Different control strategies for a yeast fermentation bioreactor

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Abstract: Biological systems are usually highly sensitive to process conditions variations, such as temperature, pH, substrate concentration. For this reason, it is important to adequately control and monitor the process in order to guaranteeing product quality while maintaining adequate performance and productivity. The production of ethanol by fermentation is certainly one of the most important industrial bioprocesses, being ethanol an alternative source of energy. For this reason, valuable models of this process based on different kinetic considerations are available in literature, and they can be considered a valid benchmark to investigate control system and estimation techniques for biological reactors. Three different control strategies have been analysed: direct reactor temperature control, cascade control where the primary loop uses delayed ethanol measurements, and 2x2 control system with inferential control for the product concentration. The proposed configurations have been compared at different operating conditions and results show that the use of the inferential control is the most effective in case of severe disturbances.

Keywords: Bioreactor, extended Kalman filter, inferential control, cascade control, delayed measurement

1. INTRODUCTION

The need of monitoring and control systems for biological processes have become important due to the quality requirements imposed on the products, combined with constraints related to performance and productivity of the plants (Gomes et al., 2019). Design of a control system for biological processes is not an easy task due to model uncertainties, nonlinear nature of the system and slow response of the process. The complexity of biological processes is mostly due to the presence of living organism and their metabolism is sensitive to process conditions, such as temperature, pH, substrate concentrations (Spigno and Tronci, 2015). Furthermore, the lack of suitable and robust on-line sensors for measurement of biomass or product concentration makes more difficult the obtainment of an efficient control of biological processes. Soft sensor is an alternative to hardware sensor, through which available on-line measurements are used in conjunction with a process model and an estimation algorithm to estimate unmeasured variables (Lisci et al., 2020a).

Among the several biological processes, ethanol production through fermentation is surely one of the most investigated. Bioethanol represents the cleanest fuel alternative to fossil fuels and it can be obtained from different sources such as agro-food residues, municipal waste or dedicated energy crops which are collectively called “biomass”. Most of the worldwide production of ethanol occurs through fermentation and although in recent years many advances have been made in ethanol fermentation technology, there are still significant challenges that need further investigations (Lin et al., 2006).

A model of the process for a continuous reaction has been proposed in Nagy (2007) and it constitutes an effective benchmark to evaluate control and state estimation strategies. Starting from the neural network based control of the reactor temperature developed by Nagy (2007), other linear and nonlinear control techniques have been proposed by several authors, evidencing that the control problem for this system is not trivial. Imtiaz et al. (2013) developed a temperature controller using inverse neural networks. A robust model-based predictive control with integral action was presented in Bakošová et al. (2019), showing that the developed method can ensure high product yield and minimize energy consumption. Recently, Pachauri et al. (2017) compared a conventional PID with a modified factional order IMC-PID and they demonstrated that the new algorithm was more robust and efficient in comparison with other designed controllers. An IMC-PID controller was successfully applied by Kumar et al. (2019), where an identification tool was used to obtain the input-output transfer function between reactor temperature and manipulated variable. A MIMO control system was presented in Imtiaz et al. (2014), where a nonlinear auto regressive moving average controller was applied to control reactor temperature, and a two degree of freedom PID was used to control pH and dissolved oxygen concentration.

In this paper the problem of control for the fermentation bioreactor proposed by Nagy (2007) is considered and solved with a classical PI algorithm, which is usually well accepted by plant operators. The linear algorithm is able to lead to the same results shown by more sophisticated methods, like neural networks. Furthermore, as a step ahead with respect to previous papers, the product concentration is also controlled, using two different approaches. A cascade control is developed, where the master is the ethanol concentration controller that gives the set-point to the temperature controller. In this case, available delayed measurement concentrations can be used to improve the process performances and assure that system is able to guarantee the required ethanol productivity for different disturbances entering the system. Then, using a state estimator for inferring product concentration, a MIMO system is developed, where both temperature and concentration are controlled. In this case, the convergence of the controlled concentration is related to the convergence of the estimator.

2. BIOREACTOR MODEL

The system investigated in the present paper is the same proposed in Nagy (2007), and it describes the dynamic behaviour of six states, which are biomass concentration (C_X), ethanol concentration (C_P), substrate concentration (C_S), dissolved oxygen concentration $\left(C_{O_2}\right)$, reactor temperature (T_r), and jacket temperature $\left(T_{ag}\right)$, as reported in Eqs. (1-6).

$$\frac{dC_X}{dt} = \mu_X\, C_X\, \frac{C_S}{K_S+C_S} e^{-K_P C_P} - \frac{F_e}{V} C_X \tag{1}$$

$$\frac{dC_P}{dt} = \mu_P C_X \frac{C_S}{K_{S1}+C_S} e^{-K_{P1} C_p} - \frac{F_e}{V}\, C_P \tag{2}$$

$$\frac{dC_S}{dt} = -\frac{1}{R_{SX}} \mu_X C_X \frac{C_S}{K_S+C_S} e^{-K_P C_P} - \frac{1}{R_{SP}} \mu_P C_X \frac{C_S}{K_{S1}+C_S}\, e^{-K_{P1} C_P} + \frac{F_i}{V} C_{S,in} - \frac{F_e}{V} C_S \tag{3}$$

$$\frac{dC_{O_2}}{dt} = k_l a \left(C_{O_2}^* - C_{O_2}\right) - \mu_{O_2} \frac{1}{Y_{O_2}} C_X \frac{C_{O_2}}{K_{O_2}+C_{O_2}} \tag{4}$$

$$\frac{dT_r}{dt} = \left(\frac{F_i}{V}\right)(T_{in} + 273) - \left(\frac{F_e}{V}\right)(T_r + 273) - \mu_{O_2} \frac{1}{Y_{O_2}} C_X \frac{C_{O_2}}{K_{O_2}+C_{O_2}} \frac{\Delta H_r}{32\, \rho_r\, C_{heat,r}} - \frac{K_T A_T\,(T_r - T_{ag})}{V\, \rho_r\, C_{heat,r}} \tag{5}$$

$$\frac{dT_{ag}}{dt} = \left(\frac{F_{ag}}{V_j}\right)\left(T_{in,ag} - T_{ag}\right) + \frac{K_T A_T (T_r - T_{ag})}{V_j \rho_{ag} C_{heat,ag}} \tag{6}$$

A detailed description of the model, parameters values and nominal conditions have not been reported for the sake of brevity, but they can be found in Nagy (2007), as well as the relationships to calculate the equilibrium oxygen concentration $(C_{O_2}^*)$, which is a function of temperature and ionic strength, the mass transfer coefficient $(k_l a)$ and the specific growth rate (μ_X) as temperature functions.

Introducing the state vector $\boldsymbol{x} = \left[C_X, C_P, C_S, C_{O_2}, T_r, T_{ag}\right]$, output measured vector $\boldsymbol{y}$ defined later (Section 3), and the inputs $\boldsymbol{u} = [F_i, F_{ag}]$, the system dynamics can be compactly written as

$$\frac{dx}{dt} = \boldsymbol{f}(\boldsymbol{x}, \boldsymbol{u}) \tag{7}$$

$$\boldsymbol{y} = \boldsymbol{h}(\boldsymbol{x}) \tag{8}$$

where $\boldsymbol{f}(\boldsymbol{x}, \boldsymbol{u})$ is the vector field of the system and $\boldsymbol{h}(\boldsymbol{x})$ is the vector relating states and measured outputs.

3. CONTROL SYSTEM DESIGN

The quality of final products is an essential parameter to be controlled in the bioreactor. The objective of the controller is to achieve the desired concentration as early as possible in the presence of disturbances. This task has been solved by studying different situations with respect to measured outputs. First, only temperature measurements (reactor and cooling agent) are considered available, and the output vector is $\boldsymbol{y}_I = \left[T_r(t), T_{ag}(t)\right]$. As second possible options, ethanol concentration is available with delay due to the time required by the analyser to perform the measurement, and the output vector is $\boldsymbol{y}_{II} = \left[C_P(t - t_d), T_r(t), T_{ag}(t)\right]$. The final case is when substrate and oxygen concentration can be measured online along with temperature, and the output vector is $\boldsymbol{y}_{III} = \left[C_S(t), C_{O_2}(t), T_r(t), T_{ag}(t)\right]$. Substrate and dissolved oxygen concentration measurements have been considered online, without delay, according to a previous study (Lisci et al., 2020a-b) and a review on the available sensors for biosystems (Holzberg et al., 2018).

3.1 Controllability

Controllability of a *n*-dimensional linear system, *m* inputs and *l* outputs in the form (9) can be assessed by considering the controllability matrix $\boldsymbol{L_c}$ (10)

$$\frac{dx}{dt} = \mathbf{A}\boldsymbol{x} + B\boldsymbol{u}, \boldsymbol{y} = C\boldsymbol{x}, \boldsymbol{x} \in \Re^n, \boldsymbol{u} \in \Re^m, \boldsymbol{y} \in \Re^l \tag{9}$$

$$L_c = [\mathbf{B}\ \mathbf{AB}\ \mathbf{A}^2\mathbf{B} \ldots\ \mathbf{A}^{n-1}\mathbf{B}] \tag{10}$$

This definition can be used to assess local controllability of a nonlinear system if **A** is the Jacobian matrix calculated at the reference conditions and the coefficients of **B** are the derivative of the functions describing the dynamics of the states with respect to the inputs. Controllability is verified if the rank of matrix $\mathbf{L}_c$ is equal to the dimension of the state vector. By taking the Jacobian matrix of (1-6), it is possible to verify that the system is locally controllable when coolant and inlet flow rates, F_{ag} and F_i, can be both manipulated. The system is still locally controllable when only F_{ag} is manipulated because kinetic parameters and mass transfer coefficient depends on reactor temperature.

3.2 Observability

Real-time information about concentration of product, substrate and biomass is the key to controlling and optimizing the bioreactor. When these variables are not measured online, soft sensors can be used to obtain information on their dynamics if observability is satisfied.

Observability of a *n*-dimensional linear system, *m* inputs and *l* outputs in the form (9) can be assessed by considering the observability matrix $\boldsymbol{L_o}$ in Eq. (11)

$$\boldsymbol{L_o} = [\mathbf{C}\ \mathbf{CA}\ \mathbf{CA}^2 \ldots\ \mathbf{CA}^{n-1}]^T \tag{11}$$

In case that only temperature measurements are available, the system is not observable therefore it is not possible to reconstruct the dynamics of all the states. Local observability is satisfied when the output vector $\boldsymbol{y}_{III}$ is considered, as reported in Lisci et al. (2020a-b).

3.3 Temperature control

Because of the controllability property, it is theoretically possible to drive the system to the required conditions for all the six states by using only one manipulated variable. When considering that only temperature measurements are available, the first proposed solution is to design a temperature controller using the coolant flow rate as manipulated variable. Temperature set-point has been selected such that the required product composition has been obtained. A PI from IMC (Internal Model Control) algorithm (Skogestad, 2003) has been used to control the output and a step-response identification method has been applied to obtain the input-output model. A first-order-plus-time-delay has been used to represent the data.

3.4 Cascade control with concentration delayed measurements

Even if controllability is satisfied, some changes in the process conditions (disturbances) may cause a discrepancy between the desired species concentration and actual values even if temperature is maintained at set-point. In this case it could be useful to add another control loop that guarantees the respect of product quality. Indeed, this variable generally influences the successive separation process. The delayed ethanol concentration measurement has been used in a cascade arrangement, where the outer loop exploits a discrete regulator to keep the product concentration around a desired value, while the inner loop guarantees that the bioreactor temperature was maintained at a predetermined set-point. The delay in the composition measurements of the product has been included in the simulation so that the updated C_P value was available only after 18 minutes. The use of a cascade control guarantees a faster response because temperature measurement is continuously available, while the outer loop reduces when necessary the offset for the ethanol concentration.

3.5 Inferential control

When ethanol concentration measurement is not available online, but the system is observable, that is the case of measured output $\boldsymbol{y}_{III}$, inferential control can be used to ensure product quality. The strategy used in the present work has been developed by using the state estimator reported in Lisci *et al.* (2020b). The ethanol concentration has been inferred by applying the extended Kalman filter, which is one of the most widely used estimation techniques for monitoring bioprocess (Dewasme et al., 2013). The estimated value has been used in a classical feedback control strategy manipulating the inlet flow rate. This control solution has two loops, one for ethanol composition and the other for reactor temperature.

4. STATE ESTIMATION

The development of a state estimation for the bioreactor in (1-6) has been discussed in previous papers by the authors (Lisci *et al.*, 2020a-b). For sake of clarity, the obtained estimator structure is here reported. The estimated states have been partitioned in innovated ($\hat{\boldsymbol{x}}_i$) and not innovated ($\hat{\boldsymbol{x}}_u$) states (12-15), defined in (16), following the procedure reported in Salas et al (2019). In more details, the innovated states are dynamic states of the estimation model whose changes are captured by the secondary measurements (Eq.12), while the not innovated states are inferred by the estimation model in an open loop mode (Eq.13) (Porru and Özkan, 2017).

$$\frac{d\hat{x}_i}{dt} = \boldsymbol{f}_i(\hat{\boldsymbol{x}}_i, \hat{\boldsymbol{x}}_u, \boldsymbol{u}) + \boldsymbol{K}(\boldsymbol{y} - \hat{\boldsymbol{y}}), \hat{\boldsymbol{x}}_i(t_0) = \hat{\boldsymbol{x}}_{i,0} \quad (12)$$

$$\frac{d\hat{x}_u}{dt} = \boldsymbol{f}_u(\hat{\boldsymbol{x}}_i, \hat{\boldsymbol{x}}_u, \boldsymbol{u}), \hat{\boldsymbol{x}}_u(t_0) = \hat{\boldsymbol{x}}_{u,o=0} \quad (13)$$

$$K = \boldsymbol{P}(t)\boldsymbol{H}^T\boldsymbol{R}^{-1} \quad (14)$$

$$\dot{\boldsymbol{P}}(t) = \boldsymbol{P}(t)\boldsymbol{F}(t) + \boldsymbol{F}^T(t)\boldsymbol{P}(t) + \boldsymbol{Q}(t) -$$

$$\boldsymbol{K}(t)\boldsymbol{H}(t)\boldsymbol{P}(t), \boldsymbol{P}(t_0) = \boldsymbol{P}_0 \quad (15)$$

$$\hat{\boldsymbol{x}}_i = \left[\hat{C}_X, \hat{C}_S, \hat{C}_{O_2}, \hat{T}_r, \hat{T}_{ag}\right], \hat{\boldsymbol{x}}_u = \left[\hat{C}_P\right] \quad (16)$$

$\boldsymbol{F}(t)$ is the Jacobian of the vector field $\boldsymbol{f}_i(\hat{\boldsymbol{x}}_i, \hat{\boldsymbol{x}}_u, \boldsymbol{u})$, calculated with respect to the innovated states, $\boldsymbol{P}(t)$ is the error covariance matrix of the innovated states, $\boldsymbol{H}(t)$ is the matrix of the derivative of the map $\boldsymbol{h}$ with respect to the states, **Q** and **R** are, respectively, the covariance matrix of the model and measurements errors (Jazwinski, 2007). The constant matrix **Q**, **R**, and $\mathbf{P}_0$ are tuning parameters of the estimation model and they have been calculated minimizing the error between the states calculated with the simulated plant and the estimator along a reference trajectory.

As reported in Lisci *et al.* (2020a), the estimator is more robust and efficient with the selected configuration with respect to the use of a full order structure (all states are innovated). It has been demonstrated that ethanol concentration trajectory is well reconstructed by the EKF even if it is not innovated and it can be used to design an inferential control.

5. PERFORMANCE INDEXES

In order to optimize the choice of the best control structure among those proposed here, the time-integral performance criteria have been used. In particular, the integral of the squared error (ISE), the integral of the absolute value of the error (IAE) and the integral of the time-weighted absolute error (ITAE) have been calculated to compare the performance of the analysed control structures. The indexes have been calculated using the following equations (17):

$$ISE = \int_0^\infty e^2(t)dt, IAE = \int_0^\infty |e(t)|dt, ITAE = \int_0^\infty t|e(t)|dt \quad (17)$$

Because the goal of the control structure is to obtain the desired ethanol concentration, *e(t)* is the error signal obtained as the difference between the required ethanol concentration and the output signal.

6. RESULTS

This section analyses and compares the performance of different designed controllers for disturbance rejection. Three different control strategies are compared: (i) reactor temperature control (SISO system), (ii) cascade control using ethanol delayed measurements where temperature control is the secondary loop, (iii) inferential control for ethanol concentration and reactor temperature control (2x2 MIMO system). In the simulations, step variations of the following three inputs have been considered as disturbances: the inlet temperature (T_{in}); the substrate inlet concentration ($C_{s,in}$); the biomass specific growth rate (μ_X) in order to simulate a hypothetical pH variation. The steps used to excite the system are reported in Figure 1. For sake of brevity, the results obtained when inlet temperature has been changed is only reported in terms of performance indexes (Tables 1-3). Inlet temperature variations have a smaller effect on the ethanol composition than the other disturbances. Indeed, when T_{in} varies, the SISO configuration with only feedback temperature controller is able to maintain the ethanol concentration at the required set-point.

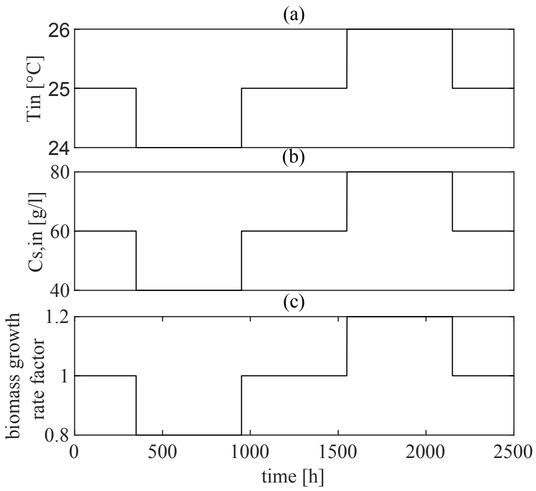

Figure 1. Disturbance trajectories used to analyse the control for the three runs: inlet temperature (a), substrate inlet concentration (b), and biomass growth factor (c).

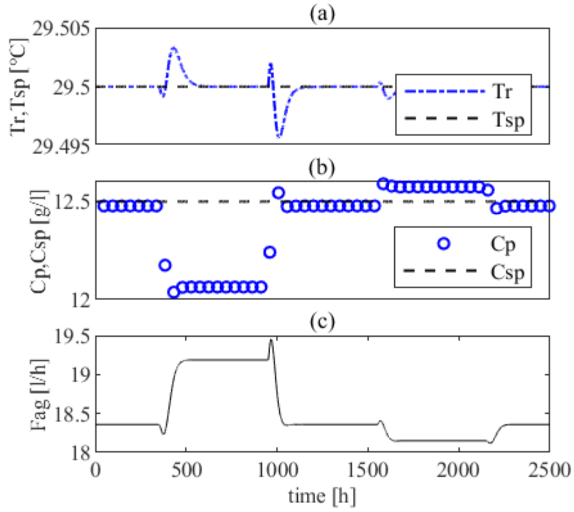

Figure 2. SISO control performances: (a) controlled reactor temperature; (b) ethanol concentration (open loop); (c) manipulated coolant flow rate.

Figs. 2(a) and 2(b) show the closed-loop dynamic simulation of the bioreactor temperature T_r and the product concentration C_p respectively, with only temperature feedback control, along with the manipulated variable F_{ag}, when a step-change in $C_{s,\,in}$ is introduced. Figs. 3(a) and 3(b) represent the simulated closed-loop trend of the variables T_r and the ethanol concentration C_p, when varying specific growth rate μ_X.

Table 1. Controller performance indexes for SISO control structure

	SISO		
	IAE	ISE	ITAE
T_{in}	62.87	1.42	9.91E+04
$C_{s,in}$	340.32	115.39	4.62E+05
μ_X	1.76E+03	2.44E+03	2.98E+06

Results show that temperature controller cannot guarantee the desired value of ethanol composition and an offset is registered (Figs. 2(b) and 3(b)). The offset is higher when the reactor conditions imply a change in the biomass growth rate, as it may happen when pH varies.

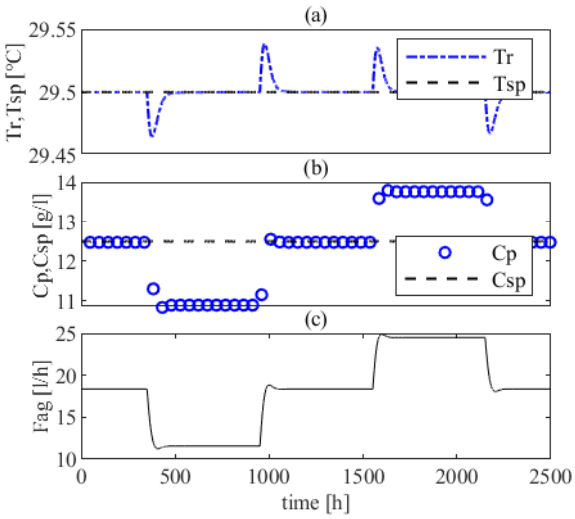

Figure 3. SISO control performances: (a) controlled reactor temperature; (b) ethanol concentration; (c) coolant flow rate.

Table 2. Controller performance indexes for cascade control structure.

	Cascade		
	IAE	ISE	ITAE
T_{in}	5.85	0.04	9.10E+03
$C_{s,in}$	44.12	7.52	6.08E+04
μ_X	216.04	106.79	3.76E+05

In Figs. 4 and 5 the results obtained when cascade control is used are reported. As expected, this control structure has proven to be more effective despite the time delay of ethanol composition measurements. This can be confirmed by evaluating the error indices shown in Table 1 and Table 2. The cascade controller is more performing than the SISO system, thus determining a smaller error and a faster achievement of the desired ethanol composition.

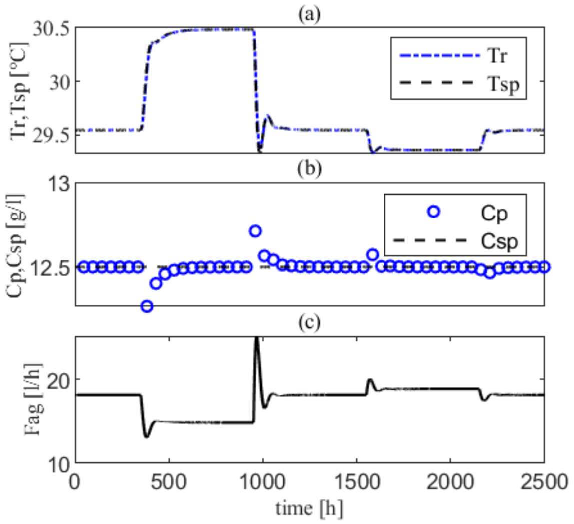

Figure 4. Cascade control performances: (a) controlled reactor temperature (secondary loop); (b) controlled ethanol composition (primary loop); (c) manipulated coolant flow rate.

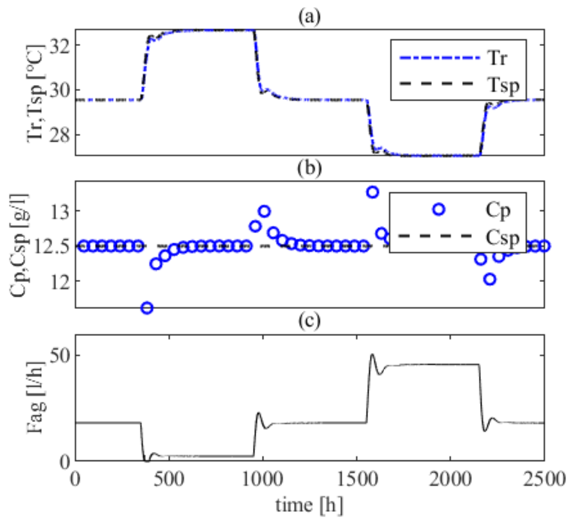

Figure 5. Cascade control performances: (a) controlled reactor temperature; (b) controlled ethanol composition (primary loop); (c) manipulated coolant flow rate.

Table 3. Controller performance indexes for MIMO control structure that used the inferential control for ethanol concentration

	MIMO		
	IAE	ISE	ITAE
T_{in}	4.12	0.02	6.62E+03
$C_{s,in}$	34.34	1.73	4.99E+04
μ_X	164.02	27.38	3.04E+05

It is possible to observe, in presence of the disturbances, how the ethanol concentration can quite well follow the setpoint value by the action of outer loop (Figs. 4 and 5(b)). In this way, the set-point of T_r is modified in order to ensure the required product concentration. The temperature controller is effective to follow the set-point variations.

In Figs. 6 and 7 the trends obtained with MIMO configuration are reported, where an inferential control is used for the composition. In this case, the inferred concentration control loop allows to maintain the product close to the set-point. As it can be observed in Figs. 6(b) and 7(b), in correspondence to the variations of μ_X factor, it can be observed that C_p moves further away from the setpoint value than when $C_{s,in}$ disturbance is applied. However, the controller brings it back quickly enough to the desired value compared to the cascade control configuration. Therefore, the MIMO control system handles the situation of bioreactor temperature and composition control more effectively compared to other designed structures, when disturbances include substrate concentration or conditions affecting the growth of microorganisms. The quality indexes reported in Table 3 confirm such considerations.

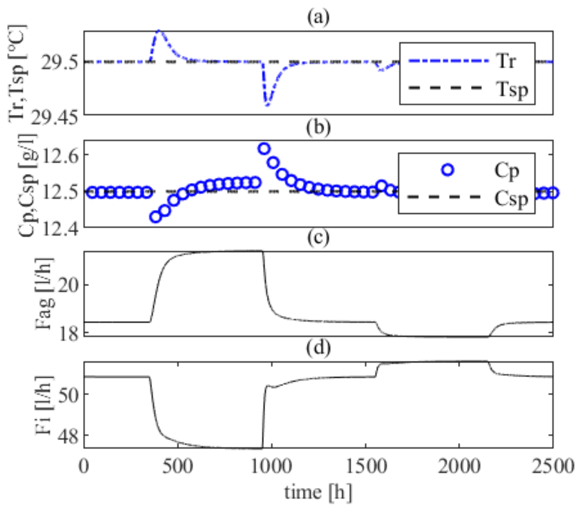

Figure 6. MIMO performances: (a) controlled reactor temperature; (b) controlled ethanol composition; (c) manipulated coolant flow rate; (d) manipulated inlet flow rate.

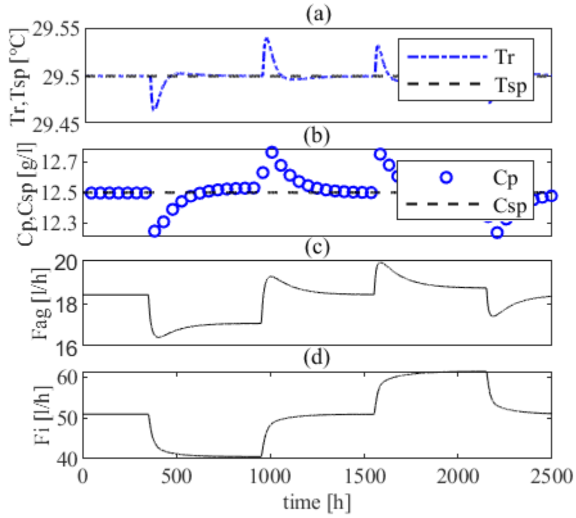

Figure 7. MIMO performances: (a) controlled reactor temperature; (b) controlled ethanol composition; (c) manipulated coolant flow rate; (d) manipulated inlet flow rate.

7. CONCLUSIONS

In this work, the issue of biotechnological process control such as the production of ethanol by fermentation has been addressed. The importance of having a suitable control system is due to the sensitivity of this process to the conditions in which it is performed. Different control strategies have been designed and implemented to achieve a precise and efficient control of temperature and composition. A comparative analysis of the designed controllers showed that temperature control was not able to maintain the ethanol concentration at the required set-point when disturbances varied substrate concentration in the reactor or when process conditions (e.g. pH) affected the biomass growth rate. When severe disturbances are present, as the ones used in this study, it is necessary to develop different control strategies that can efficiently suppress disturbances effect on the ethanol concentration. To improve system performances, two different situations were considered: (i) online analyser for measuring ethanol concentration with significant delay; (ii) estimation of ethanol by means of secondary available measurements. In the first case a cascade control was proposed, where temperature control received the set-point from ethanol concentration control. The use of delayed measurement in a primary loop diminished the offset in product composition with respect to using only temperature controller. The second situation was addressed by using an inferential control for the ethanol concentration in conjunction with the temperature controller. The 2x2 MIMO control outperformed the cascade structure, but the successful of this solution is due to the good performance of the estimation system and its robustness.

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