CFD-guided scale-up low pH viral inactivation

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

Due to advancements in upstream technologies, the production capacity for monoclonal antibodies (mAbs) has evolved from a few milligrams to grams per liter. These increasing titers lead to a bottleneck on downstream processes (DSPs).[1], [2] One of the solutions to this issue is continuous DSP bioprocessing for intensified manufacture of antibodies.[3]

Viral inactivation (VI) is one of the unit operations that belongs to the mAb DSP cascade. It aims to reduce the viral content to meet the International Conference on Harmonization (ICH) Q5A guidelines for viral safety.[4] This can be done via a low pH or solvent/detergent (SD) approach. The protein A eluate (PAE) has an acidic content and therefore the low pH method is often preferred for VI. It includes an acidification step of the PAE, which is prolonged to a specific incubation time that ensures adequate viral inactivation, followed by a neutralization step to adjust the pH for further DSP.[5]

Computational fluid dynamics (CFD) is a tool that enables a comprehensive overview about the entire flow field of an investigated system. This offers a significant advantage as experimental methods are constrained, in part, by measurements at specific locations in the system and under particular conditions/settings.[6] CFD can be used for the analysis and optimization of the performance of bioprocesses, through up- and downscaling simulations.[7]

This project is part of an public-private collaboration between TU Delft (TUD) and Janssen Biologics (JBV), aiming to develop intensified and/or continuous biomanufacturing of mAbs. In this thesis you will develop a scale-up CFD model for a VI step using the low pH approach. You will be able to understand how fluid flows change inside a reactor/mixer and identify computationally quantifiable parameters for effective homogenization. A design concept is expected to be reached by the end of this project, where a thorough exploration of factors relevant to scaling up of VI is detailed.

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 detailed planning up until end M8. Moreover, you will dive into the CFD software practice (M-Star), understanding its fundamentals and how it works/what can be done with it. Tutorials and hands-on exercises will be used.

Key deliverable

- Literature review report
- Planning until M8
- Software practice

WP 2: Scale-up study

A CFD modelling study to investigate the impact of scaling up a VI step will be performed. Parameters subject to variation may include reactor/mixer attributes, operating scale, processing mode (batch and/or continuous), entry points, concentration and addition rates of components, among others. This information will be employed to perform a computational comparison between scale-up models and scale-down models. The aim is to understand variations in homogenization patterns, mixing duration, power input, energy dissipation rate, and other factors across the different scales being investigated.

Key deliverable

- Scale-up CFD model VI operation
- Comparison of scale-up and scale-down models

WP 3: Design concept

The impact of process and equipment parameters on large-scale VI will be analyzed, which includes the definition of computationally quantifiable parameters for effective homogenization. Furthermore, a computational workflow to choose the optimal VI setup will be developed, ultimately resulting in a design concept for the scale-up of VI.

Key deliverable

- Identification of critical process and equipment parameters on VI
- Design concept for large-scale VI step

3. Proposed timeline

Months / Activity	M1	M2	M3	M4	M5	M6	M7	M8
WP 1: Project scoping								
Literature review and planning								
Software practice								
WP 2: Scale-up study								
Scale-up CFD model VI operation								
Comparison of scale-up and scale-down models								
WP 3: Design concept								
Identification of process and equipment parameters								
Design concept for large-scale VI step								
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

- Scale-up CFD model VI operation (M4)
- Comparative study scale-up and scale-down model (M5)
- Critical process and equipment parameters (M6)
- Design concept large-scale VI operation (M7)

5. References

[1] D. S. Chahar, S. Ravindran, and S. S. Pisal, "Monoclonal antibody purification and its progression to commercial scale," *Biologicals*, vol. 63, pp. 1–13, 2020, doi: https://doi.org/10.1016/j.biologicals.2019.09.007.

[2] P. Gronemeyer, R. Ditz, and J. Strube, "Trends in Upstream and Downstream Process Development for Antibody Manufacturing," *Bioengineering*, vol. 1, no. 4, pp. 188–212, 2014, doi: 10.3390/bioengineering1040188.

[3] L. Gerstweiler, J. Bi, and A. P. J. Middelberg, "Continuous downstream bioprocessing for intensified manufacture of biopharmaceuticals and antibodies," *Chem Eng Sci*, vol. 231, p. 116272, 2021, doi: https://doi.org/10.1016/j.ces.2020.116272.

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[5] W. Jin *et al.*, "Protein aggregation and mitigation strategy in low pH viral inactivation for monoclonal antibody purification," *MAbs*, vol. 11, no. 8, pp. 1479–1491, Nov. 2019, doi: 10.1080/19420862.2019.1658493.

[6] I. Masic, J. Parojcic, and Z. Djuric, "7 - Computational fluid dynamics: applications in pharmaceutical technology," in *Computer-Aided Applications in Pharmaceutical Technology*, J. Djuris, Ed., Woodhead Publishing, 2013, pp. 233–259. doi: https://doi.org/10.1533/9781908818324.233.

[7] C. Haringa, "An analysis of organism lifelines in an industrial bioreactor using Lattice-Boltzmann CFD," *Eng Life Sci*, vol. 23, no. 1, p. e2100159, Jan. 2023, doi: https://doi.org/10.1002/elsc.202100159.