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Bioprocess Intelligent Controllers

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Abstract: Artificial neural networks (ANN) have been widely used for monitoring, control and optimization of various bioprocesses mainly because of their ability to understand a function from observations. However in the last two decades the application of intelligent controllers has grown tremendously in the field of bioprocess control. This paper provides a brief review the different theories of intelligent control along with a survey of their applications in various bioprocesses of control strategies in terms of type of controller, the structure, the algorithms, the objectives and the results of the work. Apart from demonstrating the successful applications of intelligent controllers in several control applications, the versatility of the controllers to be applied in multiple control methods has also been shown.

Keywords: Bioprocess control, intelligent control, Artificial neural network, Bioprocess control

I. INTRODUCTION

The use of biological agents such as cells, antibodies or even enzymes for research, production, etc. has been acknowledged and employed for centuries. Processing of biological materials known as bioprocess has number of applications including production of chemical compound amalgamated by some microorganism, cultivation of biomass, extraction of metabolites, production of antibodies and degradation of pollutants [1-3]. Bioprocesses are carried out in vessels called bioreactors, which provides necessary optimum conditions for bioprocesses to take place by using appropriate control strategies. Bioreactors are usually cylindrical vessels whose size varies from a few litres to cubic meters. They are a combination of controllers and various sensors to measure the pH level, temperature etc [4]. Bioreactors are classified into three types based on the mode of operation. They are batch, fed batch and continuous. In batch reactors feeding is done once before operation after no more feeding is done until the process is completed. The product or any other material withdrawals are made after completion of the process. In fed batch addition of feed (nutrients) is done by a predetermined rate during the fermenter operation but no withdrawals of any sort are done till the process is completed. In continuous mode feed is added to the bioreactor and product is removed continuously [5,6]. The control of optimum condition in bioreactor is achieved by using appropriate control strategies with a combination of various sensors to measure the pH level, temperature etc. and controllers.

For high productivity and high quality products, basic process parameters, that is pH, Dissolved Oxygen (DO), stirring speed, foam level temperature, etc. in bioreactor need to be controlled appropriately and these parameters must follow a specific profile of temperature, pH and DO in bioreactor for optimum cellular activity [7]. This is achieved indirectly by changing some other parameters. For example, pH, temperature and DO is manipulated by varying the flow rate of acid or base, by changing the flow rate of fluid through the cooling coil/jacket and agitation of mixture in the bioreactor respectively. Many researchers have been developing control strategies to optimize the bioreactor process, but this still remains a challenging task.

This paper provides a review of different applications of intelligent control strategies namely nonlinear model predictive control, adaptive control and fuzzy logic control in terms of their theory and a few applications scenarios.in terms of type of controller, the structure, the algorithms, the objectives and the results of the work have also been highlighted.

II. NONLINEAR MODEL PREDICTIVE CONTROL

A few case studies on applications of Non Linear Model Predictive Controllers to bioprocesses are discussed in the following sections.

A. Cultures of budding yeast in a continuous bioreactor

A model predictive controller was formulated as an infinite horizon open loop to control the dilution rate and the feed substrate concentration Zhu et al. [8]. The control was based on nonlinear ordinary differential equation model formed by spatially discretizing the population balance equations (PBE) for the cell mass distribution to the substrate mass balance.

Two controllers were developed, the first one used full order output vector which results in a configuration of 2 inputs and 110 outputs. The control horizon for this controller was chosen as 5. The second controller uses reduced-order output vector which results in a lower dimensional problem i.e. 2 inputs and 14 output variables. The control horizon for this controller is also 5. Both controllers were tested with and without disturbance models. Simulations showed that when a subset of discretized cell number distribution is used much better results are obtained. Ability of the MPC controller based on the full-order ouput vector to stabilize a culture which was oscillating originally at an operating point which is desirable is shown in Fig 1.

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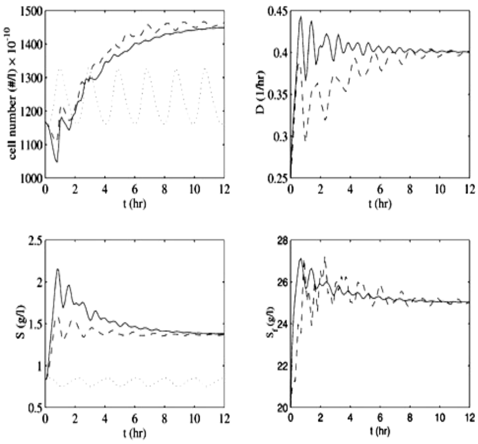

Fig 1 Oscillation attenuation: full-order output vector with (- -) and without (−) disturbance model and open loop response (.....)

The same test was simulated with reduced-order output vector in Fig 2. We find that although the results are similar but the MPC controller with reduced-order output vector gives smoother input moves.

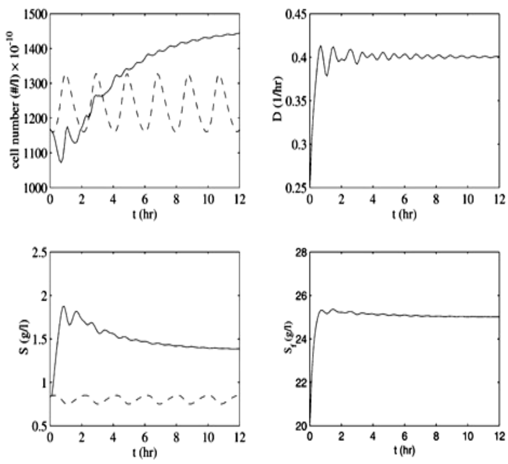

Fig 2 Oscillation attenuation: reduced-order output vector without disturbance model (−) and open loop response (--)

B. Baker's yeast production in a continuous fermenter

Optimal control of biomass growth based on substrate concentration was achieved by Ramaswamy et al. [9] by applying model predictive control to a non-linear continuous fermenter used in the production of baker's yeast.

The MPC control algorithm has been mathematically represented as

$$\min\{u(k|k), u(k+1|k), \ldots, u(k+M-1|k)^J\} = \emptyset[y(k+P|k)] + \sum_{j=0}^{P-1} L[y(k+j|k), u(k+j|k), \Delta u(k+j|k)] \quad (1)$$

u (k+j|k) is the input u(k+j) calculated from the information available at time k, y(k+j|k) is the output y(k+j) calculated from the information available at time k, $\Delta u(k+j|k)$ = u (k+j|k) - u (k+j -1|k) . J is the objective function. The non-linear arguments of the control horizon (M) and the prediction horizon (P) are $\emptyset$ and L respectively and are defined as

$$L = [y(k+j|k) - y_S(k)]^T Q [y(k+j|k) - y_S(k)] + [u(k+j) - u_S(k)]^T R [u(k+j|k) - u_S(k)] + \Delta u^T(k+j|k) S \Delta u(k+j|k) \quad (2)$$

$$\emptyset = [y(k+P|k) - y_S(k)]^T Q [y(k+P|k) - y_S(k)] \quad (3)$$

where $u_S(k)$ and $y_S(k)$ are steady state targets for u and y, respectively, T is the sampling interval and Q,R and S are positive definite weighting matrices.

The model control horizon was set to 1. The prediction horizon was set to 15 while the weight matrices Q, R and S were set to 10, 0 and 1. All these parameter values were determined by trial and error. It was seen in simulations that when the initial conditions have low quantities of cell mass the system behaves similar to a batch reactor with the controlled variable completely turned off. It was also noted that when high cell mass and substrate was present in the initial conditions the manipulated variable becomes very large and the valves are opened completely. In case the cell mass quantities are high but the substrate conversion is low the manipulated variable increases in the beginning but after some time decreases significantly. Hence it was concluded that well-made controller designs may provide poor control causing batch or washout modes. The schematic representation of the MPC control algorithm is shown in Fig 3.

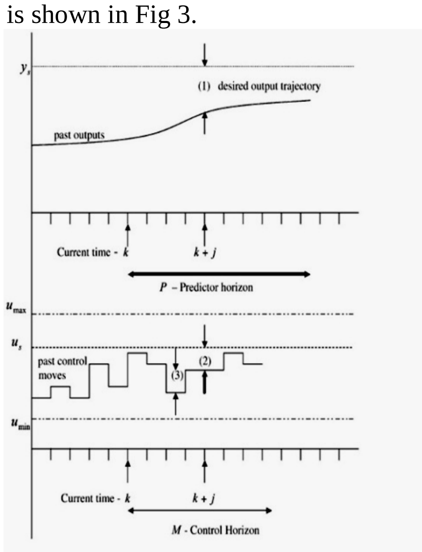

Fig 3 Schematic representation of the MPC control algorithm

C. Penicillin production in a fed-batch fermenter

Model predictive control was used for control of a penicillin production in a fed batch bioreactor by Ashoori [10]. A linear predictive controller (LPC) with prediction horizon and control horizon both set to 24h was used at first. The controller did not show satisfactory performance, which was expected since the penicillin production process is highly non-linear. After this a nonlinear predictive controller (NLPC) was used with prediction horizon was 12 hours and the control horizon was 9hours. This showed acceptable performance as the penicillin production was 25% greater than when the linear controller was used. In order to reduce computational costs piecewise linear models are used to solve the nonlinear model of the process. Neural networks are used to select

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the fuzzy weights of these models. The input space is hence divided into small subspaces which are linear and possess fuzzy validity functions. So each linear model is a fuzzy neuron based on the validity it holds in its region. The complete model is hence a neuro-fuzzy model with one hidden layer and a linear output. This model just calculates the output as the weighted sum of the locally linear models. Hence the computational cost is reduced and the production process is optimized. The multiple-model) structure is shown in Fig. 4.

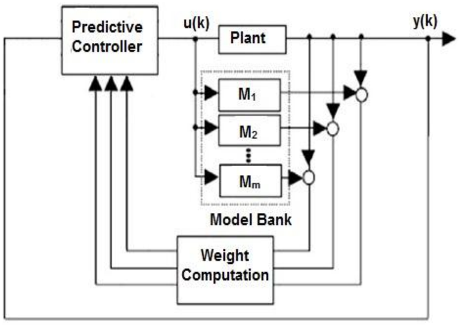

Fig 4 Multiple-model (including locally linear neuro-fuzzy models) structure

D. Hydrogen production in continuous anaerobic digesters
By manipulating the input flow rate by means of model predictive control, of a continuous fermentation reactor, the production of bio-hydrogen was increased by 75% by Aceves-Lara et al. [11]. A two liter reactor continuous stirred tank reactor with a 1270 mL useful volume was used. The control horizon is set to 15min while the prediction is set to 3.5h. To obtain values of states and process inputs at any time an asymptotic observer was used. The experiment was run for 25 days. For the first 15 days only the observer performance was studied i.e. the MPC was turned off. Estimations by the observer were seen to be very near to experimental data. After this the controller was switched on for 10 days. It was noted that the controller adjusted the input flow rate and the quantity of hydrogen produced increased by almost 75%. Hydrogen gas flow rate is shown in Fig 5 below.

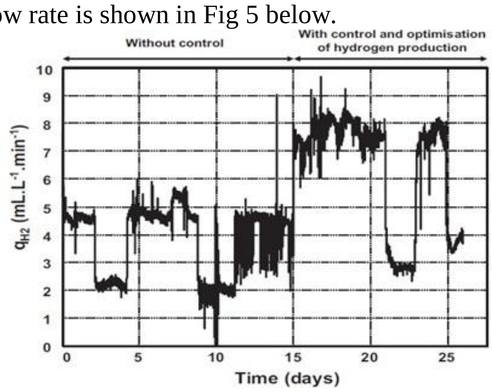

Fig 5 Hydrogen gas flow rate with and without control

III. ADAPTIVE CONTROL

A few case studies describing the applications of adaptive control to bioprocesses have been discussed in the subsequent sections.

A. Production of complex therapeutical molecules by use of micro-organisms

An algorithm for the adaptive control of dissolved oxygen concentration in a bioreactor with respect to the agitation rate was developed by Diaz et al. [12]. Recursive least-squares identification method was used for the online estimation of the parameters. The adaptive controller was based on the Generalized Predictive Control [13]. For this type of adaptive controller no theoretical knowledge of the mechanisms of the bioreactor is required. In the experimental setup a pulse pump was used to inject substrate, on-off PID controllers have been used to monitor and control the anti-foam, pH, temperature, air flow and agitation rate. The control algorithm was developed in LabVIEW. The efficiency of the dissolved oxygen control was seen to be better than 1% regardless of the disturbances caused by culture sampling, anti-foam additions and changes in air flow. Tests with high noise levels of the sensor and model errors showed the robustness of the controller as it provided correct controls under these conditions. The schematic diagram of the culture system is shown in Fig 6.

B. Microbial growth with Haldane's Kinetic
For a continuous stirred tank bioreactor with Haldane's kinetics an adaptive extremum seeking control scheme was presented by Marcos et al. [14]. Parameter estimation algorithm was derived from production rate and stabilized substrate concentration. Lyapunov function was used to derive the update laws. The proposed extremum seeking controller is used to thrust biomass and substrate concentrations to desired set points to ensure optimization of the production rate.

To make sure that the production rate converges to an area of its maximum a persistence of excitation condition is prepared. The simulation is done in two steps. The first simulation is done with a simple microbial process with Haldane's kinetics. The results showed that the production rate reaches the maximum point effectively and rapidly. even in the presence of injection of the excitation signal.

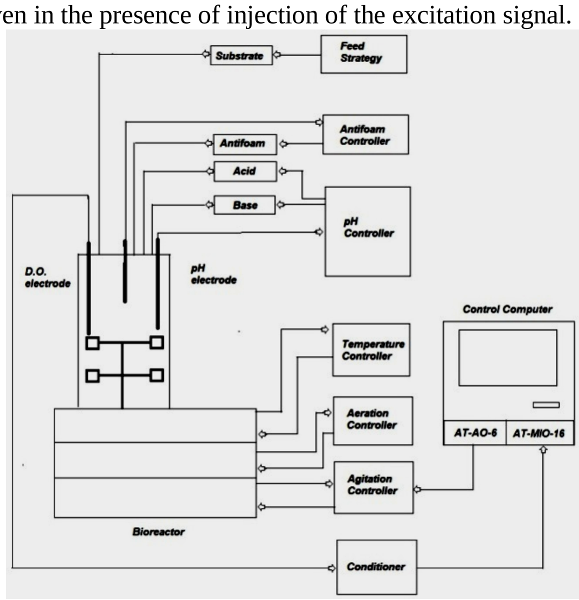

Fig 6 Schematic drawing of the culture system

The second part of simulation is done on the anaerobic digestion process which was mentioned earlier. The results

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of this simulation showed that the controller was able to track the unknown optimum although convergence of parameters to their true value was not possible due to the bias generated in the estimation routine by modelling uncertainty. Both cases however demonstrated the ability of the developed controller to recover unknown optimum. The simulation results for the anaerobic digestion process are shown in Fig. 7.

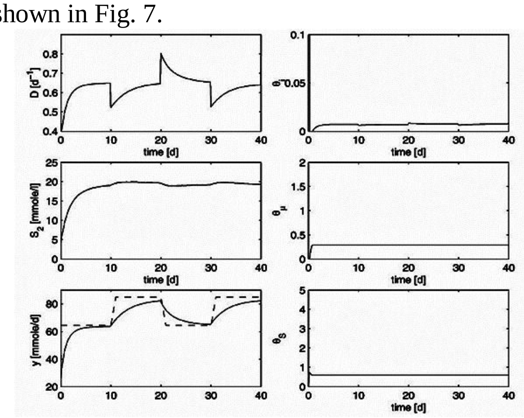

Fig 7 Anaerobic digester Performance of the extremum seeking control

(Dashed line represent square wave influent concentrations and optimum)

C. Depollution of wastewater

Depollution wastewater was carried out in a recycle bioreactor with a non-linear multivariable adaptive control strategy by Petre et al [15]. A novel state observer coupled with a parameter estimator was used for on-line estimation of parameters. The concentrations of biomass in the aerated tank and the recycled biomass were estimated by using an asymptotic state observer while the parameter vector which contains the unknown kinetics and/or the yield coefficients were estimated on-line by an appropriately parameter estimator.

Fig. 8 shows the diagram of the designed controller. The performance of the multivariable adaptive controller was compared with exact linearizing controller by simulation. It was seen that both pollutant concentration and dissolved oxygen level concentrations were tracking the preset reference profile which ensured a low level of pollution. Simulations with noise were also carried out and the results were comparable to the noise free results. It was confirmed that the controller is more effective than an exactly linearizing non-adaptive controller by simulation.

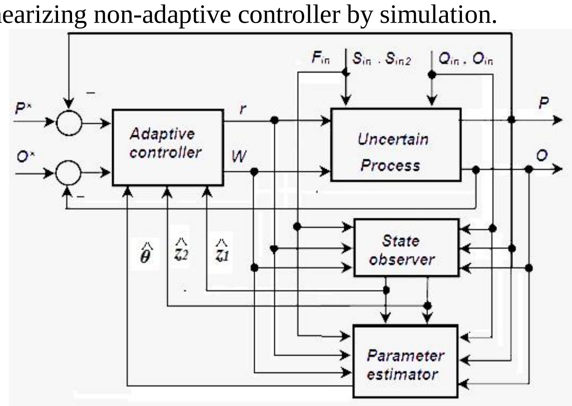

Fig 8 Block diagram of the designed adaptive system

D. Water hydro servo cylinder system

Comparison of the control performance of simple adaptive control (SAC) to water hydraulic servo cylinder system was done by Ito [16]. The aim of the control strategy was to design an adaptive input for the cylinder position which tracks a predefined reference model.

The block diagram of the designed SAC system is shown in Fig 9. The overall structure consisted of two feedback controllers and two feed forward controllers. It is implemented based on the command generator tracker which provides feed forward control input for perfect tracking and the almost strictly positive real property. Both adaptive control input and parameter update are derived from Lyapunov theory. Simulations were done for simple adaptive controller, model reference adaptive controller (MRAC) and PI controller. Overshoot was only seen in PI controller while SAC and MRAC showed almost the same control performance. Since SAC has a simpler structure and fewer adaptive parameters than MRAC and also shows nearly the same performance as MRAC, it makes SAC more practical.

IV. FUZZY LOGIC CONTROL

A few illustrations of fuzzy controls in bioprocess control are given next**.**

A. Cephalosporin C batch production

The automatic selection of the moment of feeding of inverted sucrose for Cephalosporin C batch production process was achieved using a fuzzy control system [17]. The authors in this paper have used carbonic gas percentage in the outflow as a variable to determine the moment of feeding for the process. They have carried out two experiments. The first one was to collect the data for determination of membership functions and rule base for the fuzzy controller while the second one for was testing feasibility and robustness. Isosceles triangle membership functions have been used. They have considered the input values which are to be fuzzyficated as crisp since significant noise wasn't observed in the direct readings.

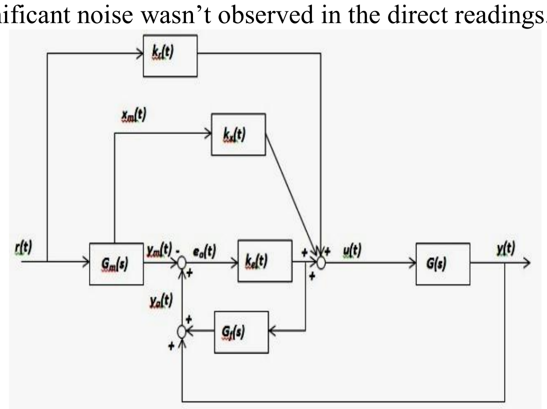

Fig 9 SAC system with parallel feed forward controller

The designed fuzzy control system operates on three reasoning levels. First one known as the attention level has 4 rules which determine only the moment at which tracking of percentage CO_2 is initiated based on how high the CO_2 percentage is present in the outflow. The second one, which is known as the action level, has 2 rules to track the variations of the CO_2 percentage (ΔCO_2) to

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determine the point of maximum percentage at which the feeding will initiate. The last reasoning level protection has 4 rules and aims to prevent possible errors which may occur at points where outflow gases passes through silica columns which removes the moisture. These points may be confused with the points of maximum CO_2 concentration. Hence the protection level identifies the difference based on the fundamental differences of the variables, specifically the fast increase in CO_2 level after a minor time interval in the column exchange.

For the defuzzification pre-determined criterion values were used to get the output. The controller was tested using the second experiment and the controller behaved as expected. The action level starts the feeding time exactly when the CO_2 percentage is maximum and the protection level cancels out the feeding in case of column exchanges. Hence the paper suggests a successful technique for the development of the feeding strategies using fuzzy logic. The response of the fuzzy controller has been shown in Fig 10.Figures.

B. Baker's Yeast fermentation in a production scale bioreactor

Baker's yeast fermentation has been carried out in a production scale fed-batch reactor to control substrate and air flow rate based on the ethanol concentration, dissolved oxygen concentration, elapsed time and specific growth (estimated) by Karakuzu et al. [18].

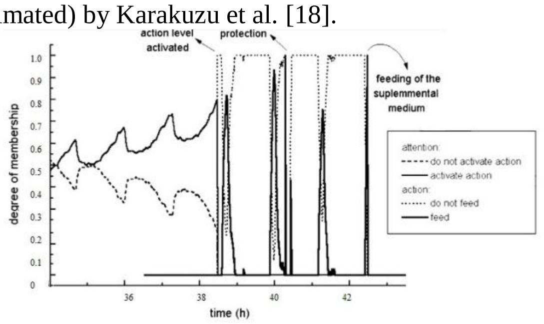

Fig 10 Fuzzy controller response

A fuzzy controller based on the Mamdami fuzzy inference system using. T-norm and T-conorm operators are used by the controller. The output the centre of area defuzzification scheme is used to obtain the output. Since the availability of cheap and reliable online sensors for measuring key parameters in the market is limited, two neural network soft sensors for estimation of biomass concentration were developed. The first one showed satisfactory results when the initial conditions were fixed but in case of varying initial conditions the results were not satisfactory. The second sensor was developed to work under varying initial conditions. The sensor showed robust and satisfactory results even in case of sharp changes in any input. The fuzzy controller was based on the results of the second sensor. The simulation was carried out in Matlab Simulink. The controller was run with conditions comparable to production scale.

The results of molasses and air feeding profiles were compared to the ones in production. A high similarity was observed in molasses feeding profile. For the air feeding profile similar but lower airflow rates were detected which shows further optimization of airflow rate as it reduces aeration costs. Block diagram of the control structure is shown in Fig 11.

C. Biodegradation of mixed wastes in a continuous stirred bioreactor

Galluzzo and Cosenza aim at controlling the phenol concentration of a continuous stirred bioreactor with cell recycle in which the biodegradation of mixed wastes is carried out in order to drive the process to a desired set point and prevent the system from bifurcating [19].

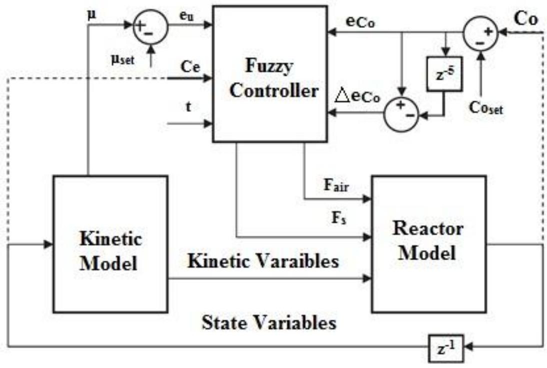

Fig 11 Block diagram of the control structure

The controller developed for this purpose is a type-2 fuzzy logic controller (FLC). The type-2 FLC just like a type-1 FLC has four components: Rules, Fuzzifier, Inference-engine and Output-processor but the output-processor of the type-1 is just a defuzzifier while that of the type-2 contains two parts: Type-reducer and Defuzzifier. The type-reducer reduces the output of the controller to an output similar to that of a type-1 FLC and the defuzzifier calculates the crisp output by simple average of the end points of an interval set.

The membership function used is the Gaussian shape since it gave the best results in simulation in terms of integral of absolute error (IAE). It has a set of 49 fuzzy control rules. The results were compared with a type-1 FLC and a PI controller. The type-2 FLC showed the best performance categorized by oscillations with amplitude smaller than that of type-1 FLC and the PI controller. It was also the first controller to reach the set point value. The type-2 FLC show robustness and ensure a control which even though is not optimal but much more efficient that the type-1 FLC and the PI controller. The Type-2 FLC is given below in Fig 12.

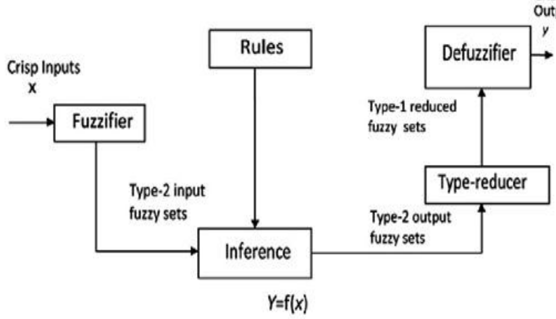

Fig 12 Type-2 Fuzzy logic controller

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D. Continuous stirred tank reactor with non-monotonic growth kinetics

A fuzzy servo controller was designed to track two switching reference signals near the optimal productivity for a continuous stirred tank bioreactor (CSTB) with substrate inhibition kinetics in order to control the CSTB near its maximum productivity condition [20]. The dilution rate was used as the control input. The two reference signals that were evaluated were substrate and biomass.

A parallel distributed compensation was used to build a fuzzy controller from the Takagi-Sugeno model. The fuzzy system was obtained through nonlinear sectors. The system has a set of 8 rules and is used to maintain a CSTB at the optimal point by switching between unstable and stable equilibrium points and uses a center average defuzzifier. Two tracking schemes were developed. First one was to track a reference signal to maintain optimal substrate concentration while the second one was to track a reference signal to maximize biomass productivity. The fuzzy servo controller was compared with PID and LQ controllers.

The fuzzy servo controller showed nearly the same settling time as the PID for reference tracking to maintain optimal substrate but there was no overshooting during the reference tracking to maximize biomass production. The settling time for the fuzzy servo controller was half that of the PID. The LQ controller in both cases showed superior performance than the fuzzy servo and the PID controllers. Moreover the biomass fuzzy controller had a bigger instability region than the substrate fuzzy controller. The comparison of the biomass fuzzy servo controller with PID and LQ controllers in Fig 13.

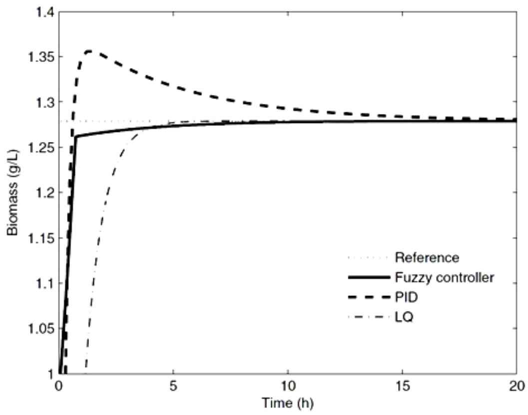

Fig 13 Comparison of the biomass fuzzy servo controller with PID and LQ controllers

V. CONCLUSION

A bioprocess like any other process is said to be controlled effectively if the set objectives of the process are completed successfully with reliability and promptness by using accurate control of the process parameters. Many researchers have been developing control strategies to optimize the bioreactor process, but this still remains a challenging task. In this paper a few applications of intelligent controllers have been discussed to show the effective and versatile use of these controllers in various bioprocesses. It was noted that majority of studies were done using simulations while very few have been implemented to actual systems which has opened a door to many implementation possibilities..

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