CFD-guided scale-down for end-in-mind bioreactor development: from 15 000 L to 2 L

Open per	*September 2024*
Duration	8 months
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1. General introduction

The development of upstream manufacturing processes for novel biotherapeutics progresses gradually from the laboratory to larger scales. However, often lab-scale bioreactor processes do not perform as expected when translated to manufacturing scale. Different dimensions and mixing/sparging capacities have a significant impact on hydrodynamics and mass transfer, which consequently affect mammalian cells [1-4]. Computational Fluid Dynamic (CFD) modelling allows the study of hydrodynamics and mass transfer inside bioreactors, posing a promising method to understand environmental conditions in large scale bioreactors and replicate these in lab-scale bioreactors.

This project is part of an public-private collaboration between TU Delft (TUD) and Janssen Biologics (JBV) aiming to develop technologies for biopharmaceutical manufacturing that will ensure patient affordability and industry competitiveness. The main goal is to develop a CFD model of a 2 L bioreactor where limiting environmental conditions of a 15K bioreactor are mimicked. The focus of the CFD simulations will be to study the large-scale (15 000 L) bioreactor limitations related to mixing, oxygen transfer and/or shear stress, and how to translate these into a lab-scale (2 L) bioreactor. The final model will serve as a proof-of-concept for routine application of CFD models for scale-down and end-in-mind bioreactor development for biotherapeutics manufacturing.

2. Work packages

WP 1: Project scoping

In this first work package you will get to know the research field and the topic of your thesis. You will perform a literature review and summarize your findings in a literature review report. You will also make a full project plan until M8. The deadline for the full project plan is end of M1. Additionally, you will also spend time learning how to use M-Star CFD by following tutorials and experimenting with an existing M-Star 2 L bioreactor model.

Key deliverable

- Summary of literature review
- Planning until M8
- Proficiency in M-Star

WP 2: CFD modelling of a 15k L bioreactor

In this work package, you will build the CFD model of a 15k L bioreactor. You will first get acquainted with relevant characteristics of an industrial 15k bioreactor (dimensions, impeller, operational setpoints, etc.) and perform back-of-the-envelope calculations to determine the most relevant timescales. Then, you will start building the 15kL bioreactor model on M-Star and later perform a grid independence study to find the proper balance between computation time and accuracy. Once the resolution has been selected, you will validate the model based on known power number and oxygen transfer data, and use this model to study the limiting environmental conditions related to mixing, oxygen transfer and/or shear stress. You will finally conclude which phenomena is the most hindering for microorganisms and select the most important bioreactor process parameters to consider for future scale-down work.

Key deliverable

- CFD model of a 15k L bioreactor on M-Star
- Selection of most important parameters for scale-down work

WP 3: CFD scale down to a 2 L bioreactor

In this work package, you will use the existing M-Star 2 L bioreactor model already used in WP1 and improve it as needed based on the gained knowledge during WP2. You will use this model to mimic the limiting environmental conditions identified in WP2. You will propose different bioreactor set-ups and operational settings and test them in the CFD model to achieve a specific limiting condition. You will finally conclude what the best method is to mimic the 15k L limiting conditions in a 2 L bioreactor model.

Key deliverable

- CFD model of a 2 L bioreactor on M-Star
- Selection of best 2 L bioreactor set-up and settings to mimic 15k L bioreactor

3. Proposed time line

Months **Activity**	M1	M2	M3	M4	M5	M6	M7	M8
WP 1: Project scoping								
Literature review and planning								
Learning M-Star CFD								
WP 2: 15k L bioreactor modelling								
Relevant timescales								
15kL model building								
Grid independence study								
Model validation								
Parameter selection for scale-down								
WP 3: CFD scale-down to 2 L bioreactor								
2L model improvement								
Testing bioreactor configurations								
Selection of best method								
Thesis writing + presentation								

4. Overview of deliverables

MEP deliverables

- Literature report (M1)
- 8M planning (M1)
- 3M Progress report (M3)
- Intermediate presentation at TU Delft (M5)
- 6M Progress report (M6)
- Written MEP thesis and final presentation (M8)

Project deliverables

- CFD model of a 15k L bioreactor on M-Star
- Improved CFD model of a 2 L bioreactor on M-Star
- Selection of the best 2 L bioreactor set-up and settings to mimic limitations in 15k L bioreactor

5. References

[1] L. Gaugler, Y. Mast, J. Fitschen, S. Hofmann, M. Schlüter, and R. Takors, "Scaling-down biopharmaceutical production processes via a single multi-compartment bioreactor (SMCB)," *Engineering in Life Sciences*, vol. 23, no. 1, p. e2100161, 2023, doi: 10.1002/elsc.202100161.

[2] F. Delvigne, R. Takors, R. Mudde, W. van Gulik, and H. Noorman, "Bioprocess scale-up/down as integrative enabling technology: from fluid mechanics to systems biology and beyond," *Microbial Biotechnology*, vol. 10, no. 5, pp. 1267–1274, 2017, doi: 10.1111/1751-7915.12803.

[3] Z. Xing, B. M. Kenty, Z. J. Li, and S. S. Lee, "Scale-up analysis for a CHO cell culture process in large-scale bioreactors," *Biotechnology and Bioengineering*, vol. 103, no. 4, pp. 733–746, 2009, doi: 10.1002/bit.22287.

[4] A. Humphrey, "Shake Flask to Fermentor: What Have We Learned?," *Biotechnology Progress*, vol. 14, no. 1, pp. 3–7, 1998, doi: 10.1021/bp970130k.