Implementing Advanced Control Strategies to improve the Bioprocess Applications

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ABSTRACT

Problem:
- Recombinant protein production by various host organisms is strictly regulated, and this is primarily determined by host cell genetics and also by control of various process parameters in the reactor.
- Since the process dynamics typically exhibit nonlinear interactions amongst the critical process parameters, the commonly employed controllers are suboptimal for control of most bioprocesses.

Solution:
- Implementation of a hybrid controller augmenting DAC and DIOLC strategy that effectively allows simultaneous control of two critical process parameters.

INTRODUCTION

- Human serum albumin (HSA) is a protein consisting of 583 amino acids which is a major protein in human plasma and is synthesized in the liver.
- Accurate control of the process and optimal design of the media are critical for robust and stable production of recombinant proteins.
- We propose a control scheme which can maintain higher consistency in process parameters that ultimately leads to maximum productivity.

Controller Perspective:
- A detailed knowledge of the process model is a prerequisite for implementing the linearizing methods.
- The decoupled input-output linearizing controller (DIOLC) derived from the principles of global linearization has been previously implemented.4-5
- Aiming to alleviate the previously identified inadequacies of the DIOLC but using a decoupled adaptive controller (DAC) for substrate control, augmented with the DIOLC scheme for DO control in Pichia pastoris fermentation.

This hybrid control scheme has been successfully employed and the results demonstrate that we achieve a 1.5 fold higher product titer compared to the traditional process controllers.

MATERIALS AND METHODS

- Strain: Pichia pastoris X-33 Mut+ strain
- Media optimization: mixed feed and single feed
- Controller used: PID, DIOLC, DAC, DAC-DIOLC.
- Process was simulated first and was also experimentally verified

Fig. 1. Experimental platform showing the implementation of the various on-line monitoring and control loops used for fed-batch fermentation.

CONTROL STRUCTURES

- Fig 2. a) Schematic representation of the Decoupled Adaptive (DAC) structure, b) Schematic representation of the Decoupled Input Output Linearizing Control (DIOLC) structure, c) Schematic representation of the DAC-DIOLC hybrid control structure

CONCLUSION

- Discrete decoupled control strategies based on non-linear reference model were tested and compared for control of a Pichia fed-batch fermentation process for the production of HSA.
- Their ability to decouple the interaction between the substrate and dissolved oxygen though simultaneously controls the process regime was assessed.
- DIOLC, with a single set of tuning parameter, and DAC with continuous adaption, were used. The control input (Fv) was obtained from the dilution rate (μ) and the airflow rate (Q) was obtained from the oxygen mass transfer coefficient (KLM) using an empirical correlation.
- The results demonstrate that performance of DAC is the case of the substrate control and DIOLC for DO control was satisfactory. DAC controller exhibited higher sensitivity and sustained oscillations during the adaptation phase in DO measurements.
- In view of these results, a hybrid DAC-DIOLC controller was implemented online, and the resulting performance was demonstrated to be superior to that with the PID controller as well as the individual decoupled controllers.

INDUSTRIAL SIGNIFICANCE

- Improved process control and automation in fermentation batches, the most common and substantially important unit process in any pharmaceutical industry leading to higher consistency and quality maintenance.
- Increased productivity with time minimizations leading to higher profits.

TECHNOLOGY READINESS LEVEL

-TRL level 5: As per TRL guidelines, we have experimentally proved our proposed concept and are currently developing technology for implementation in real time environment.

REFERENCES


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