Novel strategies for control of fermentation processes

There is increasing interest in applying more advanced control strategies to biological processes in order to optimise the operation of these complex systems. In the past years, the major increases in product titre have been achieved mainly by genetic engineering approaches, which has lead to highly optimised industrial host strains. The focus of this project is instead on en-gineering of the process. The question to be answered in this thesis is, given a highly optimised industrial host strain, how can we operate the fermentation process in order to maximise the productivity of the system?

In order to develop control strategies a significant effort must be invested into developing process models and establishing process understanding. Both data-driven modelling and mechanistic modelling approaches are considered in this work. Firstly, multivariate analysis is applied to production scale data from Novozymes A/S in order to predict the product concentration which is measured at the end of the batch. This is achieved with an average prediction error of 7.4%. The purpose of developing the model, is mainly in order to identify key process parameters which show variance relevant to the product concentration, and to identify process trends which lead to higher titres. The application of multivariate methods, in order to provide process insights, creates value from the vast datasets which are collected in industry.

A mechanistic model approach is then considered, based on previous work by Albaek et al (2012). This model describes the fungal processes operated in the fermentation pilot plant at Novozymes A/S. This model is investigated using uncertainty analysis methods in order to as-sess the applicability to control applications. A mechanistic model approach is desirable, as it is a predictive method which is able to be extrapolated outside of the conditions used to develop the model. For this reason, the mechanistic model approach is further investigated in this work.

The mechanistic model analysis showed that it provided a robust description of the physi-cal system, however there was a relatively high uncertainty in the description of the biological processes. For control applications the model is applied on-line, and therefore it is investigated whether the model prediction may be improved by incorporating available measurement data. A stoichiometric balance approach is applied in order to estimate model parameters including the rate of biomass formation and the rate of product formation. This leads to an increased prediction accuracy in the biological part of the model. The mechanistic model may then be applied as a valuable on-line monitoring tool.

The control strategy development follows on from the on-line model application. The aim of the control strategy is to maximise the total product achieved per batch. There is a demand to maximise the total product in each batch in industry, in order to meet increasing product demands with a limited capacity. The control algorithm is then defined in order to maximise the mass in the system, subject to the oxygen transfer rates in the system. Since the aim is to control to a target fill in a target time, a predictive model-based control algorithm is developed where by the model is simulated to the end of batch time at each model iteration. This provides a prediction of the future trajectory of the process, so that it is possible to guide the system to the desired target mass. The control strategy is applied on-line at 550L scale in the Novozymes A/S fermentation pilot plant, and the method is challenged with four different sets of process operating conditions. The controller reliably reaches the desired maximum tank fill, with a maximum error of under 5% of the target in eight experimental runs. The product concentration is not affected by the control strategy when compared to batches utilising a reference controller. This method has the benefit of reducing the variance in the final fill, which not only allows for a more reproducible product mass in a batch operation, but also aids downstream process scheduling and resource allocation activities in the industrial setting.