IDP:
Integrating non-linear process kinetics in production planning & scheduling in biopharmaceutical production

Contact: Mirko Beißner (mirko.beissner@tum.de)

Topic:

Biopharmaceuticals are pharmaceutical drugs derived from biological sources used for therapeutic or diagnostic purposes. They possess a particularly high efficacy and efficiency in treating complex health conditions, like cancer, inflammatory diseases or metabolic disorders.

The primary biological production process is structured into two main stages: The upstream process (USP) contains all production steps related to the cultivation of the living organisms, while the down-stream process (DSP) comprises the separation and purification of the target molecule. Subsequently the purified active pharmaceutical ingredient (API), obtained from the primary biological production process, is formulated into its final dosage form, e.g. a syringe, during the secondary pharmaceutical production.

This IDP focuses on the operation of bioreactors in the USP. Process kinetics like cell growth, substrate concentration in the fermentation media and product formation kinetics can be described using non-linear differential equations (Buchanan et al. 1997, Zwietering et al. 1990, Chmiel et al. 2017). Existing literature on planning and scheduling in the biopharmaceutical production mostly simplifies product formation kinetics. Those models assume deterministic processing times, product yields or simplified linear product formation kinetics. This can lead to inaccuracies or even infeasible production schedules. Nevertheless, the impact of those simplifications have not been investigated so far.

In the wider process industries literature, non-linearity has been considered in integrated scheduling and process control approaches. See reviews by Dias and Ierapetritou (2016) Chu and You (2014) and Baldea and Harjunkoski (2014). In biopharmaceutical production non-linear process characteristics are only considered in process design (Liu et al. 2016, Brunet et al. 2012).

The objective of this IDP is to assess whether non-linear, biopharmaceutical production process kinetics can be integrated into production planning & scheduling and if this approach leads superior production schedules.

**Tasks:**

Your task will be to:

1. Summarize non-linear process kinetics relevant in upstream biopharmaceutical production.
2. Conduct a literature review on approaches to include non-linear process kinetics in operational decision making; i.e. production scheduling and process control.
3. Develop an integrated optimization model and a suitable solution approach for this model.
4. Implement the mathematical model in an appropriate modelling environment, e.g. Python or IBM ILOG CPLEX Optimization Studio and conduct a numerical study.

**Prerequisites:**

You should have taken the course “Modelling, Optimization and Simulation in Operations Management” or an equivalent course and therefore have an understanding of mathematical modelling. Also, you should be familiar with biotechnological production processes or have a sincere interest in acquiring that knowledge during the IDP. Some technical insights to bioreactor design, operations and control are necessary for this IDP.
References:


