

# A Comparison of Robust Model Predictive Control Techniques for a Continuous Bioreactor

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**Abstract:** Biotechnology industry is expanded rapidly due to the progress in the understanding of bio-systems and the increased demand for products. Since bioprocess dynamics are almost always affected by physical parameter variations and external disturbances, the need for robust control techniques is of major importance in order to ensure the desired behavior of the process. The overall process equilibrium is guaranteed if all quantities in the bioreactor remain into prescribed ranges. In recent years, closed-loop control methods have been used in order to cope with uncertainty and an important number of constraints imposed by the physical system. For this purpose, predictive control is a quite promising technique. In the present paper three robust model predictive control (RMPC) techniques are used in order to regulate the substrate concentration and the biomass production in a bioreactor. These techniques are applied to a continuous bioreactor in which the pH changes are considered as disturbances while the air pressure is ignored by the process model. For the simulation purposes a linearized model of the system has been used in which the uncertainty is described in the form of a disturbance term. The effectiveness of the methods is illustrated by means of simulation results.

## 1 INTRODUCTION

Since many physical systems can be modeled as uncertain dynamic systems, methodologies and algorithms related to the robust predictive control have been developed during the last twenty years. Their characteristics depend on marked differences in uncertainty, performance criteria, the type of stability constraints and calculation. In the sequel, some of the basic principles that govern them are presented.

The RMPC was proposed in (Campo and Morari, 1987) based on min-max algorithms and since then improved by several authors considering various situations (see e.g. (Allwright and Papavasiliou, 1992), (Kothare et al., 1996a), (Scokaert and Mayne, 1998), (Lee and Yu, 1997), (Kerrigan and Maciejowski, 2004) and related references). The min-max algorithms generally do not promise robust stability; to ensure the robust stability of the controlled system, uncertainty should be variable with time (Zheng, 1995). The robust predictive control of stable linear systems with constraints described by multiple models was solved in (Badgwell, 1997) by generalizing the results in (Rawlings and Muske, 1993). In a different context MOAS theory (Gilbert and Tan, 1991) was developed for the reinforcement of strong restrictions

on predictive control situations, despite the presence of input disturbances, by calculating the minimum required output horizon. Since then, the theory was further developed (Mayne and Schroeder, 1997), (Bemporad, 1998), (Bemporad and Garulli, 1997), (A Cuzzola et al., 2002), (Mayne et al., 2006).

In recent years some new methods have been proposed for robust predictive control: (i) In (Kothare et al., 1996b), the so-called parametric approach was proposed for the predictive control of linear uncertain systems ensuring robust stability constraints. Moreover, it was noted that the cost function may be a convex function of any type on the horizon forecasting. The procedure guarantees closed loop stability by using an LMI approach. Furthermore, the construction of a standard computation algorithm in the convex optimization framework has been proposed in (Abate and El Ghaoui, 2004). (ii) Supervisory control was proposed in (Wang and Rawlings, 2004a), (Wang and Rawlings, 2004b); this robust predictive control methodology guarantees stability and offset-free set point tracking in the presence of model uncertainty. First, a min-max optimization is used to determine the optimal control actions subject to the input and the output constraints. A tree trajectory allows forecasting time-varying model uncertainty. The

controller design procedure uses integrators to reject disturbances and maintain the process at the optimal operating conditions. (iii) A method based on Quadratic Programming methods (QP) was presented in (Schmid and Biegler, 1994); this method guarantees stability and fast response to the set point in the presence of model uncertainty.

In the present paper, these three above mentioned approaches for robust predictive control are applied to a bioprocess control system. They are chosen between different RMPC methods, since they are well adapted to the precise problem formulation. Evaluation and comparison of the three methods are based on simulation results.

The paper is organized as follows: In Section II the problem of RMPC for linear uncertain systems is formulated. The effect of uncertainty is modeled as a disturbance term. The parametric, supervisory and QP approaches are presented in Sections III, IV and V respectively. Then, they are applied to a bioreactor process in Section VI. Finally, Section VII provides concluding remarks.

## 2 ROBUST MODEL PREDICTIVE CONTROL AND DISTURBANCES

The robust model predictive control consists of robust analysis and robust synthesis. During the process of analysis it is decided whether the system is stable and meets the requirements of performance in the presence of uncertainty of a given class. The synthesis process leads to designing a controller such that the controlled system remains robustly stable and satisfies the requirements of robust performance. The control algorithms differ in the type of uncertainty characterizing the system and how one copes with it. Hence, the resulting optimization procedures can include LMIs and dynamic programming.

In most cases, it is assumed that:

1. the nominal system belongs to  $S_0$ , where  $S$  is a given family of linear, time-invariant (LTI) systems and
2. a non-measured noise signal  $w(t)$  is introduced to describe any type of uncertainty.

Consider a discrete-time linear system described by the equations

$$\sum \left\{ \begin{array}{l} x_{t+1|t} = Ax_{t|t} + Bu_{t|t} + Hw_{t|t} \\ y_{t|t} = Cx_{t|t} + Kw_{t|t} \end{array} \right\} \quad (1)$$

where  $w(t) \in W$  and is a given set. The uncertainty may generally be either a parametric variation, or a

disturbance. The robust control scheme predicts the systems behaviour in presence of uncertainty and adjusts the control signal with regard to the systems errors.

## 3 THE PARAMETRIC APPROACH FOR RMPC

In this section, the RMPC method proposed in (Kothare et al., 1996b) is presented. The model of a discrete-time LTI system is

$$\begin{aligned} x_{t+k+1|t} &= Ax_{t+k|t} + Bu_{t+k|t} + Hw_{t+k|t} \\ y_{t+k|t} &= Cx_{t+k|t} \\ h(x_{t+k|t}, u_{t+k|t}, w_{t+k|t}) &\leq 0 \\ x_{t|t} &= x_0 \end{aligned} \quad (2)$$

where  $t$  and  $k$  refer to time and future times, respectively. The vectors:  $x_t \in X \subset R^n$ ,  $y_t \in R^r$  and  $u_t \in U \subset R^s$  denote the state, measured outputs and control inputs, respectively, while  $w_t \in W \subset R^q$  is the vector describing the disturbance inputs.  $A, B, C$  and  $H$  are constant matrices of appropriate dimensions. Since the system is subject to some physical limitations, the sets  $X, U$  and  $W$  are determined to meet inequality constraints of the form

$$\left. \begin{array}{l} x^L \leq x_{t+k|t} \leq x^U \\ u^L \leq u_{t+k|t} \leq u^U \\ w^L \leq w_{t+k|t} \leq w^U \end{array} \right\}, k = 0, 1, \dots, N_c \quad (3)$$

where  $N_c$  is the control horizon and the superscripts  $L$  and  $U$  refer to lower and upper bound, respectively. Based on the following assumptions: (i) the pair  $(A, B)$  is stabilizable (ii) the sets  $X, U$  and  $W$  contain the equilibrium point and (iii)  $U$  and  $W$  are compact sets, the RMPC is reformulated as an optimization problem:

$$\begin{aligned} \min_{U=\{u_t, \dots, u_{t+N_y-1}\}} & J(U, x_t) \\ x_{t+k+1|t} &= Ax_{t+k|t} + Bu_{t+k|t} + Hw_{t+k|t} \\ y_{t+k|t} &= Cx_{t+k|t} \\ h(x_{t+k|t}, u_{t+k|t}, w_{t+k|t}) &\leq 0, k = 0, 1, \dots, N_c \\ x_{t|t} &= x_0 \end{aligned} \quad (4)$$

where  $J(U, x_t)$  is the cost function and  $N_y$  is the forecasting horizon of the output. The aim of control is to ensure that the final state converges to the equilibrium point. More precisely, the method uses a Lyapunov function to guarantee asymptotic stability of the predictive control algorithm, based on the results in (Keerthi and Gilbert, 1988). Therefore, the objec-

tive function is chosen to be of the quadratic form

$$J(U, x_t) = \sum_{k=1}^{N_y-1} \|Qx_{t+k|t}\|_q + \sum_{k=0}^{N_y-1} \|Ru_{t+k|t}\|_q + \|Px_{t+N_y|t}\|_q \quad (5)$$

Then, the optimization problem is solved computationally by using a language for advanced modeling and solution of convex and non-convex optimization (Yalmip) (Lofberg, 2004),(Löfberg, 2008).

In the presence of a permanent disturbance, the aim of control is modified and consists of ensuring that the final state converges to an area as close to the equilibrium point, as possible. For this purpose, the above mentioned computation language has been appropriately adapted, in the present paper.

#### 4 THE SUPERVISORY APPROACH FOR RMPC

In (Wang and Rawlings, 2004b) an RMPC method is proposed to guarantee stability and offset-free set point tracking in presence of model uncertainty. A min-max optimization problem that explicitly accounts for model uncertainty is used to determine the optimal control actions subject to input and output constraints. The robust regulator uses a tree trajectory to forecast time-varying model uncertainty. The controller design procedure uses integrators to reject disturbances and maintain the process at the optimal operating conditions or set points. Constraints may cause offset, which occurs when the set points are unreachable. Finally, it should be noted that the method considers polytopic system uncertainty, since this description can approximate many forms of uncertainty.

The method comprises a closed-loop stability condition which requires the control to cope with uncertainty. A novelty of the algorithm is to use a tree diagram to predict the state of the system with time-varying uncertainty. The control procedure is achieved when all branches of the tree converge to steady-state values of the state and control variables.

The uncertain dynamic system is described by the following discrete state-space model:

$$\Sigma = \left\{ \begin{array}{l} x_{t+1} = A_t x_t + B_t u_t \\ y_t = C x_t \end{array} \right\} \quad (6)$$

in which  $A_t, B_t$  are the time-varying state-space model matrices of appropriate dimensions;  $C$  describes the relationship between the output and the state in the absence of uncertainty; as in the parametric method,  $x_t, y_t$  and  $u_t$  denote the state, measured outputs and

control inputs, respectively. When model uncertainty is present, the exact plant model  $A_t, B_t$  is not known. The model uncertainty region is described by the convex hull  $\Pi = \{(A_1, B_1), (A_2, B_2), \dots, (A_I, B_I)\}$ . The convex hull is defined as the linear convex combination of all models in  $\Pi$ . Let  $i, i = 1, 2, \dots, I$  be the model index.  $(A_t, B_t) \in \Pi$ , if and only if there exist  $\mu_1(t), \mu_2(t), \dots, \mu_I(t) \in R$ , such that

$$A_t = \sum_{i=1}^I \mu_i(t) A_i \quad (7)$$

and

$$B_t = \sum_{i=1}^I \mu_i(t) B_i \quad (8)$$

for any  $[0 \leq \mu_i(t) \leq 1$  and  $\sum_{i=1}^I \mu_i(t) = 1$ . The system is said to be at steady state at time  $T$ , if  $u_s = u_{s+1} = u(s)$ ,  $x_s = x_{s+1} = x(s)$  and  $y_s = y_{s+1} = y(s)$ , for all  $s \geq T$ . In the above relations,  $u_s, x_s$  and  $y_s$  are the steady-state control, state, and controlled output vectors, respectively, that satisfy the constraints  $u_s \in U, x_s \in X$  and  $y_s \in Y$ . Since there is no uncertainty in the output matrix,  $y_s = Cx$  is at steady state.

#### 5 THE QP METHOD

The MPC technique used in the sequel consists of minimizing

$$J(z, \epsilon) = G^T W_u^2 G + F^T W_{\Delta u}^2 F + K^T W_y^2 K + \rho \epsilon \epsilon^2 \quad (9)$$

where  $z = [G \ F \ K]^T$  is the vector of optimization variables with

$$G = \begin{bmatrix} u(0) \\ \dots \\ u(p-1) \end{bmatrix} - \begin{bmatrix} u_{target}(0) \\ \dots \\ u_{target}(p-1) \end{bmatrix} \quad (10)$$

$$F = \begin{bmatrix} \Delta u(0) \\ \dots \\ \Delta u(p-1) \end{bmatrix} \quad (11)$$

$$K = \begin{bmatrix} y(0) \\ \dots \\ y(p-1) \end{bmatrix} - \begin{bmatrix} r(1) \\ \dots \\ r(p) \end{bmatrix} \quad (12)$$

Besides, the weight matrices  $W_u, W_{\Delta u}$  and  $W_y$  are defined as

$$W_u = diag \left( w_{0,1}^u, w_{0,2}^u, \dots, w_{0,n_u}^u, w_{p-1,1}^u, \dots, w_{p-1,n_u}^u \right) \quad (13)$$

$$W_{\Delta u} = diag \left( w_{0,1}^{\Delta u}, w_{0,2}^{\Delta u}, \dots, w_{0,n_u}^{\Delta u}, w_{p-1,1}^{\Delta u}, \dots, w_{p-1,n_u}^{\Delta u} \right) \quad (14)$$

$$W_y = \text{diag} \left( \begin{matrix} w_{0,1}^y, w_{0,2}^y, \dots, w_{0,n_y}^y, w_{p-1,1}^y, \\ w_{p-1,2}^y, \dots, w_{p-1,n_y}^y \end{matrix} \right) \quad (15)$$

The parameters  $\varepsilon$  and  $\rho_\varepsilon$  are a slack variable and its weight, respectively;  $\rho_\varepsilon$  penalizes the violation of the constraints. As  $\rho_\varepsilon$  increases with respect to the input and output weights, the controller gives a higher priority to minimization of constraint violations. The  $u_{target}$  is the set point for the input vector,  $p$  is the prediction horizon,  $w_{i,j}^*$  are non negative weights for the corresponding variables,  $r(k)$  is the current sample of the output reference and are input increments (Rawlings and Mayne, 2009), (Seborg et al., 2006). Finally, after substituting  $u(k)$ ,  $\Delta u$  and  $y(k)$  in (9), it obtains the form

$$J(z, \varepsilon) = \rho_\varepsilon \varepsilon^2 + z^T K_{\Delta u} z + 2z^T \left\{ \begin{matrix} r(1) \\ \dots \\ r(p) \end{matrix} \right\}^T K_r \\ + \left[ \begin{matrix} v(0) \\ \dots \\ v(p-1) \\ u_{target}(0) \\ \dots \\ u_{target}(p-1) \end{matrix} \right] \left\{ \begin{matrix} K_v + u(-1)^T + K_u \\ K_u + x(0)^T K_x \end{matrix} \right\} z + c \quad (16)$$

where  $c$  is constraint. The last term in (16) introduces the initial conditions into the minimization procedure. The problem constraints are expressed in the terms of (17) in which  $M_z, M_\varepsilon, M_{lim}, M_u, M_x$  are constant matrices of appropriate dimensions that depend on the constraint bounds.

$$M_z z + M_\varepsilon \varepsilon \leq M_{lim} + M_v \left[ \begin{matrix} v(0) \\ \dots \\ v(p-1) \end{matrix} \right] + M_u u(-1) \\ + M_x x(0) \quad (17)$$

Initially, the controller computes the optimal solution  $z^*$  and  $\varepsilon^*$  by solving the quadratic program (QP) described in (16) – (17). The model predictive controller QP solver converts an MPC optimization problem to the general QP form

$$\min_x \left( f^T x + \frac{1}{2} x^T H x \right) \quad (18)$$

under constraints

$$\hat{A}x \leq b \quad (19)$$

where  $x^T = [z^T \quad \varepsilon]$  are the decisions,  $H$  is the Hessian matrix,  $\hat{A}$  is a matrix of linear constraint coefficients,  $b$  and  $f$  are vectors. The elements of  $H$  and  $\hat{A}$  are constant. The controller computes them during initialization and retrieves them from the computer memory when needed. It computes the time-varying

and vectors at the beginning of each control instant (Rawlings and Mayne, 2009), (Seborg et al., 2006).

The MPC controller is implemented by using the MPC control toolbox of Matlab. The toolbox uses the KWIK algorithm to solve the QP problem (Schmid and Biegler, 1994).

## 6 APPLICATION TO BIOPROCESS CONTROL

Biotechnology industry is expanded rapidly due to the progress in the understanding of bio-systems and the increased demand for products (e.g. those widely used in pharmaceutical and food industry, in various chemical compounds etc). Their production is made in special reactors called bioreactors. The main feature of a bioprocess consists of the material transformation procedure in presence of bacteria (or cells). The incoming material concentration should be controlled, such that it ensures the bacteria growth and provide the desirable quantity of outgoing products. The overall process equilibrium is guaranteed if all quantities in the bioreactor remain into prescribed ranges. Three types of bioreactors, namely batch, fed batch and continuous, are mainly used. In this paper the abovementioned robust model predictive control techniques are applied to a continuous bioreactor. In this process material quantities are constantly added and removed to the reactor throughout the fermentation. In most cases, bioreactor operation is based on empirical knowledge; however, in recent years, closed-loop control methods have been used (see e.g. (Rubio et al., 2001), (Mailleret et al., 2004), (Fukushima and Bitmead, 2005), (Ashoori et al., 2009) and related references).

Bioreactor systems are of increasing industrial importance given their current use in pharmaceuticals, bioremediation and specialty chemical production. Although the majority of industrial bioprocess operate in fed batch mode, a higher throughput could be achieved in continuous operation. Unfortunately, the biological organisms utilized in these reactors are generally not well understood, and the cellular-level metabolic pathways are poorly characterized. This partial understanding makes advanced controller design difficult, as most advanced control techniques utilize process models (Parker and Doyle, 1998). In what follows, the RMPC approaches presented in Sections 3, 4 and 5 are applied to a continuous bioreactor in order to cope with uncertainty and an important number of constraints imposed by the physical system.

### 6.1 Description of the Process

The physical process in the bioreactor is modelled in terms of non linear state-space equations (Freitas and Teixeira, 1998), (Grossmann et al., 1983).

$$\begin{aligned} \frac{dx}{dt} &= [\mu(s) - D]x \\ \frac{ds}{dt} &= -\frac{1}{Y}\mu(s)s + D(S_a - s) \end{aligned} \quad (20)$$

with state variables,

- $x(g/l)$ : Cells concentration in the bioreactor
- $s(g/l)$ : Substrate concentration in the bioreactor and time-varying parameters
- $\mu(s)$ : Function that describes the cell growth
- $D(1/h)$ : Rate of dissolution
- $Y$  : Yield coefficient of biomass
- $S_a(g/l)$ : Incoming substrate concentration

The expression for  $\mu(s)$  differs with respect to each cell type. A common expression that has been experimentally validated and used almost exclusively in the literature is:

$$\mu(s) = \frac{\mu_{max}}{\frac{k_s}{s} + 1 + (\frac{s}{k_1}) + (\frac{s}{k_2})^2 + \dots + (\frac{s}{k_n})^n} \quad (21)$$

where

- $\mu_{max}$ : Constant
- $k_s$ : Constant of substrate saturation
- $k_i, i = 1, \dots, n$ : Constant parameters

For  $n = 0$  one obtains the well-known Monod kinetics

$$\mu(s) = \mu_{max} \times \frac{s}{k_s + s} \quad (22)$$

In the case where  $s$  takes large values with respect to  $k_s$  in (20),  $\mu(s)$  becomes equal to  $\mu_{max}$ . As a result, the differential equation (20) obtains the form

$$\frac{dx}{dt} = \lambda x \quad (23)$$

where  $\lambda = \mu_{max} - D$ . In order to ensure a quite fast bacteria growth, a positive value of  $\lambda$  has to be selected.

Moreover, it is assumed that:

1. the volume of the bioreactor is constant and the quantity of the incoming materials is equal to the one of the outgoing materials
2. losses in temperature and changes into kinetic energy are neglected
3. pressure conditions, air supply, and the appearance of unwanted gases are neglected.

### 6.2 RMPC Application

In this subsection, the parametric approach, the supervisory approach and the QP for robust predictive control are applied to a continuous bioreactor. The RMPC objective is to maintain the substrate concentration in the bioreactor almost constant (set point), in order to produce the desired amount of biomass, despite sharp decrease of pH, considered as a disturbance. It should be noted that an acid environment in the bioreactor may cause inhibition of the bacteria growth.

For the application purposes, a linearized model of the process (20) is used describing the type of the bioreactor

$$\begin{aligned} \dot{x} &= Ax + Bu + Hw \\ y &= Cx \end{aligned} \quad (24)$$

In the above model it is (Parker and Doyle, 1998)

$$A = \begin{bmatrix} -2.564 & -0.6792 \\ 1 & 0 \end{bmatrix} \quad (25)$$

$$B = \begin{bmatrix} 1 \\ 0 \end{bmatrix} \quad (26)$$

$$H = \begin{bmatrix} 1 \\ 1 \end{bmatrix} \quad (27)$$

$$C = [-1.5302 \quad 0.459] \quad (28)$$

$$x_0 = \begin{bmatrix} -1.530163 \\ 0.0174593 \end{bmatrix} \quad (29)$$

The performance index weighting matrices are

$$Q = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} \quad (30)$$

$$R = 10 \quad (31)$$

and the set point is 15g/l.

The system is implemented by using the Yalmip wiki (Löfberg, 2008) and the Model Predictive Control Toolbox of Matlab. Yalmip is a modeling language for advanced modeling and solution of convex and non-convex optimization problems. The main motivation for using Yalmip is the rapid algorithm development. Moreover, it can implement a large amount of modeling tricks, allowing the user to concentrate on the high-level model, while Yalmip takes care of the low-level modeling, in order to obtain efficient and numerically sound models. For the simulation purposes, the Yalmip wiki has been appropriately adapted to cope with uncertainties in the form of description (24). The simulation results are obtained for all cases (i) for the system without uncertainty and (ii) for the system in presence of uncertainty.

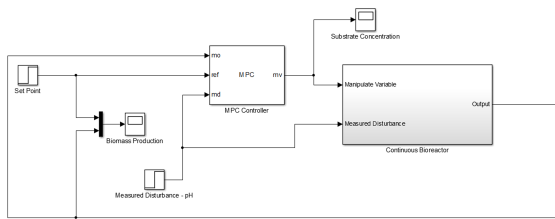


Figure 1: The simulation model in Simulink.

The simulation model in Matlab Simulink is given in Fig. 1. We first consider the nominal system i.e. without pH decrease. In this case the disturbance term is neglected by the simulation algorithm. The systems behavior is shown in Fig. 2 for the parametric, supervisory and QP approaches.

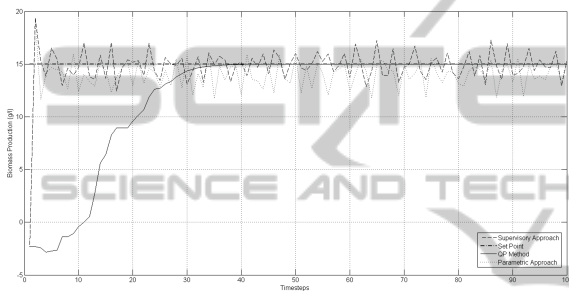


Figure 2: RMPC of the nominal system in continuous bioreactor.

Note that after 20 steps of the algorithm execution, the QP method produces the desired biomass 15g/l (set point), while the parametric and the supervisory control do not. Fig. 3 shows that the substrate concentration with the QP method remains constant.

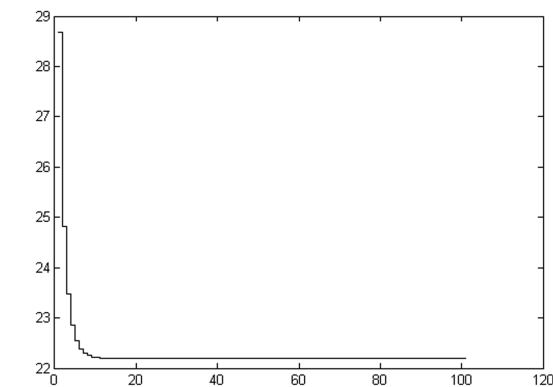


Figure 3: Substrate concentration for the QP method.

Consider now the case in which a sharp decrease of pH occurs. The disturbance term is now taken into account by the algorithm. The systems behaviour and the substrate concentration obtained by the parametric, supervisory and QP approaches are shown in Fig. 4 and 5 respectively.

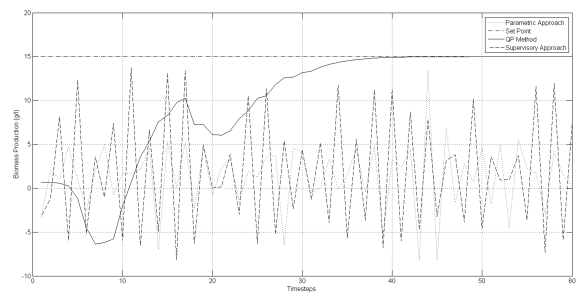


Figure 4: RMPC of the uncertain system in continuous bioreactor.

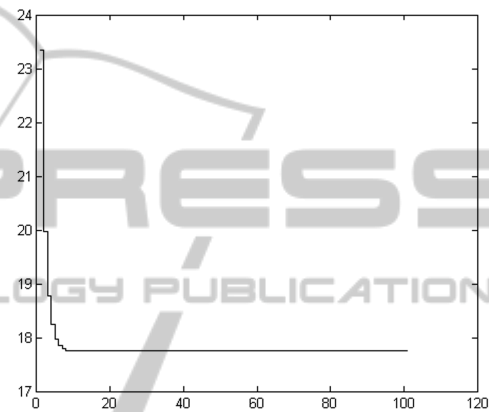


Figure 5: Substrate concentration for the QP method.

Note the important overshoot due to the disturbance; it is also noted that, despite the pH decrease, only the QP method ensures closed-loop systems stability. Furthermore, important fluctuations of the substrate concentration are produced when the parametric and supervisory control methods are applied and not in the QP one. However, it is considered that the range of fluctuations is acceptable for the systems equilibrium.

## 7 CONCLUSIONS

In this paper three robust predictive control approaches, namely parametric, supervisory and QP, are used to the control of a bioreactor. The system is generally nonlinear and uncertain due to pH changes. Moreover, many physical constraints have to be met. The control action has to ensure the overall process stability and some desired level of performance, the main design specification being a set-point of the substrate concentration and biomass production. For the simulation purposes a linearized model of the system has been used in which the uncertainty is described in the form of a disturbance term.

Comparison of the three methods based on simulation results has shown the following: 1) the QP method allows to achieve the design objectives after a small number of iterations, while both of the parametric and supervisory methods fail. 2) In the case when a sharp decrease of pH occurs, the QP method is the only one that ensures closed-loop systems stability. 3) Application of the parametric and supervisory control methods seem to produce important substrate concentration fluctuations, in contrast to QP method. 4) Although, due to the nature of the bioreactor, a certain range of variations of the substrate concentration may occur at the steady-state, the range of these variations occurring by using the parametric and supervisory approaches is often not acceptable.

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