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Control Implementation in Bioprocess System: A Review

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Abstract

Bioprocess control consists of establishing a strategy for the management of the biocatalyst environment. Bioprocesses include several different units in which a near optimal environment is desired for microorganisms to grow, multiply, and produce a desired product. However, bioprocess control provides special challenges due to significant process variability and the complexity of biological systems. In this paper, various control strategies that have been implemented in bioprocess reactor for the last twelve years from 1995 to 2006 are reviewed. Four major control schemes; i.e. model predictive control, neural network based control, adaptive control and fuzzy control are mainly discussed in this work and their effectiveness control schemes are also highlighted.

Keyword: *Bioprocess Control; Advanced Control; Bioreactor*

1. Introduction

The processing of biological materials and employing biological agents such as cells, enzymes, or antibodies have been recognized since thousands of years. Bioprocess is currently involved in producing some chemical compound synthesized by a microorganism; cultivate a biomass for its utilization, extraction of its metabolites, and to degrade a pollutant [1]. Temperature, pH and dissolved oxygen are the most widely measured and controlled parameters. In production, only critical parameters may be measured to enable proper control of the process and ensure high quality and yield; however, in practice, less of suitable sensors and tools for online monitoring have not allowed this idea to be widely implemented [2].

Advanced control methods have been effectively employed for this type of industry. However, recently only model-based control strategies have been implemented for biological processes. The combination of more than one type of model in a hybrid form was shown to perform well for bioprocess control applications [3]. There are many types of models which can be categorized in various ways such as deterministic, non-deterministic, logistic (linguistic), mathematical equations base, data-driven and knowledge driven.

In this paper, the recent applications of major controlled schemes to industrial biological processes are summarized, compared and discussed in term of the system features, control purpose, input and output variables, development and its effectiveness. The characteristic of controller implementation systems and the usefulness of controller for the bioprocess are described.

Bioreactor requires advanced regulation procedures to ensure the bioprocesses performance and efficiency. However, the control of bioreactors is a delicate problem since most of the time the available biological models are only rough approximation. The dynamic nature of bioprocesses results in varying growth rates, oxygen uptake rate and product formation rates under different operating conditions. Bioprocess employs most of the same types of control as are used in other chemical industries such as model predictive control, neural network, adaptive control and fuzzy control methods.

2. Model predictive control

Model predictive control (MPC) algorithms have been widely used in industrial processes in recent years. These algorithms are well suited for high performance control of constrained multivariable processes because explicit pairing of input and output variable is not required and constraints can be incorporated directly into the controller design. Model-based control of bioprocess is a difficult task due to the challenges associated with bioprocess modeling and lack of on-line measurements.

Costa et. al. [4] studied the design, optimization and controls of extractive alcoholic fermentation process using non-linear predictive control. In their works, they applied Functional Link Network (FLN) to identify the process using simulated data generated by a deterministic model whose parameters were obtained from experiments. The FLN could describe the non-linear dynamics of the process. The predictive controller for this work presented good performance to lead the system to new set-points and to eliminate the influence of disturbance i.e (feed substrate concentration and feed temperature).

Dowd et. al. [5] manipulated and controlled substrate concentrations in the perfusion bioprocess using predictive modeling and control. They applied model of glucose uptake rates to estimate the state of the process and change manipulated variables. The flow rates were adjusted to drive the process close to the set point. With good model estimation of glucose uptake rates, predictive control was able to maintain the process at the set point with a small level of variability.

Foss et. al [6] investigated the use of MPC on batch fermentation processes using a non-linear model in the controller. They operated the process with combination of operating regimes and simple local state-space model into a global model structure using an interpolation method. The results showed that the operating-regime-based modeling framework can be used as a means for modeling processes that operate over a wide range of operating conditions. The results also show an improved performance by moving from a linear to a non-linear model as the basis for MPC in this type of process. However, the improvement is limited by hard upper constraints during significant parts of the batch.

Preub et. al. [7] described the necessary control and supervision steps when temperature control was implemented in a batch pharmaceutical reactor. They developed several predictive controllers and minimized objective function to make it different with conventional MPC and it has to be demonstrated that the controller keeps the temperature within predetermined ranges for the operation conditions and set-point profiles defined in the respective recipe.

Campello et. al. [8] presented and applied model-based predictive control of a complex industrial process for ethyl alcohol production. They proposed control scheme that based on the used of the well-known generalized predictive controller algorithm combined with a linearization of the orthonormal basis function hierarchical fuzzy model at each sampling instant. The MPC was able to control the ethanol concentration even in the presence of disturbance which strongly affects the process dynamics.

3. Neural Network Based Controllers

Neural network methods can provide adequate precision in estimating variables from incomplete information. Neural networks have drawn much attention because it does not require any prior knowledge about the relationship that exists between the states of the systems. When processes are complex and poorly understood in a mechanistic sense, hybrid modeling through knowledge integration can be employed with advantage because the model accuracy can be increased by the incorporation of alternative and complementary sources of knowledge. Many extensive reviews about neural network have been done by several researchers; Hussain [9] reviewed the various applications utilizing neural networks for chemical process control. The review involved three major categories of control i.e. inverse-model based, predictive and adaptive control techniques.

Glassey et. al. [10] used artificial intelligence methodologies, including artificial neural network (ANN) and knowledge based system to monitor and control batch bioprocess reactor. The missing value that's come from sensor failure can be replaced using either statistical methods or by more sophisticated methods such as auto associative ANNs. Validated data is then passed to the fault detection module where deviations from nominal process behavior such as lower productivity or expression vector instability can be detected. This system is generic in that the modules can relatively easily be modified for a particular process as has been demonstrated on industrial processes.

Oliveira [11] also come out with general framework in combining first principles modeling and artificial neural networks to improve bioprocess operation. The bioreactor system is described by a set of mass balance equations, and the cell population system is represented by an adjustable mixture of neural network and mechanistic representations. He applied a cooperative work between all factors producing knowledge which can contribute to design the accurate process model and efficient new model-based operating strategies.

Dirion et. al. [12] applied a neural controller for temperature control of a batch reactor. The system is general bioprocess and the work focused on the design and development of the neural network. They also developed a control structure based on two neural networks. First is a neural controller which computes the control variable to be applied to the reactor and second is a neural model of the process. This neural model is used to transform the error between the reactor and the set point temperatures into a signal. The results showed the good performances of the neural controller. They observed a very good tracking of the set-point and a smooth evolution of the control variable.

There are several difficulties with neural network on-line implementation. It must be trained off-line because of the long computation time needed for training. Gadkar et. al. [13] developed neural network with intra-connections within the output layer to track the dynamics of fed-batch yeast fermentation. This network architecture was capable of providing online state estimates within a reasonable domain outside its training space. The results showed that it can be implemented for online control and able to track the changing dynamics of the process due to the external disturbances.

4. Adaptive Control

The most common task considered in the design of bioreactor control system is the regulation of known set-points or the tracking of specified reference trajectories. In some applications, however the control objective could be to optimize an objective function such as the biomass production rate or the growth rate which is generally a function of the substrate concentration and the unknown parameters. Guay et. al. [14] proposed adaptive extremum seeking techniques to solve this class of control problems. They assume limited knowledge of the growth kinetics and introduced adaptive learning techniques to construct a seeking algorithm that drives the system states to the desired set-points that maximize the value of an objective function.

Arauzo-Bravo et. al. [15] implemented adaptive internal model control (IMC) strategies for penicillin production. Adaptive IMC strategies were tested in the simulated plant. They showed that adaptation can correct on the unexpected variations occurring along the fermentation. They used neural networks and fuzzy logic to build knowledge based controller. Results in adaptive cases showed better tracking of reference than the respective non-adaptive controllers. The used of fuzzy logic within neural networks allows for the expression of acquired knowledge with rules that resemble those handed by humans.

Vallentinotti et. al [16] used novel adaptive control methodology based on the internal model principle in a fed-batch fermentation of *S. Cerevisiae* to maintain the desired ethanol setpoint and reject the perturbation. In their work, the optimization, modeling, and control methodology also can be used for the regulation of other quantities related to the exponential cell growth in fed-batch fermentation. This controller demonstrated the effectiveness for rejection in closed-loop of unstable disturbance.

Smets et. al [17] designed model-independent adaptive control by developed heuristic control strategies with nearly optimal performance under all conditions. They applied this control strategy to fermentation reactor and showed the interesting perspectives to obtain robust and practically realizable, nearly optimal control solutions for biochemical conversion process.

Renard et. al. [18] used minimal process knowledge and minimal measurement information to develop robust adaptive controller and applied to ethanol regulation in cultures of *Saccharomyces cerevisiae.* The design procedure can be extended to other important control problems in fed-batch fermentations, such as the regulation of a limiting substrate concentration, the acetate regulation in E. coli fed-batch cultures and the regulation of a limiting substrate concentration. The controller showed the asymptotic rejection of unstable disturbance, good robustness to model uncertainties and noise attenuation on the control signal.

5. Fuzzy Control

Fuzzy control has been introduced in the biotechnology field for several years and recently, several applications of fuzzy control, including large-scale fermentor control, have been reported. The applications of fuzzy set theory for modeling and control of bioprocess from 1990 to 2000 has been already reviewed by Shioya et. al., [19]; Honda & Kobayashi,[20]; Horiuchi, [21]. They summarized the characteristics of fuzzy control applications in industrial biological processes as shown in Table 1. Fuzzy control was applied to various fermentation processes, but type of cultivation was fed-batch culture except for the Japanese sake brewing which requires specific fermentation techniques. They all reported that there was no difficulty in applying the fuzzy control system developed at pilot scale level to a commercial scale process without major modification of production rules and membership functions.

Nakano et. al. [28] used fuzzy logic control (FLC) to maintain the microaerobic condition in the xylitol production phase by regulating the proportion of air flow rate supplied to the fermentor. The advantage of FLC, i.e., a knowledge based control system, is its flexibility in being able to handle bioprocess information, in both mathematical and linguistic forms, within a computer-implementable system.

Karakuzu et. al [29] designed fuzzy controller based on the proposed structure using simulation model of fed-batch baker's yeast fermentation system. They used actual measurements as a basis for feedback control to estimate the biomass concentration and specific growth rate. The controller determined substrate and air flow rate, relating to status of estimated specific growth rate, elapsed time, ethanol concentration and dissolved oxygen concentration. This method was able to improve estimation even with varying initial condition. The controller has generated substrate and air flow rates as an output acceptable in large scale.

There are also others control strategies method that have been applied to bioprocess technology such as Model-based geometric control algorithm (MGA) proposed by Gomes & Menawat, [30]. They developed MGA for controlling the dissolved oxygen concentration in fermentation processes. The algorithm is developed on a generic system description witch encompasses a wide range of models commonly used to describe bioprocesses. They compared the performance of algorithm with performance of an IMC and classical PI controller and the results showed that MGA performed better than the IMC and PI controllers. The MGA is adaptive, robust, incorporates an integral component and converges within a finite number of steps.

All the controller models applied to the bioprocess reactor from 1995 to 2006 are summarized in table 2.

6. Conclusions

The bioprocess suffers from a lack of good mathematical models, because of its complexity, since it is highly non-linear, has time varying parameters. It is also has many important variables that cannot be measured on-line, along with others that can present high levels noise. A few advanced control strategies implemented in bioprocess have been reviewed. It was found that the designed and application of advanced control strategies in bioprocesses have been successfully achieved over past two decades. The common control strategies applied were model predictive control (MPC), neural networks based control, fuzzy control and adaptive control. All the controller strategies showed good performance in maintaining the set point and give better disturbance rejection for controlling bioprocess system. The purpose of this work is to spell out some of the prospects for advanced control in the current and future bioprocess technological environment, it is because the field will play important part in food, pharmaceutical, and scientific industrial over the next decade. The knowledge discovery on this research can be ported to industrial scale processes and helps professionals define, develop and apply a model control scheme in a virtual plant.

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TABLE 1: Applications of fuzzy control to industrial biological processes (Horichi J.I (2002))

Company	Ajinomoto	Sankyo	Japan Beet Sugar Mfg	Gekkeikan Sake	Nippon Roche
Product	Glutamic acid	ML-236B	Yeast	Sake	Vitamin B_2
Type of culture	Fed-batch	Fed-batch	Fed-batch	Sake brewing	Fed-batch
Culture time	About 35 (h)	About 350 (h)	12(h)	18(d)	48(h)
Control purpose	Control of residual sugar conc.	pH control by sugar feeding	Optimal control of sugar feeding	Dtermination of optimal temperature	Optimal control of sugar feeding and pH
State variables (inputs to fuzzy control)	Culture time, DO, dDO/dt	Total CO_2 evolution, pH, dpH/dt	Ethanol conc. (E), dE/dt, DO	Baume, difference in Baume, ethanol and pyruvate conc.	Culture time, CER, total CO_2 evolution, DO
Control variables (outputs from fuzzy control)	Molasses feed rate	Sugar feed rate	Sugar feed rate	Culture temperature	Sugar feed rate, pH
Inference method	Min-max operation	Indirect inferencing using culture phases	Min-max operation	Min-max operation	Indirect inferencing using culture phases
Rule number	18	5	15	196	4
Source of control rules	Experienced operator	Experienced operator	Analysis of fermentation characteristics	Experienced operator	Knowledge accumulated during commercialization
Result	Stable operation by automatic control	Increased productivity and stable operation	Increased productivity and automatic operation	High quality sake brewing by automatic control	Increased productivity and yield by automatic operation
Current status	Pilot	Commercial	Pilot	Commercial	Commercial
Reference	Nakamura et. al (1985) [22]	Hosobuchi et. al (1993) [23]	Ishiguri (1994) [24]	Oishi et. al. (1991) [25]	Horiuchi et. al. (1998;1999) [26,27]

TABLE 2: Summary- models controller applied in bioprocesses

No	Model	Batch Process	Note	Ref.
1	Non-linear predictive control	Alcoholic fermentation	The internal model for predictive controller was presented using FLN	[4]
2	Predictive control	Perfusion	The MPC controller gave smooth transition between batch and perfusion culture.	[5]
3	Non-linear predictive control	Fermentation	Used operating-regime-based modeling framework for modeling process and the performance was limited by hard upper constraints	[6]
4	Predictive control	Pharmaceutical	Application of MPC controller in industrial	[7]
5	Predictive control	Ethanol production	The control scheme is based on the GPC algorithm combined with a linearization of the fuzzy model.	[8]
6	Neural network	-	Applications of neural networks both in simulation and online implementation	[9]
7	Neural network	Cultivation	The system can easily be modified for a particular process.	[10]
8	Neural network	-	The process is in semi-batch pilot-plant reactor	

				[11]
9	Neural network	Ethanol fermentation	Only dissolved oxygen conc. measured online, the neural network was used to predict the state variables.	[12]
10	Adaptive extremum seeking control	-	For unknown growth kinetic model.	[13]
11	Adaptive control	Penicillin production	Based on neuro-fuzzy models.	[14]
12	Adaptive control	Fermentation	The adaptive controller allowed rejection of unknown unstable time-varying disturbance	[15]
13	Adaptive control	Aerobic fermentation	The controller can be applied to both define and complex media cultivation processes with unknown composition.	[16]
14	Adaptive control	-	The concepts are applied to a non-perfectly mixed chemical conversion process	[17]
15	Adaptive control	Fed-batch fermentation	The robust controller using minimal process knowledge and minimal measurement information.	[18]
16	Fuzzy control	-	Knowledge-Based design	[19]
17	Fuzzy control	-	Industrial practices of fuzzy control are introduced.	[20]
18	Fuzzy control	-	Applications of fuzzy control to industrial biological processes.	[21]
19	Fuzzy control	Microbial production	The flexibility of FLC in being able to handle bioprocess information.	[28]
20	Fuzzy control	Baker's yeast fermentation	Fuzzy control was design based on simulation model of fed-batch fermentation system.	[29]
21	Model-based geometric control algorithm (MGA)	Fermentation	Comparing the performance of IMC, PI and MGA	[30]

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