ERA CoBioTech

BioTech Research & Innovation Hack

2021

ERA CoBioTech Funded Projects at A Glance: ComRaDes

Computation for Rational Design: From Lab to Production with Success

PART OF
EUROPEAN BIOTECH WEEK
INNOVATION IS IN OUR GENES

ComRaDes

Computation for Rational Design: From Lab to Production with Success

The ComRaDes project is developing a robust and model-based simulation platform to rationally design scale-up techniques driven by profound biological and physical understanding to replace conventional, empirical scale-up methods.

Accelerating bioprocess development from lab to production scale in a sustainable way

The ComRaDes project is developing a robust and model-based simulation platform to ramp up the scale-up techniques driven by profound biological and physical understanding. In essence, the project aims to replace conventional, empirical scale-up criteria by predictive modelling and rational design, based on combined biological and physical expertise. The work is focusing on two leading industrial cases, comprising the micro-organisms Penicillium chrysogenum and Saccharomyces cerevisiae, but has general implications.

Development and application of computational approaches helps to design better scale-down simulators, enable faster scale-up, and improve the energy and resource efficiency of fermentations, thus accelerating bio-innovations to the markets. This bio-based drive is further essential to help solving the mega-issues of climate change, food security and energy supply.

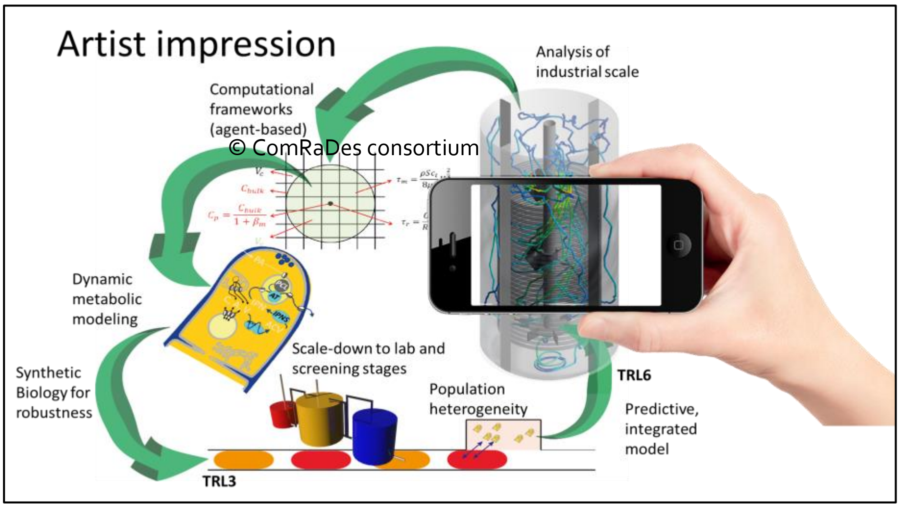

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Figure 1: Artistic impression of ComRaDes project (Overview of the elements that are developed and integrated in ComRaDes project)

The different parts of the platform are being developed by the three academic partners, Delft University of Technology, University of Liège, University of Stuttgart. The industrial partners of the consortium - DSM, Centrient Pharmaceuticals (formerly DSM-Sinochem Pharmaceuticals) and Syngulon are the end-users of the technology and will benefit from the platform to enhance their fermentation process development capability.

High-precision CFD-CRD (computational fluid and reaction dynamics) models.

Two industrial workhorses, Saccharomyces cerevisiae and Penicillium chrysogenum were studied in parallel. Data from industrial scale was analyzed using extensive, high-precision CFD-CRD (computational fluid and reaction dynamics) models. Models were applied to downscale the microbial environment in scale-down simulators. Execution of scale-down experiments in the lab included dynamics of oxygen and glucose concentrations, and shear forces. Microbial responses were evaluated on metabolome and

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Consortium:

Delft University of Technology, (The Netherlands)

Centrient Pharmaceuticals, (The Netherlands)

DSM, (The Netherlands)

University of Liège, (Belgium)

Syngulon, (Belgium)

University of Stuttgart, (Germany)

Project duration:

25 July 2018 - 31 December 2021

Total budget: 2 M€

This project has received funding from the European Union´s Horizon 2020 research and innovation programme under grant agreement No [722361]

This revealed novel insights in metabolic regulation and adaptation under representative industrial conditions. Data management was executed using FAIR principles, and proved to be key for successful, high-quality intra-laboratory research (different labs working on the same microbial strains, applying similar test conditions and recipes).

Main results

Some of the important conclusions from these studies:

1. For baker's yeast production, ethanol production is inevitable around the feeding point. With CFD simulations for industrial scale fermentor it is possible to distinguish the ethanol production due to overflow metabolism (Crabtree effect) from dO_2 limitation (Pasteur effect). Such information can prove crucial for process optimization.
2. For S.cerevisiae, intermittent feeding regime (IFR) fermentations using 2 STR's reveals condition-specific (non-adapted vs. adapted) and time-dependent differential gene expression. Targets will be analyzed for their control via Transcription factors and significant regulation will be proposed as engineering targets for strain improvement.
3. Novel tools such as segregostat have been designed and tested for studying population dynamics under Scale down conditions using S.cerevisiae. Individual and population responses could be clearly visualized and quantified.
4. For P.chrysogenum, CFD guided scale down experiments suggest that the Penicillin production rate is impacted due to coupled gradients of glucose-oxygen, providing ways to optimize the feeding of substrates

Future prospect

We have made industrial data available to the scientific community, to assist in executing highly relevant academic research. We also have presented results in the scientific literature and on scientific meetings. Further, the new Advanced Course has provided a rich podium to educate and transfer tools and insights to key experts in industry and at universities, addressing solutions to overcome the "innovation valley of death".

The project has brought a rich diversity in various dimensions, merging academic and industrial (incl. SME) cultures, as well as different nationalities of key project members (from several S, E and NW European countries, Asia, China, Middle-East).

Communication was transparent among industrial and industrial partners, and further resulted in joint scientific publications a well as a tailored, annual one-week Advanced Course (post-graduate) set up at the TU Delft.

The research part of ComRaDes is at TRL 3-4, the final delivery at TRL 5-6. The presence of DSM and Centrient as active partners in our consortium secured focus on reaching TRL 6, i.e. demonstrating the CFD-CRD and scale-down tools on existing processes from industry (not only for the model organisms, but also applied to other industrial hosts, e.g. B. subtilis and E. coli.

Clearly, the computation tools apply to assessing industrial processes and scale-down in the lab, however, the slow computation speed only allows off-line evaluation. To overcome this, at TU Delft and DSM we have initiated a follow-up collaboration on Artificial Intelligence and Machine Learning (https://www.dsm.com/corporate/news/news-archive/2021/2021-01-11-dsm-and-tu-delft-establish-artificial-intelligence-laboratory-to-drive-bioscience-innovation.html), applied to industrial fermentations.

Several publications have been published until now and many more are in the pipeline to be submitted soon. The information generated during this project is pioneering in the field for making next steps in understanding, designing and executing bioprocesses in years to come.

Following is the list of publications

1. Haringa, C.; Mudde, R. F. ; Noorman, H. J. From industrial fermentor to CFD-guided downscaling : what have we learned?. In: Biochemical Engineering Journal. 2018; Vol. 140. pp. 57-71. https://doi.org/10.1016/j.bej.2018.09.001
2. Haringa C., From Lab to Production with Success, NPT magazine, 2019.
3. Hajian C. S. S., Zieringer J., Takors R. Euler-Lagrangian simulations – a proper tool for predicting cellular performance in industrial scale bioreactors. In: Adv Biochem Eng Biotechnol. 2021; 177:229-254. DOI: 10.1007/10_2020_133
4. Hajian C. S. S., Haringa C., Noorman H., Takors R. Predicting By-Product Gradients of Baker's Yeast Production at Industrial Scale: A Practical Simulation Approach" In: Digital Twins - Applications to the Design and Optimization of Bioprocesses. 2020; 1554, 8(12) DOI: 10.3390/pr8121554

Project website: https://www.comrades-cobiotech.com/
Twitter: https://twitter.com/Comrades_eu

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