Toulouse Biotechnology Institute
Bio & Chemical Engineering

PhD Proposal

Digitalization tools for up-scaling bioprocesses: A modeling approach coupling metabolism and hydrodynamics

Subject integrated into the GalaxyBioProd project of the PEPR B-Best France 2030

Context and Objectives of the PhD Project

The implementation of bioeconomy requires digitalization tools allowing to assess the feasibility of the proposed technology before being implemented at industrial level. Although available, fast and reliable digitalization tools need to be developed to address properly the scale-up of bioprocesses at industrial scale and test their impacts into an integrated bioeconomy. Nowadays, many bioprocesses show promising results at lab-scale, while their transfer to industrial scale remain uncertain due to the difficulty of predicting the effects of scale-up especially in the bioreactor (e.g. reduced titer, lower yields and productivity, and by-product formation). These effects are mainly due to mixing, heat and mass transfer limitations since the repeated exposure to concentration changes lead to the drift from the expected biosynthesis route. The number of existing works coupling hydrodynamics and biokinetics in a rigorous way, through a combination of chemical engineering, heterogeneous catalysis and multiphase flow principles, is limited [1], [2], [3]. An effort is necessary to develop a generic bioreactor model for industrial scale applications. While considering cell functioning with fluid dynamics, it should provide fast and reliable results to better predict the process performance across scales with minimal losses.
Besides bioreactors, digitalization tools are also needed to conceive a complete production chain including up-streaming and down-streaming processes which must be evaluated in a whole to guarantee that the emerging bioprocesses meet the environmental criteria and generates less impacts than the chemical production. The scientific core of the PhD relates to chemical, biochemical process modeling and simulation with special emphasis on the multiphase reaction step.

The objective of this PhD is to develop digitalization tools considering an integrated modeling framework to predict the variability on process performances through scale-up and the inclusion of the bioreactor into an environmentally friendly production chain. Starting from our understanding of the interplay between bioreaction and hydrodynamics we aim at representing the consequences of scale-up effects on bioprocess performances in the reactor and in the downstream process. The coupled full-scale model will allow the evaluation of technical and environmental performances of a case study value chain.

The outcome of the PhD project consists in producing a case study for the scale-up a bioproduction including model, code and documentation to be published in an open-access platform.

The scientific questions that will be addressed are:

- How to couple biokinetics with hydrodynamics?
- How to manage the gas/liquid transfer and the mixing in the bioreactor?
- How to integrate the bioreactor model with the production chain?

The PhD thesis will follow three parts: 1) coupling hydrodynamic models with reduced metabolic models, 2) application to a well-known case study, 3) integration of the bioreactor in the production chain and evaluation of technical and environmental performances.

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University and host laboratory

INSA-Toulouse is a French engineering school that is part of the University of Toulouse, with 8 engineering specializations, including process engineering applied to the environment, computer science, civil engineering, mathematical engineering and biochemical engineering. INSA Toulouse welcomes about 2900 students each year, and graduates 450 master engineers and 55 PhDs each year.

Toulouse Biotechnology Institute (TBI, Toulouse, France) is a multidisciplinary research laboratory located on the INSA campus, with 350 collaborators in multiple scientific disciplines and skills to develop a 'gene to process' approach. The mission of this unit is to generate knowledge in support of industrial biotechnology and processes for the bio-economy. The PhD student will integrate the Sustainable Process engineering pole and the Transfer Interfaces and Mixing (TIM) team and SOPHyE team. A transversal activity of TIM group is the modelling of bioreactors (Kinetic Phenomenological models coupled with Hydrodynamic Models,) while SOPHyE team focuses on supply chains and environmental analysis. For more information please visit https://www.toulouse-biotechnology-institute.fr/en/poles/genie-des-procedes-durables/

Candidate profile

You have a Master's degree in the field of **process engineering**, **chemical engineering** or a related field or an equivalent engineering degree. The qualities expected from the candidate are **creativity, motivation** and willingness to explore new areas. **Strong knowledge on software coding** (e.g. Matlab, Python, Fluent) and **very good English language skills** are mandatory. Knowledge of French is an advantage, but not a requirement.

Conditions

The position is a 3 year-contract, and is based at INSA-Toulouse. Salary follows national directives including full social and health benefits (gross monthly salary: 2 110 €). PhD Students have 51 days of leave/year. The candidate will be in contact with the project partners to ensure communication and data/information exchanges, and to periodically adjust the work orientation. The candidate will have opportunities for professional development, for presenting his/her research results at international conferences. The PhD student will be supervised by Dr. Carlos Robles Rodriguez, Prof. Arnaud Cockx and Prof. Jérôme Morchain.

Expected starting date: July 2024

How to apply?

Applications should be sent by e-mail to carlos.robles-rodriguez@insa-toulouse.fr, arnaud.cockx@insa-toulouse.fr, and jerome.morchain@insa-toulouse.fr **before May 1st.** Please send as one pdf file: your CV, a cover letter describing your research interests and motivation.

References

[1] J. Morchain, J.-C. Gabelle, et A. Cockx, « A coupled population balance model and CFD approach for the simulation of mixing issues in lab-scale and industrial bioreactors », *AIChE Journal*, vol. 60, nº 1, p. 27-40, 2014, doi: 10.1002/aic.14238.

[2] G. Wang *et al.*, « Coupled metabolic-hydrodynamic modeling enabling rational scale-up of industrial bioprocesses », *Biotechnology and Bioengineering*, vol. 117, nº 3, p. 844-867, 2020, doi: 10.1002/bit.27243.

[3] G. Wang, C. Haringa, H. Noorman, J. Chu, et Y. Zhuang, « Developing a Computational Framework To Advance Bioprocess Scale-Up », *Trends in Biotechnology*, vol. 38, nº 8, p. 846-856, août 2020, doi: 10.1016/j.tibtech.2020.01.009.