\eta}\mathrm{d}} = T_0^{\,2}\begin{bmatrix} 0.001 & 0 & 0 & 0 \\ 0 & 0.001 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0.05 \end{bmatrix},\ D_{\xi} = 0.0025, \tag{A-2}$$

where: $\mathbf{D}_{\boldsymbol{\eta}_\mathbf{d}}$ is covariance matrix of discrete-time process noise $\boldsymbol{\eta}_\mathbf{d}(k) = T_0\boldsymbol{\eta}(t)$; D_{ξ} – the covariance of measurement noise.

The $\mathbf{P}(\cdot)$ and $\mathbf{F}(k)$ are obtained from:

$$\mathbf{P}(k+1) = \left(\mathbf{I} - \mathbf{K}_{\mathbf{EKF}}(k+1)\mathbf{H}^{\mathrm{T}}\right)\left(\mathbf{F}(k)\mathbf{P}(k)\mathbf{F}(k)^{\mathrm{T}} + \mathbf{D}_{\boldsymbol{\eta}_\mathbf{d}}\right), \tag{A-3}$$

$$\mathbf{P}(0) = \mathrm{diag}(0.02 \quad 0.02 \quad 0 \quad 10), \tag{A-4}$$

$$\mathbf{F}\left(\hat{\mathbf{x}}(k)\right) = \mathbf{I}_4 + T_0\boldsymbol{\Phi}\left(\hat{\mathbf{x}}(k)\right), \tag{A-5}$$

where

$$\boldsymbol{\Phi}(\hat{\mathbf{x}}(k)) = \begin{bmatrix} a_{11} & a_{12} & a_{13} & a_{14} \\ a_{21} & a_{22} & a_{23} & a_{24} \\ 0 & 0 & a_{33} & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}, \tag{A-6}$$

$$a_{11} = \frac{\hat{\mu}_{\max}(k)\hat{S}(k)}{k_S + \hat{S}(k)} - \frac{F(k)}{\hat{V}(k)},\ a_{12} = \frac{\hat{X}(k)\hat{\mu}_{\max}(k)\left(k_S + \hat{S}(k)\right) - \hat{X}(k)\hat{\mu}_{\max}(k)\hat{S}(k)}{\left(k_S + \hat{S}(k)\right)^2},$$

$$a_{13}=\frac{F(k)\hat{X}(k)}{\hat{V}^2(k)},\ a_{14}=\frac{\hat{X}(k)\hat{S}(k)}{k_S+\hat{S}(k)},\ a_{21}=-\frac{\hat{\mu}_{\max}(k)\hat{S}(k)}{Y_{S/X}\left(k_S+\hat{S}(k)\right)},$$

$$a_{22}=-\frac{F(k)}{\hat{V}(k)}+\frac{\hat{X}(k)\hat{\mu}_{\max}(k)\hat{S}(k)-\hat{X}(k)\hat{\mu}_{\max}(k)\left(k_S+\hat{S}(k)\right)}{Y_{S/X}\left(k_S+\hat{S}(k)\right)^2},$$

$$a_{23}=-\frac{F(k)\left(S_{in}-\hat{S}(k)\right)}{\hat{V}^2(k)},\ a_{24}=\frac{\hat{X}(k)\hat{S}(k)}{Y_{S/X}\left(k_S+\hat{S}(k)\right)},\ a_{33}=-\frac{F(k)}{\hat{V}^2(k)}.$$

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