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Unified Structure of Adaptive System for Control of Basic Process Variables in Biotechnological Cultivation Processes: pH Control System Case Study

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A unified scheme for control of the important bioprocess variables is proposed in this case study. The scheme includes feedback PI controller, controller adaptation algorithm based on statistical characteristic of the controlled variable, and feedforward compensator. In this case study, an adaptive pH control system is investigated. The adaptation algorithm analyses statistical characteristic of the controlled variable in on-line mode and performs adaptation of the controller's parameter when dynamics of the control channel has changed. The feedforward compensator employs oxygen uptake rate estimates to compensate system's load disturbances related to the time-varying biomass growth rate and biomass concentration in the bioreactor. Simulation runs of the pH control system have demonstrated that the proposed unified control scheme can increase performance of the control system.

1. Introduction

The modern food, chemical and pharmaceutical industry walk hand in hand with biotechnology. Production of various recombinant proteins makes a big part among pharmaceutical ingredients. These processes can be described as nonlinear and nonstationary, making modeling and control a complicated control engineering task (Galvanauskas et al., 2019). In the biotechnology industry this is even more challenging due to strict safety regulations and operational constraints (Boudreau et al., 2007, Dochain, 2008, Schuler et al., 2012). Therefore, often application of complex and time-consuming mathematical models for off-line optimization, indirect state estimation and optimal online control is required. On the other hand, control systems should use mathematical models as simple as possible to avoid high computer resource usage and numerical problems.

High quality control of pH is difficult because of many reasons: very strong nonlinearity of biochemical processes, titration curves and pH measurement itself, high sensitivity of the microorganisms even to small temporary deviations of pH level in the cultivation media, and drift of the pH sensors (Carr-Brion, 1991, McMillan et al., 2005). The academic community has proposed various PID controller parameter tuning approaches for high-quality pH control. Nevertheless, most of them suffer from the drawbacks already described (Henson et al.,1994, Ylöstalo et al., 2001, Nsengiyumva et al., 2018), such as complex controller design, huge time investments for development, expensive hardware, or many tuning parameters. On the other hand, well-functioning pH control systems can be used to monitor biological reaction rates (Siano, 1995). Therefore, it is of primary importance to elaborate simple, robust, and easy to implement methods for precise pH control.

In this paper, the performance of a simple and innovative pH adaptive control system, which does not require additional hardware and software as compared to the ordinary control systems implemented in commercial controllers is investigated.

2. Mathematical model for pH control simulation

In this study, a mathematical model (Galvanauskas, 2009) was used to simulate the biotechnological process. The process PI&D is presented in Figure 1. This study focuses on the adaptive pH control loop marked as QC4.

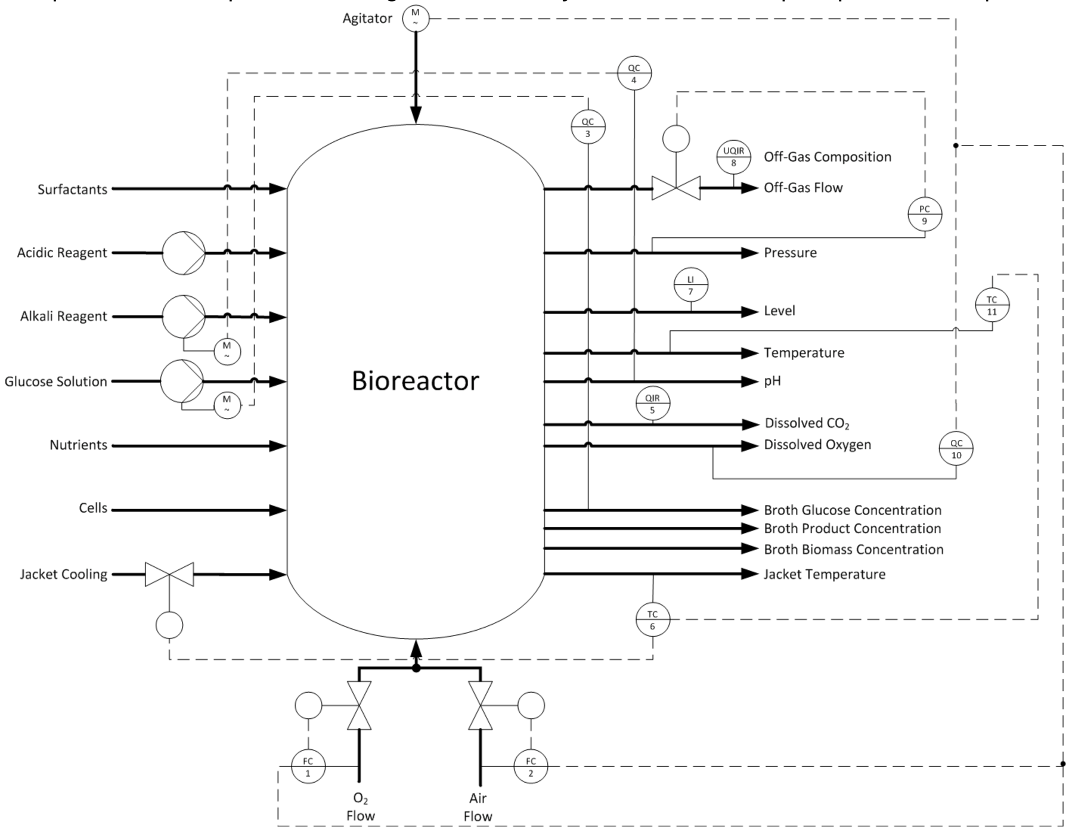

Figure 1: Basic control system loops for a typical microbial cultivation process (Galvanauskas et al., 2019).

The main control variable in the analysed system is the pH level of the medium. pH can be described as the concentration of free hydrogen-ions as

$$pH = -\log_{10} C_{H^+} \tag{1}$$

where C_{H^+} is the concentration of hydrogen-ions in the cultivation medium. Concentration of hydrogen-ions in a fed-batch cultivation process can be modelled considering influence of bacterial growth, addition of acid and alkali solutions during pH control and dilution effects:

$$\frac{dC_{H^+}}{dt} = (\alpha_1 \mu x + \alpha_2 x) + \frac{F_{pH}(C^0_{H+} - C_{H^+})}{V} - \frac{F_s C_{H^+}}{V} \tag{2}$$

where C^0_{H+} is the concentration of hydrogen-ions in the alkali solution. This concentration can differ from the one calculated theoretically and is subject to model-based identification. *x* – biomass concentration in the cultivation medium, g/l; *μ* – biomass specific growth rate, 1/h; F_{pH} – flow of the alkali solution for pH control, l/h; *Fs* – flow of the feeding solution, l/h; *V* – cultivation medium volume, l; α_1, α_2 – model parameters to be identified from experimental data.

The initial value $C_{H^+}(0)$ is equal to 10^{-7} mol/l, and this level corresponds to pH 7. The biomass growth in the fed-batch process can be modelled by means of the differential equation:

$$\frac{dx}{dt} = \mu x - \frac{F_s + F_{pH}}{V} x \tag{3}$$

Oxygen uptake rate (OUR) is modelled as follows:

$$OUR = \beta_1 \mu x V + \beta_2 x V \tag{4}$$

where β_1 ,β_2 are model parameters that need to be identified from experimental data.

Additionally, for the simulation purposes, the model for evaluation of feeding solution flow is described as:

$$F_s = \frac{\mu_{set} x V}{Y_{xs} S_0} \tag{5}$$

where S_0 – substrate concentration in the feed, g/l; Y_{xs} – biomass/substrate yield coefficient, g/g.
In this study, $\mu = \mu_{set}$, since the real specific growth rate is not measured directly, and the process is controlled under substrate limitation conditions. Values of the model parameters are given in Table 1.

Table 1: Values of the model (1)-(5) parameters.

Parameter	Value	Parameter	Value
Model parameter α_1	$0.422 \cdot 10^{-7}$ mol/g	Initial biomass concentration	2 g/l
Model parameter α_2	$0.011 \cdot 10^{-7}$ mol/g	Initial hydrogen-ions concentration	10^{-7} mol/l
Model parameter β_1	0.8646 g/g	Initial medium volume	5 l
Model parameter β_2	0.0180 g/gh	Substrate concentration in feed S_0	450 g/l
Biomass/substrate yield coefficient Y_{xs}	0.52 g/g	pH setpoint	7

As the real measurements of pH and OUR are corrupted by noise, the measurements in this simulation study were simulated by adding white Gaussian noise:

$$c_{el\_m}(k) = c_{el}(k) + \sigma \cdot Randn \tag{6}$$

where c_{el_m} is the measured value of pH or OUR; σ is standard deviation estimated from real measurements (σ= 0.1 % in the analysed case), $Randn$ is a number from Gaussian random numbers sequence with zero mean and unit variance; k denotes an index of discrete measurement point. Time discretization step of the adaptation and the control algorithms is set to $\Delta t = 0.18\ s$.
In the simulation experiments, time profile of the biomass specific growth rate variation, presented in Figure 2, is chosen to simulate close to realistic operating conditions in fed-batch cultivation process. In this study, the specific growth rate μ was maintained constant at 0.5 1/h. To simulate a system malfunction (feeding pump failure or negative influence of the antifoam agent addition), it was reduced to 0.1 1/h for 0.2 h every 2 hours starting from the 1st hour of the cultivation process.

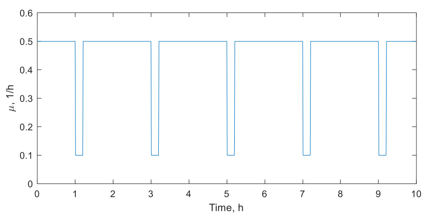

Figure 2: Specific growth rate μ trajectory during a simulation run.

3. Adaptation of PI controller parameters based on feedback signal statistical analysis

Previous studies of pH control systems in bioreactors have shown that due to changes in the process dynamics, it would be appropriate to adapt the parameters of the PI controller, especially the integral time constant T_i, that was proven to be the main tuning parameter that depends on the process load. The optimal value of the control parameter K_r depends only on the culture broth volume, that does not change significantly during the process (Galvanauskas 2009). The adaptation of the controller parameter T_i is based on statistical analysis of the feedback signal of the system. In the controller adaptation algorithm, the average value of the error of the feedback signal c_{ave} is calculated on-line from a moving window:

$$c_{ave}(k) = \frac{1}{n} \sum_{i=k-n}^{k-1} c_{el}(i) \tag{7}$$

$$O_{ff\_set}(k) = c_{set} - c_{ave}(k) \tag{8}$$

where *n* is the moving window length that is subject to model-based optimisation. c_{el} is the feedback signal value and c_{set} is the setpoint value.
Additionally, the average absolute deviation is calculated from the feedback signal:

$$D_{abs\_ave}(k) = \frac{1}{n}\sum_{i=k-n}^{k-1}|c_{el}(i) - c_{ave}(k)| \tag{9}$$

The above statistical parameters are applied for on-line tuning of the controller integration constant T_i using the following rule:

$$\begin{aligned}&IF\left|O_{ff\_set}(k)\right| > O_{max}\ OR\ \ D_{abs\_ave}(k) > D_{max}\ THEN\ T_i\ (k) = T_i\ (k-1)\left(1 - a_1 O_{ff\_set}(k)\right)\\&ELSE\ T_i\ (k) = T_i\ (k-1)\end{aligned} \tag{10}$$

where a_1, O_{max} and D_{max} are tuning parameters and are subject to model-based optimization. Controller gain K_r was not changed and held constant during the controlled process. Block-diagram of the adaptive pH control system is presented in Figure 3.

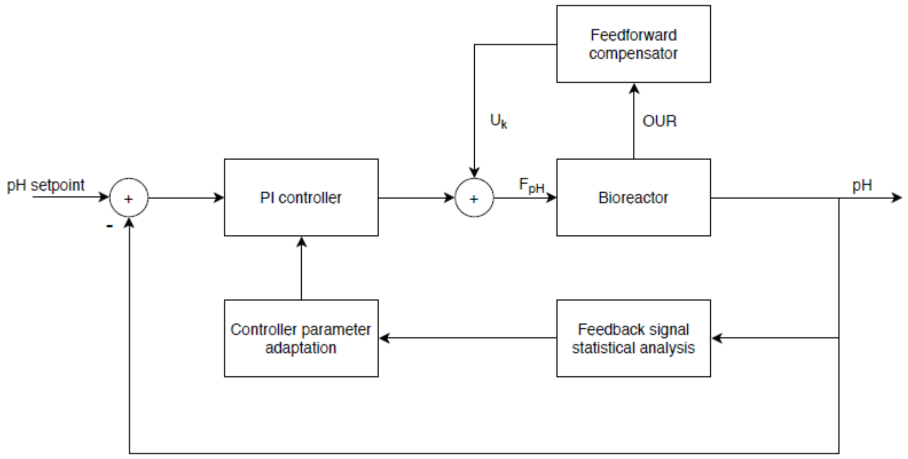

Figure 3: Block-diagram of the adaptive pH control system

To account for the variation of the bioprocess state, the adaptive PI controller is additionally supported by a feedforward compensator block (Di Capaci et al., 2017), which produces control action based on the OUR online estimation. Basic changes in the bioprocess state can be reflected by OUR, that also correlates well with the dynamic of the system. This signal can be used as a basis for the feedforward compensation block in the proposed hybrid adaptive control. Currently, the industrial bioreactors are equipped with affordable and reliable off-gas composition (O_2, CO_2) and aeration gas flow rate measurement devices. This allows on-line estimation of the OUR signal. The feedforward compensator can be described as follows:

$$U_k = a_2 OUR \tag{11}$$

where a_2 is a tuning parameter that can be calculated from other model parameters and manually tuned.
The feedforward part defines the main part of the control signal, and the PI output signal is used for more precise tracking of the set pH value. The feedforward part of the control algorithm alone cannot assure sufficiently precise pH setpoint tracking under real conditions due to occurring unpredictable metabolic shifts within the culture. The feedforward part is also inefficient because it cannot compensate large transients caused by the disturbances, even when used with a standard PI algorithm. There are various possible technological or specific growth control-related reasons why pH set-point can change or be manipulated, and system malfunctions could be one of them. It should be considered that manipulating the pH set-point during the controlled process distorts the data in moving window and, therefore, the statistical parameter estimates as well. Since these values are used for the controller parameter adaptation, the adaptive control system based on feedback signal statistical parameters is preferable to control the pH at constant set-point only.

A suitable width of moving window and the value of the coefficient a_1 in the tuning rule (10) was determined from early simulation experiments by evaluating the IAE criterium with different parameter values. Different widths of the moving window *n* were tested. Optimal values of the tuning parameters are given in Table 2.

Table 2: Values of the control system tuning parameters

Parameter	Value
Controller gain K_r	6.6 h/l
Width of moving window n	2.7 s
a_1	0.0205
a_2	0.8174 l/g
O_{max}	0.0001
D_{max}	0.0015

4. Results and discussion

The simulation results show that the investigated pH control system with the properly selected values of the tuning parameters provides reliable adaptation of controller integration parameter T_i and stable performance. Simulation results, including trajectories of OUR (Figure 4a), alkali solution addition rate (Figure 4c), and adaptation of the controller tuning parameter T_i (Figure 4b) are shown in Figure 4. For comparison, performance of the standard PI control system with constant parameters (tuned to minimize the IAE criterion) is presented in Figure 4d.

The adaptive control system tended to perform better at disturbance rejection, where the adaptive controller reduced the IAE criterion almost 2.5 times (Table 3).

Table 3: Comparison of the adaptive and standard control system performance

Control type	IAE	
	Standard PI	Adaptive PI
Disturbance rejection	0.00408	0.001662
Setpoint tracking and disturbance rejection	0.01261	0.009852

Analysis of the simulation results (Figures 5a and 5b) shows that in the late phases of the cultivation process the adaptive controller decreases the overshoot by approx. 80 % in the adaptive system. Such a reduction in pH fluctuations is very important for cultivation process monitoring algorithms, where the rate of carbon dioxide production rate, CPR, is used to monitor the state of the process and the fluctuations in pH can cause drastic changes in CPR estimates. These disturbances can occur due to temporary substrate feeding disruption, faults of the bioreactor aeration or mixing systems or sudden metabolic shifts. The presented results prove efficiency of the pH adaptive control system and potential of implementation in industrial controllers.

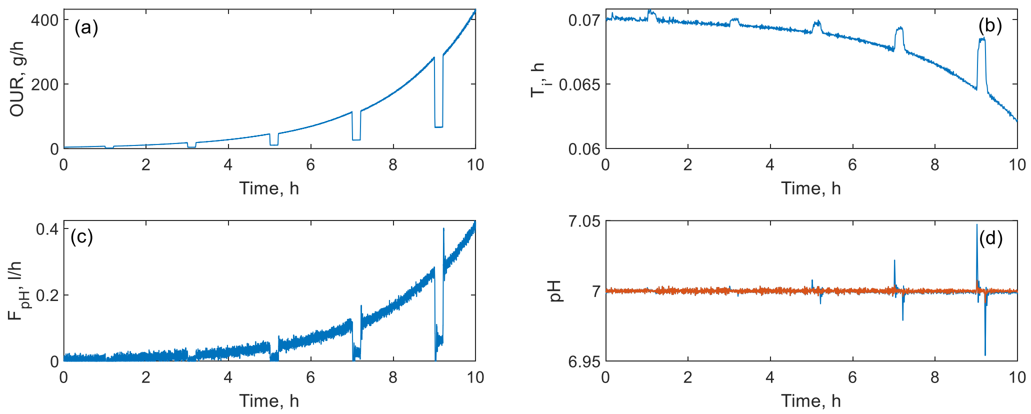

Figure 4: Adaptive control system output: (a) time profile of OUR, (b) adaptation of T_i controller parameter, (c) feeding solution rate (control variable), (d) comparison of the adaptive (–) and standard (–) PI controller performance

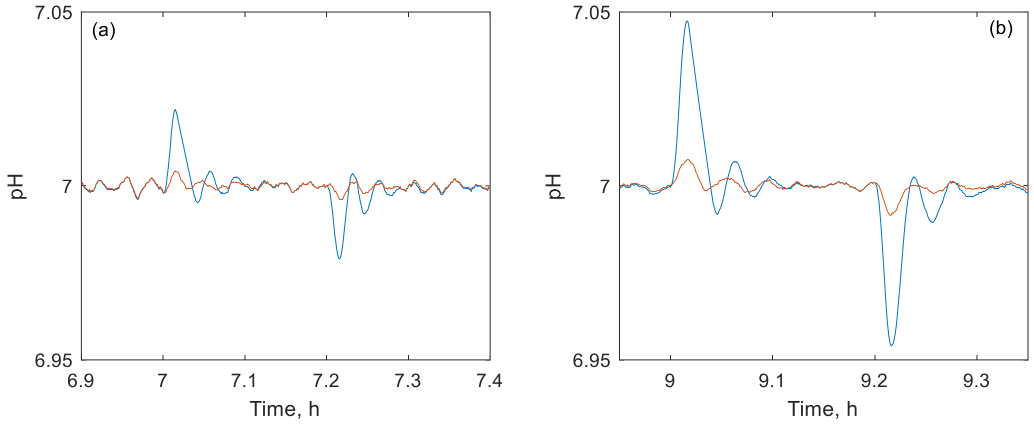

*Figure 5: Transient processes of pH during a simulation run - disturbance rejection when using adaptive (**–**) and standard (**–**) PI controller*

5. Conclusions

The developed simple adaptive PI control system has been investigated for controlling pH in a fed-batch fermentation process. The control system remained stable and showed improvements of the pH control accuracy in comparison with the standard PI control system with fixed controller parameters.

The adaptive control system based on the statistical analysis of the feedback signal can be easily implemented in many commercial controllers. It can be applied for controlling pH at steady set-point in standard fed-batch fermentation processes under ordinary conditions. The application of the proposed adaptive control system with feedforward compensator can be extended to control of other basic process variables of biotechnological cultivation processes.

Acknowledgments

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