Master thesis
Digital Twin Development of an iPSC Seed-Train

Bayer is a globally active company with core competencies in the life science sectors of health and agriculture. Through its products and services, Bayer aims to benefit people and contribute to improving their quality of life. Bayer values the passion of its employees for innovation and provides them with the means to effect change. Digitalization is a core topic and a driver of innovation at Bayer. In this context, methods of machine learning, artificial intelligence and digital twin concepts play a role in many areas. This thesis offers an opportunity to learn more about the applications of hybrid and mechanistic models for the development of digital twins in the field of cell and gene therapy.

Thesis Directions

As part of a Master thesis, the key challenges to investigate include:

1. **Hybrid modelling of iPSC seed train**: A seed train presents a critical process step in expansion of induced pluripotent stem cells (iPSCs). During the seed train, iPSCs are cultivated in cell factories that provide the surface for adherent growth conditions. In a typical seed train, passages between cell factories of increasing size are performed at regular intervals depending on the achieved confluency. The aim is to integrate mechanistic and data-driven models to capture the dynamic behavior of the culture conditions in terms of adherent cell growth and metabolite consumption and production.
2. **Model-based confluency estimation:** Given an adequate mechanistic or hybrid model to describe the culture conditions, the next step is focused on applying the model for real-time estimation of confluency. To that end, moving horizon estimation (MHE) should be explored as a method to update the model in real-time and to provide a forecast for the remainder of the cell factory cultivation. The aim is to achieve an accurate forecast of confluency and thus to improve decision making during the seed train operation.

Scope and Tasks

The thesis encompasses the following tasks:

- **Hybrid modelling of iPSC seed train:**
  - Understanding iPSC culture and seed trains in the context of cell therapy
  - Analyze available data and identify of promising data sets for model development
  - Determine the appropriate tool (e.g., Python, Julia, Matlab) for model development and simulation

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- Evaluate data-driven and mechanistic models to comprehensively represent growth conditions in individual flasks and cell factories
- Develop a robust model with the potential for end-to-end description of a complete seed train process

- **Model-based confluency estimation**:
  - Assess various MHE approaches for confluency estimation
  - Develop a methodology integrating the spatial variability of different cell factory segments into the MHE scheme
  - Adequately account for the uncertainty of image-based confluency estimation into the MHE algorithm
  - Evaluate the applicability and scalability of the estimation technique for real-time monitoring of iPSC seed train process

Requirements

Background in biochemical engineering or related fields is beneficial. Proficiency in Python or other programming languages. Familiarity with data driven and mechanistic modelling methodologies.

Background / Literature

- Hille, R., Brandt, H., Colditz, V., Claßen, J., Hebing, L., Langer, M., Kreye, S., Neymann, T., Krämer, S., Tränkle, J., Brod, H., Jockwer, A., Application of model-based online monitoring and robust optimizing control to fed-batch bioprocesses, *In: Proceedings of the IFAC World Congress*, 2020, 53(2), 16846-16851
- Elsheikh, M., Hille, R., Tatulea-Codrean, A., and Krämer, S. A comparative review of multi-rate moving horizon estimation schemes for bioprocess applications. *Comp Chem Eng*, 2021, 146
- Hernández Rodríguez, T., Posch, C., Pörtner, R., and Frahm, B., Dynamic parameter estimation and prediction over consecutive scales, based on moving horizon estimation: applied to an industrial cell culture seed train. *Bioproc Biosys Eng*, 2021, 44, 793-808
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