Nonlinear Geometric Controller for Bioprocesses:

Application to the Production of Saccharomyces Cerevisiae

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Abstract: This work describes the simulation of a nonlinear geometric control with state estimation by extended Kalman filter (EKF) in its continuous/discrete form. Measurements with delays and different sampling periods are used following previous simulation studies. The biological process studied is a fed-batch reactor for baker's yeast production. The state variable estimations are applied to the nonlinear control law developed in the framework of differential geometry theory.

Keywords: **Nonlinear Control, Delay systems, Fermentation, Extended Kalman Filter.**

I. INTRODUCTION

Biotechnological processes are characterized by a strongly nonlinear and unsteady behavior, so that linear control is not well adapted Bastin (1990). Recently, nonlinear techniques, which can deal with nonlinear and unsteady processes, have been developed Isidori (1989); Kravaris (1990) and particularly applied to chemical engineering Soroush (1993).

Nonlinear control based on differential geometry transforms a nonlinear into a linear system by a global or local coordinate change, either with respect to the state space equations or the input-output behavior Isidori (1989). The first method was introduced by Brocket(1978), Su(1982) and Hunt & Su(1983), who proposed a coordinate change and state feedback, which transforms a nonlinear state space model into a linear state space with specific characteristics. Examples can be found in works by Hoo (1986).

In the same context of linearization of the state space equations, Gilbert(1984) considered also error equation linearization. Isidori(1989) developed input-output linearization, which has been applied here in this work on a complex model of a pilot plant of baker's yeast production, a highly nonlinear fermentation process.[1],[5]

II. INPUT-OUTPUT LINEARIZATION OF NONLINEAR SYSTEMS

The SISO system, affine with respect to the input *u,* is modeled as :

$$\begin{cases} \dot{x} = f(x(t)) + g(x(t))u \\ y = h(x(t)) \end{cases} \quad (1)$$

where $x \in R^n$ is the state vector, $u \in R$ the input and $y \in R$ the output.

A necessary and sufficient condition for input-output linearization is the existence of a positive integer r defined as the relative order. In this case, the nonlinear system can be transformed as:

$$y^{(r)} = v \quad (2)$$

to realize asymptotic tracking, a control law must be synthesized such that the output $y(t)$ asymptotically follows a reference trajectory $y_c(t)$. Consequently, the error $e(t) = y(t) - y_c(t)$ must satisfy the following equation :[6]

$$e^{(r)}(t) + \alpha_{r-1} e^{(r-1)}(t) + ... + \alpha_1 e^{(1)}(t) + \alpha_0 e(t) + \rho \int_0^t e d\delta = 0 \quad (3)$$

where $\alpha_{r-1}, ..., \alpha_0, \rho$ are chosen so that the polynomial:

$$s^{r+1} + \alpha_{r-1} s^r + ... + \alpha_1 s^2 + \alpha_0 s + \rho \quad (4)$$

is Hurwitz. As :

$e = y - y_c, e^{(1)} = y^{(1)} - y_c^{(1)}, ..., e^{(r)} = y^{(r)} - y_c^{(r)} = v - y_c^{(r)}$, the equation (3) can be solved with respect to *v* to deduce the control law:

$$v = y_c^{(r)} - (\alpha_{r-1} e^{(r-1)}(t) + ... + \alpha_1 (t) + \alpha_0 e(t)) - \rho \int_0^t e d\delta \quad (5)$$

which realizes an asymptotic tracking for system (2). Thus the control law:

$$u=\frac{-L_f^r h(x)+y_c^{(r)}-\sum_{j=0}^{r-1}\alpha_r e^{(r)}-\rho\int_0^t ed\delta}{L_g L_f^{r-1}h(x)} \qquad (6)$$

realizes asymptotic tracking for original system (1).

III. KNOWLEDGE OF THE GLUCOSE METABOLISM OF SACCHAROMYCES CEREVISIAE

Saccharomyces cerevisiae is a facultative anaerobic yeast, sensitive to glucose catabolic repression. The nature of the carbon substrate leads the yeast cell to use one or another metabolic pathway. Generally, in the presence of molecular oxygen, glucose consumption by the yeast is achieved either by respiratory metabolism in the case of a fairly low glucose concentration or through fermentation with ethanol production. Ethanol uptake is always a respiratory phenomenon.

A fed-bath process figure 1 is a procedure to limit the bioreactor glucose concentration and allow the best yeast growth. Substrate feed rate can be controlled either from the glucose measurement with the aid of an autosampler or a specific glucose sensor, or from another molecule as , for example, ethanol by membrane sensors. [4]

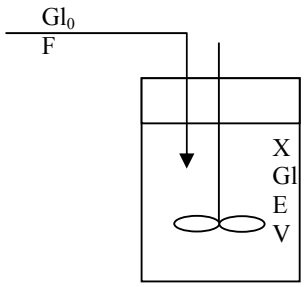

Fig.1. Schematic representation of a fed-batch representation process. F substrate rate;Gl_0, feed glucose concentration; Gl, glucose concentration; X, total biomass concentration; E, ethanol concentration; V, volume of liquid medium.

A. STATE MODELING AND OBSERVATION

A physiological model for yeast growth was employed. The kinetic model for yeast growth proposed by Rajab (1986) considers three different states: one for glucose fermentation producing ethanol and acetic acid; one where glucose is metabolized through the respiration pathway to sustain cellular growth; and one for ethanol respiration where ethanol is reconsumed for cellular growth. Kinetic equations correspond to an aerobic growth, with only one substrate limitation. Transitions between different physiological states are determined by the reactor contents in glucose and ethanol figure 2. [7],[9]

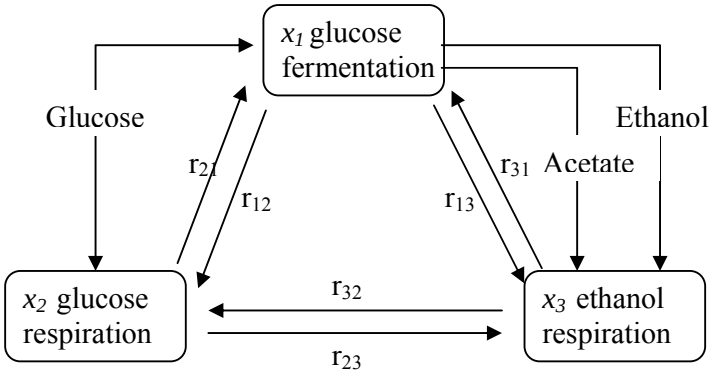

Fig.2. Model of the yeast metabolism, r_{ij} transition rate from state x_i to x_j

The states are respectively : biomass in three physiological states (x_1 to x_3), glucose (x_4), ethanol (x_5), acetic acid (x_6), volume *(V)*. The input is the glucose feed rate (*1/h*). The state space model is the following:

$$\begin{cases} \dot{x}_1=r_{x1}+r_{21}+r_{31}-r_{12}-r_{13}-x_1u \\ \dot{x}_2=r_{x2}+r_{12}+r_{32}-r_{21}-r_{23}-x_2u \\ \dot{x}_3=r_{x3}+r_{13}+r_{23}-r_{31}-r_{32}-x_3u \\ \dot{x}_4=-r_{g1}-r_{g2}+u(C_{gin}-x_4) \\ \dot{x}_5=r_{e1}-r_{e3}-x_5u \\ \dot{x}_6=r_{a1}-r_{a3}-x_6u \\ y=x_4 \end{cases} \qquad (7)$$

r_k are kinetic rates, which in general depend nonlinearly on the states according to Monod models. In this study, the extended Kalman filter in its continuous/discrete form was used for state estimation; it is continuous in respect to states and error covariance propagation between two measurements, discrete for correction at measurement times. The volume is assumed to be known and is not estimated. The model can be written in the following form: [2],[3],[10]

$$\begin{cases} \dot{x}=f(x(t),u)+w(t) \\ z(t_k)=h(x(t_k))+v(t_k) \end{cases} \qquad (8)$$

where $\dot{x}(t)$ is the state vector, $f(x(t),u)$ is the state function vector, $z(t_k)$ is the observation vector at discrete times t_k, $h(x(t_k))$ is the observer equation vector.

where $w(t)$ and $v(t_k)$ are independent, zero-mean, Gaussian noise processes of covariance matrices Q and R_k, respectively.

The propagation of state estimation and of the error covarriance matrix on the time interval $[t_{k-1},t_k]$ are:

$$\dot{\hat{x}}(t)=f(\hat{x},u,t) \qquad (9)$$

$$\dot{P}(t)=F(\hat{x},t)P(t)+P(t)F^{t}(\hat{x},t)+Q(t) \quad (10)$$

where $F=\left(\frac{\partial f}{\partial x}\right)_{x=\hat{x}}$

The correction of the state estimation and the error covarriance matrix on the time t_k equal to:

$$\begin{aligned}\hat{x}(t_k/t_k)&=\hat{x}(t_k/t_{k-1})+K(t_k)[z(t_k)-h(\hat{x}(t_k/t_{k-1}))]\\ P(t_k/t_k)&=[I-K(t_k)H]P(t_k/t_{k-1})\end{aligned} \quad (11)$$

where $H(\hat{x}(t_k/t_{k-1}))=\left(\frac{\partial h}{\partial x}\right)_{x=\hat{x}}$

and $K(t_k)$ is the Kalman gain matrix equal to :

$$\begin{aligned}&K(t_k)=P(t_k/t_{k-1})\,H^{T}(\hat{x}(t_k/t_{k-1}))\cdot\\ &\left[H(\hat{x}(t_k/t_{k-1})P(t_k/t_{k-1})\right]^{-1}H^{T}(\hat{x}(t_k/t_{k-1}))+R_k\end{aligned} \quad (12)$$

B. Optimal process control for biomass production

The glucose concentration is the key factor in the regulation of the yeast metabolism during the fermentation process, so it is quite naturally the one chosen as the control variable. The optimal process control must maximize both cell yield and productivity, yet there is no way of obtaining both the highest growth rate and the highest yield simultaneously. The best compromise consists of working with a glucose concentration that offers the best specific growth rate without any notable decrease in efficiency. The specific growth rate is considered to be optimal if it is not accompanied by the production of ethanol, and when the growth yield is equal to $0.5g$ of yeast per g of consumed sugar. This yield is obtained during physiological state X_2, but the glucose concentration has to remain consistently quite low, i.e below $0.07g/l$ in the culture medium (Mosrati and al, 1991). [8]

VI. Application of nonlinear control to the pilot plant

to obtain the system relative order, the following Lie derivates are calculated after explanation of kinetic laws:

$$L_g h(x)=C_{gin}-x_4$$

$$\begin{aligned}L_f h(x)=&-\frac{\mu_{\max 1}}{Y_{(x/g)1}}\left[\frac{x_4}{K_{g1}+x_4}\right]\left[\frac{1}{1+\frac{x_6}{K_{a1}}}\right]x_1\\ &-\frac{\mu_{\max 2}}{Y_{(x/g)2}}\left[\frac{x_4}{K_{g2}+x_4}\right]x_2\end{aligned} \quad (13)$$

As the glucose concentration x_4 in the reactor is always different from the feed concentration C, the Lie derivative $L_g h(x)$ is not null and the relative order is equal to 1.

From the equation (6) the following control law results:

$$u=\frac{v-L_f h(x)}{L_g h(x)} \quad (14)$$

where v is a new external input:

$$v=K_c\left[(y_c-y)+\frac{1}{\tau_i}\int_0^t (y_c-y)d\delta\right] \quad (15)$$

the controller parameters of PI(proportional integral) are chosen so that the following characteristic equation has roots with a negative real part ensuring sufficient robustness:

$$s+K_c\left(1+\frac{1}{\tau_i s}\right)=0 \quad (16)$$

Parameters value are K_c=14.29, τ_I=0.2 and closed loop poles are : s_1=-7.14+4.51j, s_2=-7.14-4.51j

V. Simulation

In an actual fermentation, the process is performed in two stages: a discontinuous one where the input u is null (batch reactor) and a fed-batch stage where u is not null anymore (feed-batch reactor). The first stage is thus performed to open loop and the second to closed loop. Transition from open loop to closed loop occurs when the threshold $x_5 \le 10^{-3} g/l$ is reached.

The complete fermentation lasted 20 hours. From 0 to 10h, the reactor operated as a discontinuous fermentation, thus in open loop. After 10 hours of fermentation, it operated in closed loop. The glucose feed concentration was equal to C_{gin}=320g/l.

The state observation and control were effectively implemented when the inoculum was introduced in the 10 liter reactor. The initial conditions for state variables are the following: $x_{10}=0.35 g/l$, $x_{20}=0.1\,g/l$, $x_{30}=0.1\,g/l$, $x_{40}=8\,g/l$, $x_{50}=0.057\,g/l$, $x_{60}=0.0057\,g/l$.

The ethanol sampling period is 3min, the glucose sampling period is 15min. Glucose and ethanol measurements present delays of 15min and 3min respectively; estimation between $(t\text{-}15)$ and (t) for glucose, between $(t\text{-}3)$ and (t) for ethanol are used to compensate delays.

Glucose fermentation phase corresponds to the period $0 \le t \le 4h$; during this time, glucose concentration decreases from 10 to $0g/l$ figure 3. At $t=16h$, closed loop control begins and glucose concentration increases slowly towards the set-point $0.07g/l$, this latter corresponding to a nearly quasi-optimal biomass productivity. It must be mentioned that the set-point is filtered by a first order filter to smooth the trajectory and avoid input saturations figure 4.

After $t=10h$, ethanol was already completely consumed and the semi-continuous phase of fermentation began;

during this second phase, the ethanol concentration always remained lower than 0.1*g/l* figure 5.
Figure 6 show the feed flowrate which incrised exponetially after 10*h*

IV. CONCLUSION

Nonlinear control based on differential geometry has been executed in simulation of a semi-continuous bioprocess. Simulations that were performed, despite of important and unpredictable technical difficulties, this control technique has shown a very good performance for trajectory tracking. A state observer was necessary because of incomplete state measurement; the extended Kalman filter that was used performed satisfactory in general, despite different measurement sampling periods and important delays due to the measurement techniques.
The fixed objective is to maximize the productivity. The gotten control has some remarkable stability properties, although the model of state of the process is greatly nonlinear and no stationary. Simulations show that this control has a good performance and robustness near the set-point.

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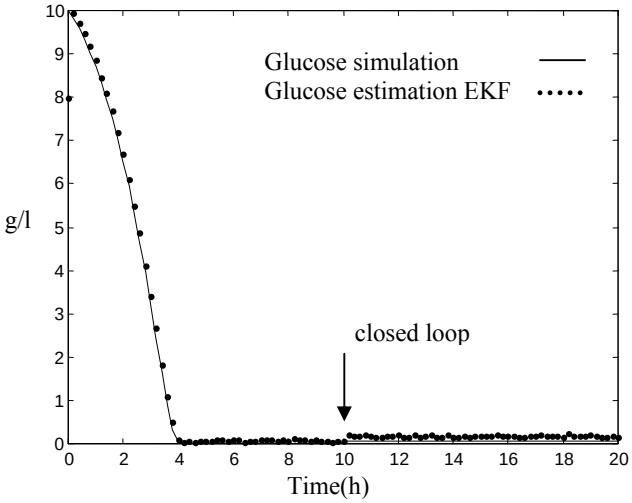

Fig. 3. Glucose concentration evolution

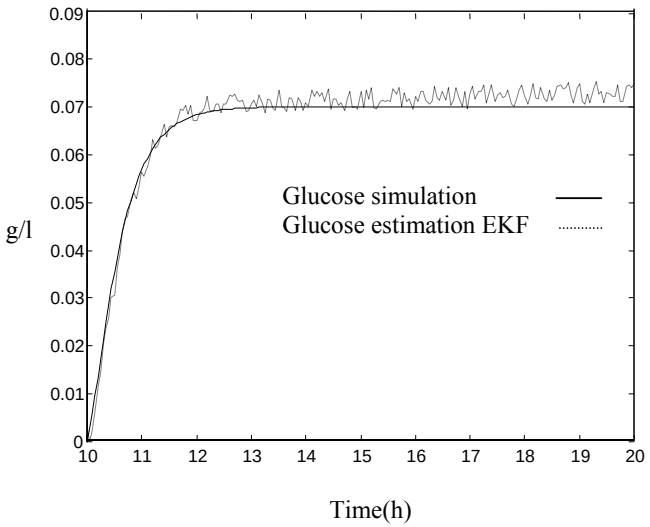

Fig. 4. Glucose concentration during the control phase set-point value 0.07*g/l*

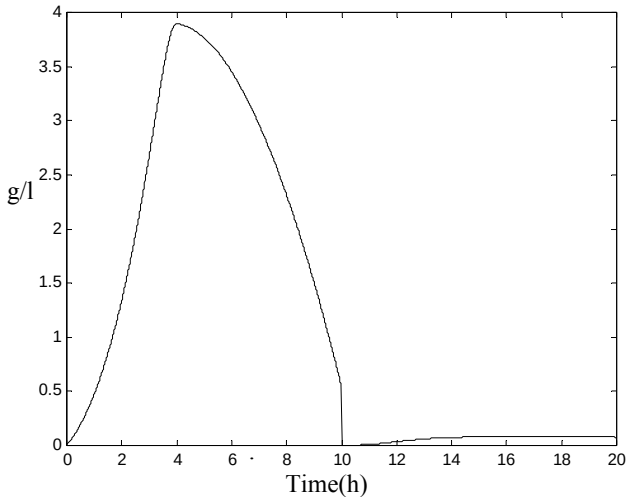

Fig. 5. Ethanol concentration evolution

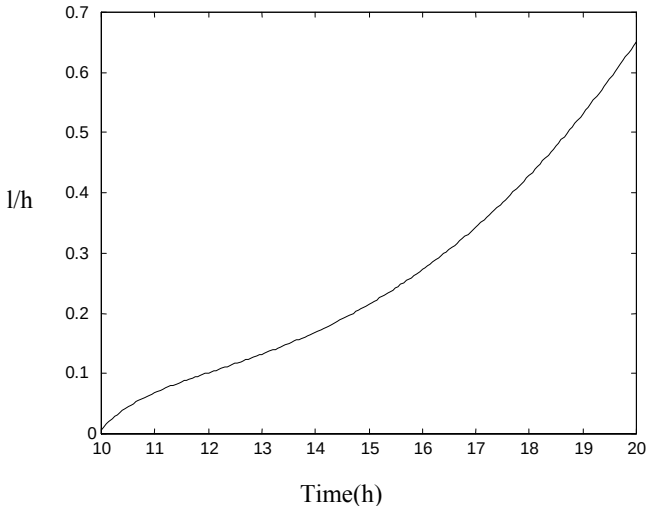

Fig. 6. Glucose feed flowrate