World Academy of Science, Engineering and Technology
International Journal of Biotechnology and Bioengineering
Vol:16, No:06, 2022

Cybernetic Model-Based Optimization of a Fed-Batch Process for High Cell Density Cultivation of E. Coli In Shake Flasks

Authors : Snehal D. Ganjave, Hardik Dodia, Avinash V. Sunder, Swati Madhu, Pramod P. Wangikar

Abstract : Batch cultivation of recombinant bacteria in shake flasks results in low cell density due to nutrient depletion. Previous protocols on high cell density cultivation in shake flasks have relied mainly on controlled release mechanisms and extended cultivation protocols. In the present work, we report an optimized fed-batch process for high cell density cultivation of recombinant E. coli BL21(DE3) for protein production. A cybernetic model-based, multi-objective optimization strategy was implemented to obtain the optimum operating variables to achieve maximum biomass and minimized substrate feed rate. A syringe pump was used to feed a mixture of glycerol and yeast extract into the shake flask. Preliminary experiments were conducted with online monitoring of dissolved oxygen (DO) and offline measurements of biomass and glycerol to estimate the model parameters. Multi-objective optimization was performed to obtain the pareto front surface. The selected optimized recipe was tested for a range of proteins that show different extent soluble expression in E. coli. These included eYFP and LkADH, which are largely expressed in soluble fractions, CbFDH and GcanADH , which are partially soluble, and human PDGF, which forms inclusion bodies. The biomass concentrations achieved in 24 h were in the range 19.9-21.5 g/L, while the model predicted value was 19.44 g/L. The process was successfully reproduced in a standard laboratory shake flask without online monitoring of DO and pH. The optimized fed-batch process showed significant improvement in both the biomass and protein production of the tested recombinant proteins compared to batch cultivation. The proposed process will have significant implications in the routine cultivation of E. coli for various applications.

Keywords : cybernetic model, E. coli, high cell density cultivation, multi-objective optimization
Conference Title : ICBEB 2022 : International Conference on Bioprocess Engineering in Biotechnology
Conference Location : London, United Kingdom
Conference Dates : June 27-28, 2022