Nonlinear model predictive control of Escherichia coli culture

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1 Introduction

Escherichia coli is a popular microorganism in biotechnology applications, and the most commonly used host cell for the production of recombinant proteins and many other bio-pharmaceutical products. This production is mainly achieved through fed-batch cultures.
In order to maximize the biomass production and reach high cell densities, a substrate feeding strategy must be considered.
Feeding the culture with a rich medium containing a high glucose concentration might seem the ideal approach. However, it has been shown that exceeding a critical level of concentration of glucose can lead into Acetate production, a cell growth inhibiting byproduct.
To avoid this undesired behavior, and maintain the culture in optimal operating conditions, an optimal closed-loop regulation and feeding strategy is needed. This feeding strategy requires the development of an optimal closed-loop control algorithm based on the known measured outputs, and the estimated states.

2 Modeling

A mechanistic model of *E. coli* growth is considered. This model is based on Sonnleitner's bottleneck assumption (figure 2):
During a culture, the cells metabolism changes due to their limited oxidative capacity represented by a bottleneck.
When the substrate (glucose) is in excess, its concentration (denoted S) exceeds a critical value ($S > S_{crit}$), acetate is produced by the cells, and the regime is called respiro-fermentative regime.
Otherwise, when the substrate is low (*i.e* $S < S_{crit}$), the available glucose and/or Acetate are oxidized. The regime is called respirative regime [1–3].

3 Control strategy

An efficient control strategy of *E. coli* culture in fed-batch mode aims to maximize biomass production while maintaining Acetate concentration at a low level.
In order to achieve this objective, as a first step, an exponential feeding rate and its corresponding biomass

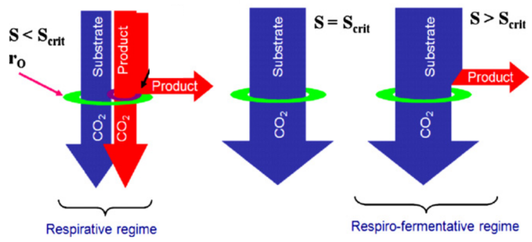

Figure 1: Sonnleitner's bottleneck assumption [3]

concentration profile are considered as a reference trajectory to track by the controller. The goal is to force cells growth to a desired regime and to maintain the culture in optimal conditions, starting from a different initial conditions and thus different regime.
The developed controller is a nonlinear model predictive controller (NMPC), minimizing a cost function that include the tracking error on biomass concentration, and the difference between the reference and applied control inputs.
The NMPC controller performance is then compared to a PID controller, in order to highlight the higher performance of the NMPC in comparison to classical control strategies [2].
This optimizing controller depends on the knowledge of the real time values of the different variables. However, reliable probes for online measurements with the desired accuracy are not always available.
To tackle the issue, in future work the NMPC controller will be coupled with an estimation algorithm to reconstruct unmeasured variables. An Unscented Kalman Filter (UKF) will be investigated.

References

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