POLITECNICO DI MILANO

PhD in CHIMICA INDUSTRIALE E INGEGNERIA CHIMICA / INDUSTRIAL CHEMISTRY AND CHEMICAL ENGINEERING - 39th cycle

PNRR 118 TDA Research Field: INTENSIFICATION AND DIGITALIZATION IN THE CHROMATOGRAPHIC PURIFICATION OF BIOPHARMACEUTICALS

Monthly net income of PhDscholarship (max 36 months)
€ 1400.0 In case of a change of the welfare rates during the three-year period, the amount could be modified.

Context of the research activity	
Motivation and objectives of the research in this field	Process intensification is incentivized by the Food and Drug Administration (FDA) and by the European Medicines Agency (EMA), as a way for reducing the costs and for improving the sustainability in the manufacturing of biopharmaceuticals (https://doi.org/10.1016/j.ces.2021.117159). The bottleneck in the manufacturing pipeline is represented by the downstream processing, typically relying on one or more single-column chromatographic operations to ensure the high purity standards required for biopharmaceuticals. Indeed, this operation is responsible for high cost of goods and large use of solvents and raw materials, reflected in a huge environmental footprint. With the aim of allowing the transition towards environmentally friendly operations, this project aims at establishing a high-throughput process development (HTPD) tool integrating continuous countercurrent multi-column chromatography and digital technologies. Specifically, multi-column countercurrent solvent gradient purification (MCSGP,https://doi.org/10.1016/j.trac.2020.116051) will be investigated as the key enabler for process intensification, allowing a more conscious utilization of the raw materials thanks to the recycling of impure side fractions and then leading to a decisive improvement in the environmental footprint of the unit operation. In this

	framework, the candidate will have the opportunity to spend 6 months in YMC ChromaCon AG, a Swiss company that pioneered the MCSGP technology, and will take advantage of the expertise of their specialists for acquiring an in-depth knowledge of the process and its potential towards process intensification and sustainability. The continuous processing, and the management of two synchronized chromatographic columns, however, increases the process complexity and makes its robust operation and optimization a labor-intensive task. Therefore, the development of a digital controller and its tuning through the implementation of genetic algorithms will be crucial for an efficient process design, optimization and monitoring. The two key enabling technologies for the transition towards the sustainable downstream processing of biopharmaceuticals, *i.e.* MCSGP and integrated digital controls, will be combined in a 3D printed microfluidic HTPD tool, capable of fast process development and high-throughput screening for different biopharmaceuticals, including PEGylated proteins and oligonucleotides, which are now breaking through the biopharmaceutical market.
Methods and techniques that will be developed and used to carry out the research	The research will focus on the integration of MCSGP and digital technologies on 3D printed high-throughput process development (HTPD) microfluidic platforms for the continuous purification of biopharmaceuticals. The candidate will then acquire expertise in chromatography, with a focus on countercurrent operations, through both experimental and modeling activities. For the former, the candidate will become expert in high performance liquid chromatography (HPLC) to be used as analytical tool throughout the research for quantification of process performance parameters like product purity, process yield and productivity. Then, the candidate will develop a 3D printed microfluidic device for the realization of the MCSGP process, to reduce the process mass intensity compared to the traditional single-column operations. In this direction, the expertise on the process will be first acquired on commercial benchtop systems (ContiChrom CUBE, https://www.chromacon.com/en/products/contichrom-

	cube-combined-1), used to demonstrate the potential in process intensification and environmental sustainability compared to the traditional chromatographic purifications, working on oligonucleotides as a case study. The competencies on the process will be brought to maturity during the internship in YMC ChromaCon AG, where the candidate will implement a digital controller AutoPeak for the robust design and conduction of MCSGP. For the realization of the HTPD tool, the candidate will make use of the latest technologies in 3D printing, with particular reference to digital light processing (DLP) and two-photon polymerization printing, exploiting the unique Nanoscribe Quantum X available at Politecnico di Milano.The realization of the HTPD tool will be guided by the development of a hybrid digital controller for the operation. First, a single-column model based on a system of partial differential equations and on lumped kinetics will be developed. For the solution of the system, the finite difference and finite volume methods will be compared in terms of computing performances in order to select the most performing one. The hybrid model will be trained through the implementation of genetic algorithms for the estimation of the adsorption isotherm parameters of different biomolecules by comparison with experimental data. Then, the model will be re-elaborated for its direct application to MCSGP. Based on this, a model-based digital controller allowing process optimization and disturbance rejection will be developed. This will guide the development of digitalized and sustainable downstream processes for biopharmaceuticals.
Educational objectives	•Awareness of the potentiality of countercurrent operation and digital technologies as drivers of sustainability •Development of digital tools for chromatographic operations •Proper design and realization of 3D printed HTPD tools •Interaction and collaboration with peers •Self-dependency and analytic thinking
Job opportunities	The candidate, after the PhD, will have the opportunity to

	operate in both academia as well as in companies focused on the manufacturing of biopharmaceuticals. The combination of modeling and laboratory experience allows the candidate to be versatile and particularly suitable for R&D sectors.
Composition of the research group	4 Full Professors 5 Associated Professors 5 Assistant Professors 20 PhD Students
Name of the research directors	Prof. M. Sponchioni

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Additional support - Financial aid per PhD student per year (gross amount)	
Housing - Foreign Students	--
Housing - Out-of-town residents (more than 80Km out of Milano)	--

Scholarship Increase for a period abroad	
Amount monthly	700.0 €
By number of months	6

National Operational Program for Research and Innovation	
Company where the candidate will attend the stage (name and brief description)	YMC ChromaCon AG - Technoparkstrasse 1 - 8005 Zürich, Switzerland - https://www.chromacon.com/en/
By number of months at the company	6
Institution or company where the candidate will spend the period abroad (name and brief description)	to be defined
By number of months abroad	6

Additional information: educational activity, teaching assistantship, computer availability, desk availability, any other information

Individual budget for research (5.700 euro):1st year: 1.900 euro; 2nd year: 1.900 euro; 3rd year: 1.900 euro

Teaching assistantship (availability of funding in recognition of supporting teaching activities by the PhD student): there are various forms of financial of for activities of support to the teaching practice. The PhD student is encouraged to take part in these activities within the limits allowed by the regulation.


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