Title:

Robust control of fed-batch cultures of Escherichia coli

Abstract:

Escherichia coli is a widespread cellular host for the industrial production of protein-based biopharmaceuticals. This production, mainly operated in fed-batch mode, aims to maximize biomass productivity. However, the accumulation of acetate during the culture inhibits the cells respiratory capacity and lowers their metabolic performance.
In this thesis, closed-loop feeding control strategies are considered to avoid acetate accumulation and maximize biomass productivity. To this end, model-based control and estimation schemes are developed to regulate the biomass growth rate and the acetate concentration. The control methods ranged from the Generic Model Control and Nonlinear Model Predictive Control, and the non-measured variables are estimated using the Unscented Kalman Filter. The developments focused on the robustness of the proposed methods due to the uncertain nature of the bioprocess. The performance and robustness of the control and estimation strategies are tested and tuned through different scenarios
of simulation runs. Fed-batch cultures of E. coli BL21(DE3) strain are successfully carried on a lab-scale bioreactor, highlighting the potential of the proposed strategies in real-time conditions. The proposed control strategies presented in this thesis lead to an average gain of up to 20% in biomass productivity compared to the conventional operating mode.

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