ScaleApp – Investigating large scale bioreactor effects in microbial application

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Motivation

The biotechnological production of enzymes and chemicals for industrial purposes in large scale bioreactors is state-of-the-art technology. However, environmental conditions are no longer homogenous in production scale, due to the formation of gradients in different zones of the bioreactor vessel (i.e. substrate, oxygen, pH, T, pCO_2). Such gradients are often responsible for performance losses during scale up. Although this is known for a long time, still no consistent strategy exists how to precisely scale down, tailored to the bioreactor and process. Rough estimations rather than knowledge-based approaches are typical, which prevent cost-efficiency during scale up. Not much advantage is taken from efforts made in sensor, -omics and strain engineering technology and computational approaches to directly address an increase of strain and process robustness related to large scale issues. Nevertheless, problems related to scale up are among the most important factors that reduce investments for the implementation of bioprocesses for novel products after a host strain has been identified at lab scale.

Project Summary

The ScaleApp project will address the next generation design of scale-down bioreactors by smart combination of powerful computational fluid dynamics (CFD) with innovative process analytical technology (PAT). CFD will be applied to model different bioreactor geometries from pilot-scale and production scale bioreactors. The CFD models will be validated using PAT allowing real-time measurements inside the bioreactor during the cultivation process. This is enabled by tailor-made multi-position

sensor devices already in place and functional, which can be moved along the height axis inside the bioreactor. Thus, the multi-position sensor devices precisely track concentration gradient profiles along the bioreactor height. In order to shed light on gradient distribution in the full space of the bioreactor volume, wireless free flowing small sensor devices will be applied to enable real-time dynamic measurements. For the first time, this will enable substantial validation of CFD and hybrid models with comprehensive data sets of spatially and timely resolved data. Validated CFD models will be used to optimise the design of a corresponding scale-down bioreactor setup. This tailor-made scale-down bioreactor setup will be physically built, validated and compared to its pilot scale representation. Different scale-down bioreactor setups will be validated for their potential and standards will be set to achieve precise scale-down applications.

ScaleApp also addresses metabolic analysis of the selected microbial systems under these precise scale-down conditions. Such investigation will deal with industrially relevant yeast strain as model for eucaryotes and protein secreting *Bacillus* strains as model for procaryotes with industrial partners. Stress response to gradients will be elucidated, i.e. at varying supply of substrate, oxygen, T or pH gradients. This is performed on the level of comparative -omics data sets, i.e. transcriptomics, proteomics, metabolomics, single-cell based physiologic and morphologic analysis. Metabolic targets identified are used to genetically engineer the microbial hosts for increased metabolic robustness providing superior applicability in large scale production. Models will be used to define acceptable operation ranges in order to describe opportunities for improved engineering of the large scale.

Improvements in the CFD-assisted design of scale-down bioreactor models and their application at early-stages of strain engineering and bioprocess development, will allow critical decisions already at the level of the lab-scale. From an economic point of view this reduces risk of failure and more reliable estimation of product development times and time-to-market. The economic impact of ScaleApp will be evaluated by process cost analysis by the industrial partners and LCA.

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