CONTROL OF A FEDBATCH BIOPROCESS USING NONLINEAR MODEL PREDICTIVE CONTROL

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Abstract: This paper presents an explorative work about a Model Predictive Control (MPC) technique. A nonlinear model predictive controller was designed and applied to a fedbatch bioprocess. First, bioprocess and its model are described. Then, a controller based in a nonlinear MPC scheme (Dual Fuzzy Model Predictive Control DF-MPC) is proposed with the aim to test the control of substrate concentration in simulation and to conclude about its ability to tackle the difficulties inherited from the bioprocess batch operation mode. In addition, different kinds of disturbances were applied showing the powerful disturbance rejection of the controller. *Copyright © 2002 IFAC*

Keywords: model based control, batch mode, nonlinearity, biotechnology, fuzzy sets.

1. INTRODUCTION

Despite most theoretical advances in process control are focused on continuous operations, batch processes have an important role in industrial field. Their inherent nonlinear nature and time variability increase complexity and make difficult the control tasks (Gutiérrez, Rincón and Alvarez, 2005).

In the last years, it is particularly amazing the introduction of biotechnological processes into the industrial field. Many commercial products like foods, pharmaceuticals and insecticides are produced by processes that involve living organisms. The increment of biotechnology-based products introduces new necessities in the industrial scope. The development of the biotechnological industry has still many challenges to affront. One of them is associated with control, mainly because most of bioprocesses operate in batch or fedbatch mode.

Controlling a bioprocess is not an easy work. Batch nature of most of bioprocesses produces difficulties when control is intended. In general, batch processes have some particularities that complicate control tasks. The major difficulty is associated with time-varying operating point. Along a batch run the transformations proceeds from an initial state to a final state under quite different conditions, therefore all process variables and some parameters are in permanent change. Such parameters time variation can generate nonlinearities. Therefore, control problem cannot be attacked using conventional linearization model techniques. In addition, the inherently transitory behavior of the variables and parameters generates internal disturbances (Gutiérrez, Rincón and Alvarez, 2004), e.g., the cells growth kinetics in bioprocesses.

Model Predictive Control (MPC) is an attractive technique to achieve a desired process behavior despite the difficulties mentioned previously. Its ability to predict future process behavior allows the controller to select the best control action according the designer criteria. Nonlinear formulation of MPC is even more attractive because the bioprocess model used here is highly nonlinear.

The aim of this work is the design of a controller for a bioprocess, able to affront difficulties inherited from batch operation mode. Additionally, a nonlinear controller is proposed making use of a restrictive enumerative optimization technique to generate a set of control policies (Alvarez, 2000), i.e., the set of possible control actions to evaluate in the cost functional.

2. BIOPROCESS MODEL

The bioprocess chosen for this work is a Fedbatch Fermentation of *Bacillus thuringiensis (Bt)*. This microorganism has been widely used to produce biologic pesticides over the world. *Bt* is specie **I** from *Bacillus* genre. Species from this group are sporulated and Gram positive bacterias.

Bacillus thuringiensis biological cycle is illustrated in Fig. 1. During vegetative stage, cellular reproduction occurs by binary fission. When vegetative cells stop growing the sporulation stage begins. Inside the cell a spore and a crystal are formed. Sporulation process finishes with the breaking of cellular wall and spore and crystal are released to the environment. This process is named cellular lysis. Finally, the spore can be isolated and prepared for its germination becoming a new vegetative cell and completing *Bt* biological cycle. Notice that *Bt* produces one or more crystalline bodies during sporulation process. Such crystals are named delta endotoxins, some of them are toxic for a variety of insect species and this property makes *Bt* an important microorganism in biological pesticides industry.
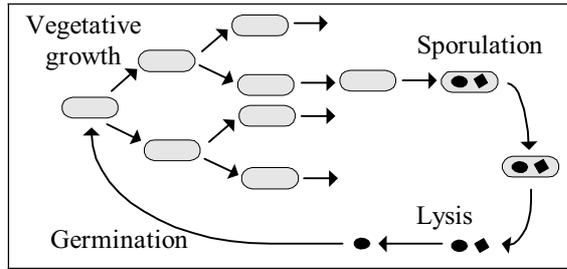
Fig. 1. Biological cycle of *Bacillus thuringiensis*

The model used in this work (Atehortúa, 2004) describes growth, sporulation, death and lysis. Other factors in *Bt* fermentation process are the dissolved oxygen, pH and temperature. The model does not include such dynamics, i.e, and suppose them to be controlled. Consider the bioprocess flow diagram in Fig. 2. Feed flow contains only substrate for cellular growth. The phenomenological model contains four states: volume V, vegetative cells concentration Xv, sporulated cells concentration Xs, and primary substrate concentration Sp.
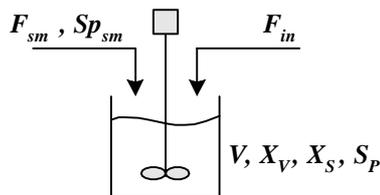
Fig. 2. Bioprocess flow diagram, the subindex *sm* indicates substrate medium feeding to the system.

The model is defined by the following differential equations:

$$\frac{dV}{dt} = F_{in} + F_{sm} \tag{1}$$

$$\frac{dX_v}{dt} = -\left(\frac{F_{in} + F_{sm}}{V}\right)X_v + (\mu - k_s - k_e)X_v \tag{2}$$

$$\frac{dX_s}{dt} = -\left(\frac{F_{in} + F_{sm}}{V}\right)X_s + k_sX_v - k_lX_s \tag{3}$$

$$\frac{dS_p}{dt} = -\left(\frac{F_{in} + F_{sm}}{V}\right)S_p + \left(\frac{F_{sm}}{V}\right)S_{p,fm} - \left(\frac{\mu}{Y_{X/S}} + m_s\right)X_v \tag{4}$$

F_{in} is the inlet flow of pH control reactants and antifoaming agent. F_{sm} is the feed flow of substrate medium, $S_{p,sm}$ is the substrate concentration in the feed flow. $Y_{X/S}$ denotes biomass-substrate yielding coefficient and m_s is the maintenance coefficient. k_s, k_e, k_l and μ are kinetic parameters defined as follows:

$$k_s = k_{s,fix}\left(\frac{1}{1+e^{a(Sp-aa)}}\right) - k_{s,fix}\left(\frac{1}{1+e^{a(Sp,ini-aa)}}\right) \tag{5}$$

$$k_e = k_{e,fix}\left(\frac{1}{1+e^{-b(t-c)}}\right) - k_{e,fix}\left(\frac{1}{1+e^{-b(t_{ini}-c)}}\right) \tag{6}$$

$$k_l = k_{l,fix}\left(\frac{1}{1+e^{d(X_v-e)}}\right) - k_{l,fix}\left(\frac{1}{1+e^{d(X_{v,ini}-e)}}\right) \tag{7}$$

$$\mu = \frac{\mu_{max}S_p}{K_s + S_p} \tag{8}$$

Where k_s denotes the specific velocity of cellular sporulation, k_e denotes the specific velocity of natural death of vegetative cells, k_l is the lysis specific velocity of sporulated cells and μ is the specific velocity of vegetative growth. μ is given by the Monod growth model where μ_{max} is the maximum specific velocity of cellular growth and Ks is the substrate saturation constant. The subindex *fix* indicates constant or fixed parameter. *a*, *aa*, *b*, *c* and *e* are constants values identified for this particular bioprocess. Notice that the equations describing the specific velocities k_s, k_e, and k_l are sigmoids in function of substrate concentration, time and vegetative cells concentration respectively, and show high nonlinearities associated to bioprocess model.

3. NONLINEAR MODEL PREDICTIVE CONTROL USING POLICIES GENERATION

MPC is an advanced control strategy that integrates many tools and fundamentals from other control techniques. The use of a process model in order to predict the plant immediate future is the main feature. MPC takes into account the feedforward and feedback control actions and integrates input and state constraints (process, economics, safety, environmentals, etc).

The NMPC (Nonlinear Model Predictive Controller) designed in this work must search for the best control action generating control policies. In order to obtain the best control policy, many works have focused on a solution through gradient based techniques (Boyd and Vandenberghe, 1996). On the other hand, there are some techniques named enumerative techniques

(ET) that require heavy computational demand but they offer more feasible control policies than others.

When ET are used, the best control policy is found by solving a programming or numeric problem. One of the difficulties of solving the numerical problem is to find a feasible control action before each sample time. When the model is nonlinear, the solution of the optimization algorithm loses convexity. Thus, finding the best solution is difficult and when it is found, the global minimum can not be guaranteed. Hence, in order to get a good control policy, the optimizer must evaluate quickly and repeatedly the cost beginning from a set of generated control policies and at each evaluation the nonlinear differential system must be solved. With the values obtained from iterations of numerical algorithm, optimizer calculates the numerical value of cost.

These tasks take more time and computation than linear case. It is important to take into account that the "optimality degree" of the problem depends on the amount of generated policies (Np). Restricted Enumerative Optimization with Control Horizon equal to three (REO3) is an evolution of Restricted Enumerative Optimization with control horizon equal to one (REO1) (Álvarez, 2000). REO1 procedure is as follows: first the controller explores all the valve possible movements, taking into account its spam and sample time constraint. When the controller selects a valve position, it maintains this value until the end of prediction horizon. Despite REO1 is a powerful policies generator, MPC needs that dynamical information delivered to the prediction model be as variable as possible. Hence REO3 generates $(Np)^3$ policies regarding all the variation possibilities with a control horizon equal to three. Notice that if the initial amount of policies Np is equal to 36 then the total policies generated $(Np)^3$ is 46.656. The next procedure of REO3 is the evaluation of each policy in the prediction model. It is computationally hard for the controller. In order to affront this difficulty, REO3 reduces the computational load applying important criteria based on control theory. The idea is to reduce the policies number to $(Np/4)^3$, e.g., $(Np/4)^3 = 729$.

4. DUAL FUZZY MODEL PREDICTIVE CONTROLLER

In this section the design of a nonlinear model predictive controller is presented: dual model predictive controller with fuzzy terminal region, **DF-MPC** (**D**ual **F**uzzy **M**odel **P**redictive **C**ontrol). The suggested control scheme has Dual Mode Controller (Mayne and Michalska, 1993), where a terminal region is defined around the set point. One disadvantage of a Dual Mode Controller is an abrupt commutation between the MPC and a linear controller tuned inside a terminal region (Ω). An important feature of DF-MPC is doing a soft transition through a Fuzzy Set that commutates step by step the controllers. Another feature that differences DF-MPC from Dual Mode Controller is that MPC is not replaced by linear controller inside

the terminal region, but the controller is gradually transformed into a PI controller, i.e., there is a cost term, whose weight parameter is a Fuzzy Set that penalizes the difference between the MPC and a well tuned PI Controller. Notice that if the MPC is similar to a PI controller, such a cost tends to its minimization.

This Controller uses Restricted Enumerative Optimization with $H_c=3$ (REO3) and a Fuzzy region, such that the transition between the controllers (MPC → PI y PI → MPC) be soft. This is accomplished through a set point proximity criterion instead an abrupt or hard commutation in a region that is mathematically hard to define in most of cases. That is, the Dual Mode Controller is similar to Gain Scheduling Adaptive Controller (Aström and Wittenmark, 1989), its stability can't be guaranteed due to hard commutation between the regions. Finally, PI controller is used as linear controller inside Ω because driving the nonlinear process model to a standard form (local linear state feedback) is so difficult.

DF-MPC is based on the state location in the state-space. The fuzzy region (conformed by Ω and a neighborhood around it) is a Z Fuzzy Set, where there are four tuning parameters: α and β usually employed in MPC and the new ones γ and λ inside the cost functional. In Fig. 3 a two-variable state-space is depicted. $\mathbf{X_1}$ and $\mathbf{X_2}$ are the states, $\mathbf{\Omega}$ is the linear region where **PI** controller operates, **SP** is the Set Point, **TR** is the Transition Region where the fuzzy commutation between the controllers (MPC to PI and PI to MPC) is effectuated.
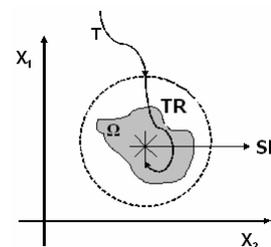
Fig. 3. Two-Variable State Space. $\mathbf{X_1}$ and $\mathbf{X_2}$ are the states. **SP** is the Set Point. $\mathbf{\Omega}$ is the linear region. **TR** is the Transition Region

In other words, controller operation is as follows: When the state is outside of transition region a pure MPC operates, that is, α, β and γ take an initial values and the fuzzy parameter λ is zero. After crossing the boundary of **TR** the controller begins to change its parameters α, β and γ according λ changes. That is, λ parameter tends to one and α, β and γ tends to zero while the state approaches to Ω. This allows operating only with the cost term related to λ and canceling the cost terms related with α, β and γ. The last idea can be shown explaining the cost functional inside DF-MPC. In this work, the cost functional is a topic that differs from the MPC regular approaches. The DF-MPC cost functional penalizes the output error and the manipulated input changes between consecutive steps. It also penalizes the output

changes and the difference between the MPC and the PI Controller. The Cost Functional is:

$$J = \sum_{j=1}^{H_P} \alpha(k) * [\hat{y}(t+j/t) - y\_SP(t+j)]^2$$

$$+ \sum_{i=1}^{H_C} \beta(k) * [\Delta u(t+j-1)]^2 \qquad (9)$$

$$+ \sum_{j=1}^{H_P} \gamma(k) * [\Delta y(t+j-1)]^2$$

$$+ \sum_{j=1}^{H_P} \lambda(k) * [u_{PI} - u_{MPC}]^2$$

Notice that the parameters change in each step of the algorithm when the state is inside the TR. H_c is the control horizon and H_p is the prediction horizon. From the cost functional, α parameter penalizes the error between output with respect to the set point. Tuning of β parameter tries to avoid the hard movements of the control final element between two consecutive steps and γ parameter executes the same task than β, but on output. γ tries to soft the output response compensating the process inertia. λ parameter looks for the MPC emulates to a PI controller on the linear region Ω. Here, the technique has a benefit in comparison to the original approach (Mayne and Michalska, 1993) because DF-MPC does not commutate the controllers. Furthermore, inside Ω the cost functional is transformed to:

$$J = \sum_{j=1}^{H_P} \lambda(k) * [u_{PI} - u_{MPC}]^2 \qquad (10)$$

That is, on Ω, λ tends to one and α, β and γ tend to zero while the output error tends to zero. Notice that in TR the MPC turns softly into a PI controller, because the difference among controllers weight (MPC and PI) has more relevance than the other weights. The Fig. 4 shows how λ changes while the output error tends to zero. The length of the transition zone is modified by a designer criterion.
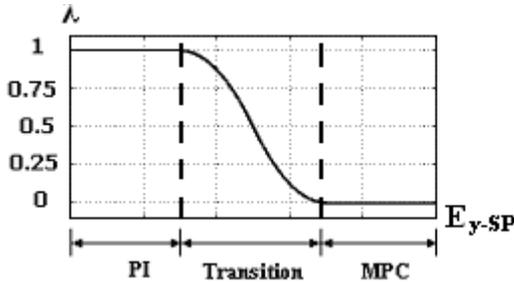
Fig 4. **Z** Fuzzy Set of the λ parameter. Lambda (λ) variates from zero to one according to the error position $E_{y\text{-}SP}$.

Finally, cost functional parameters are defined as follows:

$$\alpha(k) = [1 - \lambda(k)] * \alpha(1) \qquad (11)$$

$$\beta(k) = [1 - \lambda(k)] * \beta(1) \qquad (12)$$

$$\gamma(k) = [1 - \lambda(k)] * \gamma(1) \qquad (13)$$

Notice that α, β and γ varies at each iteration (k) and the variation depends on its initial conditions and the λ value in each sample time.

5. APPLICATION OF DF-MPC TO THE BIOPROCESS.

In this point a DF-MPC Controller for substrate regulation in a *Bt* fedbatch culture is presented. Despite the bioprocess is effectuated in a fedbatch mode, notice that the process is continuous for the substrate (defining substrate inside the bioreactor as a system) because it is being permanently fed to the bioreactor and simultaneously cells consume it. Another significant issue is: why substrate regulation? The basic idea is controlling substrate concentration inside the bioreactor, and the way is manipulating the substrate inlet flow to the bioreactor. The biotechnological knowledge about fedbatch cultures indicates that substrate concentration is one of the most influential conditions for an adequate bacterial growth.

The values used in simulation for the controller designed are the followings: **Initial values**: substrate concentration *Sp*=9.718g/l, vegetative cells concentration *Xv*=0.645g/l, volume *V*=11.0l and fresh medium flow F_{fm}=0. **Tuning parameters** of the DF-MPC are α=100, β=8, γ=10. Control horizon Hc=3 because REO3 is used, prediction horizon Hp=10. The amount of policies generated is Np=32. It implies the total evaluation of 512 policies on each sample time. Notice that REO3 makes a reduction of the possibilities. Such trim reduces the policies from 32768 to 512. **Operation conditions:** Set point is fixed in SP=10g/l, linear region Ω is defined around the SP value after 0.02 g/l and transition region TR is between 0.02g/l and 0.1g/l around the SP value. The valve span is the maximum value that the valve opens in each sample time, and it is 5%. It is important to regard that the Ω and TR values are not implementable physically, but in simulation such implementation is possible.

6. RESULTS

In this section, simulation results for the designed controller are presented. Some plots about process performance, response to external and internal disturbances are shown. A purpose is to expose how the designed controller (DF-MPC) handles the fedbatch process even when disturbances occur. First result is the performance of DF-MPC without disturbances. Cellular growth is shown in Fig. 5, notice that vegetative cells reach a maximum value when sporulation begins. Fig. 6 shows the substrate concentration during the first 7 hours until the valve saturation, as it is shown in Fig. 7. When vegetative cells reach a maximum value, the valve closes immediately to stop substrate flow. So the process evolves naturally to obtain the maximum crystal concentration (Atehortúa, 2004).

However, performance of the controller designed for regulation must be also proven with respect to

disturbances. In this work, an analysis about internal and external disturbances is made. External disturbance is defined as substrate concentration of inlet flow ($S_{p,sm}$). In addition, the batch process has particular disturbances called internal disturbances, i.e., unexpected changes into the bioreactor that are not totally known. Furthermore there are disturbances that the prediction model does not take into account. Another kind of internal disturbances are the dynamical effect of uncontrolled states (Xv, Xs, V) into the controlled state Sp in the fedbatch run. This type of disturbance is named fundamentally internal disturbance (Gutiérrez, Rincón and Alvarez, 2005). In the present work an applied internal disturbance is an unexpected consumption of substrate by other microorganism into the bioreactor for an instant.
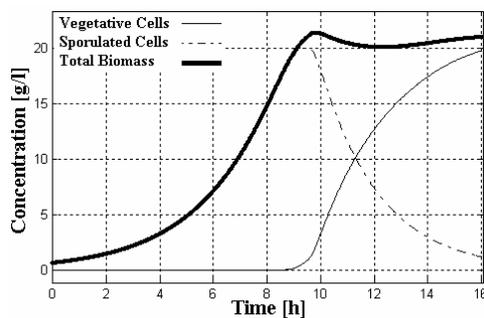
Fig. 5. Cellular Growth (Total batch run)
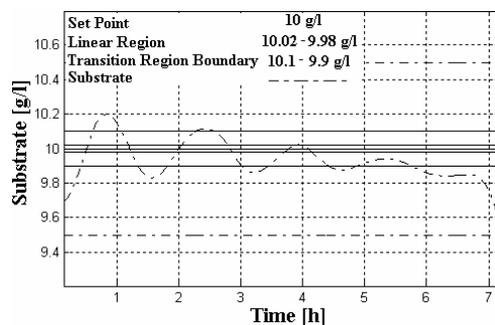
Fig. 6. Substrate Regulation (Zoom).
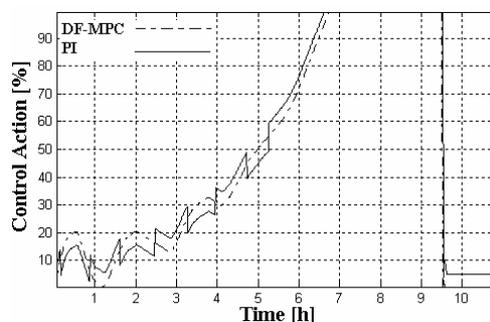
Fig. 7. DF-MPC Control Action (Zoom)

6.1. External Disturbances

DF-MPC rejects correctly the external disturbances when the substrate concentration in the feed $S_{p,fm}$ changes positively, even a high one is well tackled (100% from the original concentration). When the external disturbances are negative, the DF-MPC must saturate the valve while the substrate is consumed. Fig. 8 shows the output response to multiple disturbances with different amplitudes at different times (10%, 20%, 30% and 40% at one, two, three and four hours respectively). An important feature that difficult batch process control is the instant of the batch run when disturbance appears, that is, because disturbance effects change with time, even if the disturbance amplitude is the same.
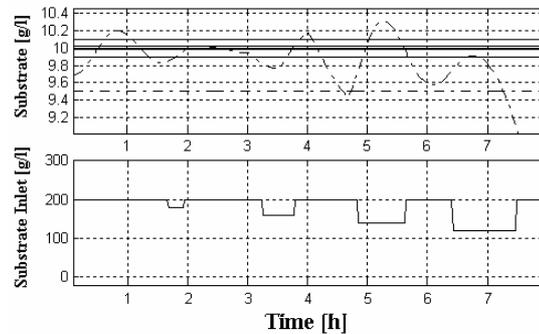
Fig. 8. Substrate Regulation with External Disturbances (Zoom).
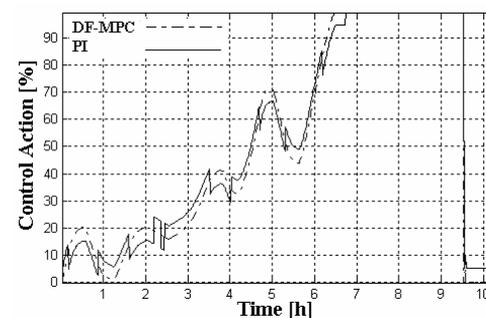
Fig. 9. Control Action when External Disturbances are applied to the Bioprocess (Zoom).

6.2. Internal Disturbances

This kind of disturbances is well rejected depending on its application instant and its amplitude. It is essential to remark that some internal disturbances occur during all the process: those produced by non controlled states, i.e, vegetative cells (X_v) are consuming substrate (Sp), so the state Xv is changing permanently. The other internal disturbances are applied to the process in two times: at the beginning of the batch run (first hour) and at the end of the controllable process phase (fifth hour). It is important to remark that internal disturbances applied are negative in sign with respect to the set point, that is, there is a substrate disappearance inside the bioreactor. If these disturbances are positive the MPC would not act because substrate would be exceeded and cells would eat with their natural dynamics. The results of internal disturbances applied at the first hour are shown in Figs. 10 and 11 for a maximum disturbance percent (80%). Notice that, the substrate concentration is also drastically reduced inside the bioreactor and the DF-MPC drives the process to the set point again. In addition, DF-MPC operates in all

the state-space because it was designed to operate in a nonlinear way, that is, a linear MPC controller cannot operate as good as a nonlinear one. The Fig. 11 shows how the final control element (a valve) moves under DF-MPC orders. Likewise, internal disturbances applied in the fifth hour are shown in Figs. 12 and 13 with a maximum disturbance (60%). Observe an important result: In this fedbatch process, disturbances are more harmful at the end of the process than the beginning. Notice that before the internal disturbance occurs, DF-MPC regulates the substrate in the set point and control actions are soft as it is shown in Fig. 13. In the same figure it can be seen that DF-MPC tries to drive the process to the set point, but in such point controllability is lost again.
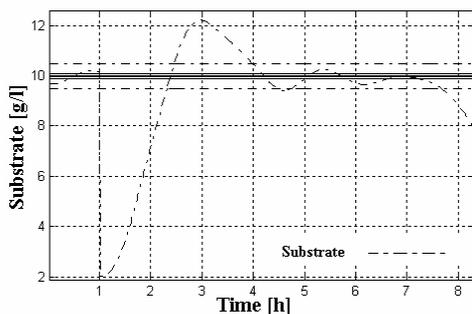
Fig. 10. Substrate Regulation with Internal Disturbance applied at the first hour (Zoom).
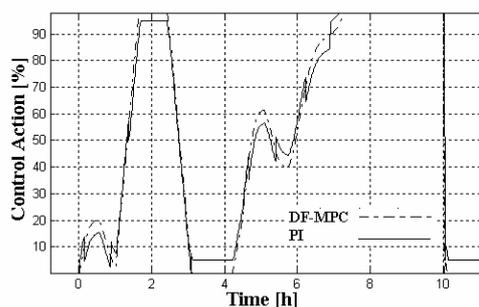
Fig. 11. Control Action when Maximal Internal Disturbance is applied at the first hour.

7. CONCLUSIONS

As it was mentioned above, this work is an exploration about a new MPC technique. A nonlinear MPC controller with dual fuzzy set strategy was designed. One of the aims of this work is verifying how the controller designed could affront the particularities that difficult the bioprocess control, specially the difficulties inherited from its batch nature (Gutiérrez, Rincón and Alvarez, 2005). Regulation was made to guarantee a maximum growth of vegetative cells. The main problem associated to regulation was the fundamentally internal disturbances, when substrate tries to maintain in the set point, the other states are permanently changing. These changes disturb the regulated substrate value. The use of a MPC technique based in Dual Mode (Michalska and Mayne, 1993) could affront the fundamentally internal disturbances, the internal (eventual) and external disturbances. In this work, PI parameters

used for the DF-MPC could not be calculated to guarantee stability. Future works must explore issues like parameter tuning of PI and MPC controllers for batch process. An interesting suggestion is making multivariable control based on the design presented in this work.
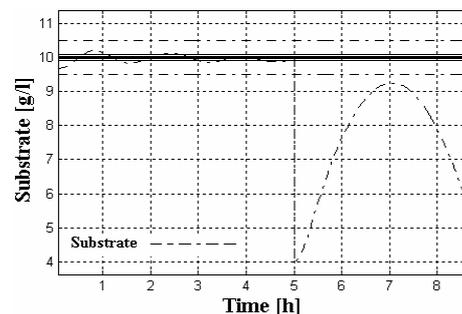
Fig. 12. Substrate Regulation with Internal Disturbance applied at the fifth hour (Zoom).
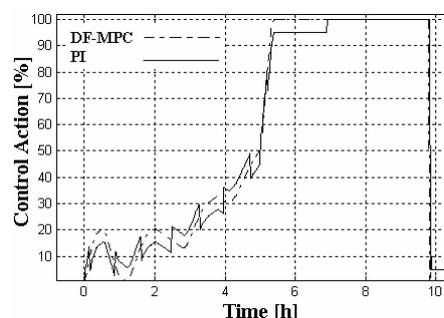
Fig 13. Control Action when Maximal Internal Disturbance is applied at the fifth hour (Zoom)

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