ERA CoBioTech

BioTech Research & Innovation Hack

2021

ERA CoBioTech Funded Projects at A Glance: ScaleApp

Investigating large scale bioreactor effects in microbial application

PART OF EUROPEAN BIOTECH WEEK

INNOVATION IS IN OUR GENES

ScaleApp

Investigating large scale bioreactor effects in microbial application

Researchers within the ScaleApp project work on the challenge to scale-up microbial bioprocesses from laboratory to industrial production scale by combining experiments with modelling and simulation.

The improved scalability of microbial bioprocesses from laboratory to industrial production is an important pillar to support a sustainable society based on renewable resources.

The biotechnological production of enzymes and chemicals for industrial purposes in large scale bioreactors is state-of-the-art technology. However, environmental conditions for the microbial cells are no longer homogeneous 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 loss during scale up from laboratory to production scale. Still, no consistent strategy exists how to predictively scale up bioprocesses, tailored to the bioreactor and bioprocess. Rough estimations rather than knowledge-based approaches are typical, which bear uncertainties during scale up usually accompanied with higher development costs. Not much advantage is taken from efforts made in process analytical technology and computational approaches to directly address an increase of strain and process robustness related to large scale issues. Nevertheless, challenges related to scale up are among the most important factors that could increase investments for the implementation of bioprocesses for novel products being a general threat for bioprocess economics.

Combination of microbial cultivation using scale-down bioreactor approaches, novel process analytical technology and computational simulation tools.

In the ScaleApp project we address next generation design of scale-down bioreactors by smart combination of powerful CFD with innovative process analytical technology. A scale-down bioreactor setup can mimic relevant characteristics of a large scale bioreactor, so that the process performance at larger scale can be simulated at laboratory scale already. Such a setup often consists of two or more reactor compartments, where one compartment represents the bulk zone of a bioreactor, while the others are used to add some disturbance, e.g., overflow of substrate, lack of oxygen or a different pH value. Tailor-made scale down bioreactor setups are validated and evaluated for their potential to facilitate bioprocess scale up. With a proper configuration to mimic a production bioreactor, the scale-down bioreactor can act as assessment center at the scale of laboratory cultivation experiments, to evaluate process performance under conditions close to large scale conditions, before doing expensive test cultivation in pilot or production scale. This is accompanied by novel process analytical technology to get insight into the extend of gradients in the pilot scale bioreactors by measurement of critical process parameters at different locations in the bioreactor. In combination with computational fluid dynamics methods the hydrodynamic properties of small and large scale bioreactors will be simulated and compared. In order to evaluate potential economic and ecologic impact of the project outcome, life cycle analysis is applied.

Main results

The ScaleApp project has already achieved major advancements in several fields. For a process producing a protease enzyme, the work of partners could identify targets for optimization of the production process. This protease is produced by the microorganism *Bacillus subtilis*, a well known and safe microbial production organism. It is a food market product already commercialized for bakery application, demonstrating the practical and economic relevance of the project results. Strikingly, the researchers could demonstrate a substantial metabolic robustness to specific bioreactor inhomogeneities, while others caused performance losses. In addition, the computational simulation of the hydrodynamics in small and large scale bioreactor vessels provided detailed characteristics of the fluid dynamics inside the bioreactors. Such information is extremely useful to tailor scale-down bioreactor setups in order to mimic large scale bioreactors in a realistic fashion. In addition, metabolic models could be connected to computational fluid dynamics models providing a link between the physical and biological description of the bioreactor process. Similar investigations were performed for a yeast production process.

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Project duration:

1 June 2018 - 15 January 2022

Total budget: 2.7 €M

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With the development of novel process analytical tools, the researchers were able to experimentally characterize gradient formation in a pilot scale bioreactor and compared the experiments with computational data.

Future prospect

The improvements in the design of scale-down bioreactor models and their predictive application at early-stages of strain engineering and bioprocess development, will allow critical decisions at the early level of the lab-scale rather than at the level of production scale. This can substantially reduce risk of failure of novel biotechnological products and processes. Moreover, it could provide a more reliable estimation of bioprocess development times for existing or new innovative products and processes from health care, food and feed as well as chemistry sector.
The results of ScaleApp project can show relevant societal and environmental impact, since it can facilitate the intensification of existing biotechnological products and processes as well as reduce the development risks for novel products and processes. This contributes to the sustainability challenge to move from a fossil based to a bio-based society.
Within the project duration various partners contributed to scientific conferences and ERACoBioTech events with oral and poster presentations, counting more than ten scientific contributions with more contributions expected for the time to come. In general, these contributions showed shared authorships between two or more partners demonstrating the fruitful collaboration of partners within the project. One oral presentation at the international BioProScale Symposium was awarded with a prize for excellent presentation and communication. The ScaleApp partner Technical University Berlin organizes the BioProScale Symposium, a biannual symposium bringing together academia and industry under the umbrella of bioprocess scale-up and down and other topics related to industrial biotechnology (https://biotechnologie.ifgb.de/). This symposium is an excellent place to present and discuss the ScaleApp results with academic and industrial experts. When the ScaleApp project activities started, the partners identified that standardization of experimental and analytical procedures between the different partner laboratories provided benefit in standardization of methods and procedures within the project. In terms of scientific publications, the ScaleApp project partners already published the first round of scientific manuscripts. Since most of the scientific relevant and valuable results are obtained in the last phase of ScaleApp more publications will be published in the time to come. In addition to scientific dissemination ScaleApp also addressed communication on a less detailed scientific level with society and an excellent example is a short story ´why microbes dislike big vessels´, which was communicated together with a bioreactor manufacturer (https://handling-solutions.eppendorf.com/cell-handling/bioprocess/processes-and-applications/detailview/news/beaker-or-swimming-pool-why-microbes-dislike-big-vessels/).

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Figure 1: Inside of pilot scale bioreactor for microbial bioproduction processes showing baffles on the inside wall, aeration device at the bottom and the stirrer shaft in the middle with mounted stirrer devices

Website: http://www.scaleapp.de

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