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# Education in Flow Chemistry

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*Abstract:* Flow chemistry is a growing and promising technology that can be used in research, development, and production. Nowadays, staff properly trained in flow chemistry are lacking in industry. To work efficiently with this technology, a mix of engineering and chemical skills is required. Although this dual education is well addressed in the chemistry major given at the Haute Ecole d'Ingénierie et d'Architecture de Fribourg, a school of the University of Applied Sciences and Arts Western Switzerland, teaching in flow chemistry should be enhanced and reinforced.

**Keywords**: Continuous process · Education · Flow chemistry· Process intensification

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## 1. Introduction

Flow chemistry is currently a hot topic in chemistry, although it is not new. Indeed, continuous operation has been used for more than a century: the Haber-Bosch process being probably one of the first continuous processes.[1] Since then, continuous processes are routinely used within the fine chemical, commodity chemical and petrochemical industries. Nonetheless, this technology is enjoying a renaissance with the emergence of microreactors.

The rapidly increasing number of publications in flow and continuous chemistry, and the growing interest of the pharmaceutical industry,[2,3] coupled with the encouragement of the FDA and the Chinese government to adopt flow chemistry, highlights the importance of continuous technologies.[4]

Moreover, numerous publications have shown that flow chemistry has many key advantages over batch chemistry: safer and faster reactions, better yield, lower operating expenses (OPEX), more environmentally friendly chemistry, and a larger operating window.[4–10] In addition, the current concern about the environment can be partly addressed by flow chemistry. Indeed, the flow reactor technology has an impact on sustainability as it decreases the footprint of the equipment required to produce a specific amount of material by intensifying the chemical processes involved. In addition, microreactor technology allows the use of green activation modes like electrochemistry and photochemistry.[11] Moreover, due to the novel process window,[10,12] more efficient reactions and a lower consumption of raw materials can be achieved in flow, thus increasing the efficiency and greenness of processes. Finally, flow chemistry in conjunction with artificial intelligence, machine learning and automation make this technology particularly suitable to speed up innovation, development and industrialization.[13]

Despite these remarkable advantages, the teaching and practice of flow chemistry in universities is still limited, and it has a low penetration in the chemical and pharmaceutical industries.

There are several factors that explain why this technology is not more widespread in research, development, and production. Besides some current technological limitations of flow processes, industries that have massively invested in batch equipment are reluctant to switch to new equipment before full return on investment. Another key reason lies in the educational background of the workforce. Indeed, for decades, students have been trained exclusively on classical batch approaches and academic research was constrained to batch equipment. This is nowadays still largely the case. The result of the lack of flow-oriented training is a mindset largely oriented to batch operations. This mentality is present everywhere in the professional world: across administrations, and public and private organizations. Changing this mindset will come largely through education.

To bridge the imbalance between the growing interest in flow chemistry and the training deficit, the early introduction of flow chemistry in undergraduate teaching and practical training is very important.[14] It even becomes crucial. In this paper, we focus on education and the responsibility we have regarding the future employers of our students by showing the initiatives we have taken to teach flow chemistry to undergraduate students at the Haute Ecole d'Ingénierie et d'Architecture (HEIA-FR), a school of the

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University of Applied Sciences and Arts Western Switzerland (HES-SO).

## 2. Education

Education and training are key for the acceptance and success of flow chemistry, as they will deliver the workforce that will enable its implementation.[14,15] Despite the fast growing interest in this field, the exposure of students to continuous process technologies, and especially flow chemistry, is very limited. The lack of trained people slows down the implementation of this technology in the industry.

### 2.1 *Challenges to Teaching Flow Chemistry*

Three main challenges explain the poor penetration of flow chemistry in undergraduate teaching: interdisciplinary topic, equipment selection and cost.

As microfluidics is an interdisciplinary area, knowledge in chemistry, as well as strong background in chemical engineering and in automation are required for one to be at ease with this technology. Indeed, reaction mechanism and kinetics, fluid dynamics, flow behaviour at a low Reynolds number, mass and heat transfer, computational fluid dynamics, pressure drop, fabrication of microfluidic devices, automation and on-line analysis must be well understood in order to properly design flow equipment and to conduct chemical reactions in a rigorous, rational and efficient way.

The second and third barriers are related to the equipment. Indeed, flow equipment is very different from batch production units. Moreover, there is a plethora of parts on the market (mixers, reactors, pumps, back-pressure regulators, connectors, *etc.*), which makes the choice more arduous. Consequently, it takes experience to make the right assembly. Although some ready-to-use flow rigs are also available, they are at a prohibitive cost for teaching. In addition to these very expensive devices, spare parts, such as pumps or sophisticated mixers,[16] necessary to build custom-made equipment, can be very costly.

### 2.2 *Opportunities Arising from Teaching Flow Chemistry*

Despite these challenges, teaching flow chemistry at the undergraduate level offers many opportunities and advantages: it opens the minds of students to work in a multidisciplinary environment; it also offers the opportunity to better integrate theoretical teaching into practical training; it motivates students by enabling them to create their own devices; it facilitates chemical reactions like photochemistry that could not be done before. Finally teaching flow chemistry provides valuable pedagogical concepts including green chemistry, catalysis, mixing and process intensification.[17,18]

Flow chemistry offers the opportunity to open the chemistry curriculum to a multidisciplinary approach, including mechanical engineering, 3D-printing[19–21] or other ways to build microfluidic channels,[22] where students can create their own devices and test chemical reactions in order to understand the fundamental principles of chemistry (acid–base reactions) and chemical engineering (mixing and laminar flow).[22] Other aspects of flow chemistry can be explored, for instance precipitations and plugging issues.[23]

Interestingly, microfluidics or flow chemistry could be used to improve the understanding of several chapters already taught in chemistry, including kinetics,[24] mass transfer, mixing, heat transfer, acid–base chemistry,[19] photochemistry,[25] biphasic reactions,[26] *etc*. Instead of dedicated courses in flow teaching, including flow aspects in various courses is not only more interesting, but it also offers a powerful pedagogical approach.[27]

Flow reactions with heterogeneous catalysts are known to deliver more efficient and greener processes than batch reactions with a homogeneous catalyst. This can be experienced by students using packed-bed reactors for the esterification of ethylene glycol with acetic acid.[28] As such, flow chemistry teaching offers a good opportunity to change conventional chemistry towards greener chemistry by exposing the students to the concepts of sustainability. Another green chemistry example is the comparison of the batch and continuous synthesis of 5-hydroxymethylfurfural from fructose.[29]

Photochemistry is a very interesting field to show the limitations of batch processing (long pathlengths, low surface area irradiation) and the superiority of a flow setup.[11,25] New opportunities for electrochemistry[30] or biocatalysis[31] also come with flow chemistry.

Besides these opportunities and possibilities to experience green, electro- and photo-chemistry, flow chemistry offers the possibility to conduct experiments in the lab that were not possible in batch, because they were too time-consuming. Since the experiments given in laboratory teaching are limited in time, reactions that are usually too long and too difficult batchwise can now be accessible in an undergraduate curriculum.[32] Indeed, as flow chemistry can often accelerate reactions, it enables students to carry out more reactions in a given time. Several reactions can be performed in a few minutes.[33]

### 2.3 *Flow Chemistry Taught at HEIA-FR, HES-SO*

The main barrier in introducing flow chemistry into practical laboratory work is the need of a dual understanding of organic chemistry as well as chemical engineering. This point is well addressed at HEIA-FR, as the chemistry students receive a very thorough chemical engineering education in addition to a sound basis in organic reaction mechanisms and kinetics. Continuous and flow chemistry are taught both practically and theoretically at HEIA-FR. Fundaments in chemical engineering regarding continuous processes are given at the Bachelor level, and more emphasis on flow chemistry is given at the Master level. The BSc degree program already integrates several aspects of continuous chemistry like simulation with Dynochem®,[34] mixing, heat exchange, or theories related to continuous stirred-tank reactors (CSTR) and tubular reactors (Fig. 1). Some courses strongly support the understanding and application of flow chemistry and continuous processes (orange boxes in Fig. 1) whereas others introduce concepts that can be linked to flow chemistry (yellow boxes in Fig. 1).

Practical training, a key part in the study plan, is possible because teaching in flow chemistry is not necessarily expensive. A simple flow setup can be constructed from tubes, connectors, T-shaped mixers, and pumps.[35–37] In our laboratories, we use LTF plates, IMM-micromixers, the Ehrfeld system and in-house built mixers and reactors (tubular, CSTR and microreactors).[38] By building their own custom flow chemistry rigs, rather than using a ready-to-use platform, students gain experience in reactor design and optimization at a moderate cost. An example is the synthesis of hippuric acid from glycine and benzoyl chloride, where a simple setup with a syringe pump and an LTF plate mixer or a T-piece used as a mixer, offers an easy entry into flow chemistry.[39]

Practice in flow chemistry is mainly acquired during the semester projects (small projects done in the last semester of BSc in chemistry) and during Bachelor theses. However, not all the students have the chance to practice flow chemistry during the semester projects or the Bachelor thesis, as it depends on the topics they are assigned. Semester projects and Bachelor theses are a good opportunity for students to mobilize the theory learned during their studies into a practical flow chemistry experience. In many cases, this offers an opportunity to expand their knowledge further. For example, a semester work was done on the topic of understanding the residence time distribution in various reactors for a project linked to the continuous synthesis of nanoparticles, where residence time distributions (RTD) correlated with the particle size distribution (Fig. 2).[40] Another example is given by the continuous alkylation in biphasic conditions using a centrifugal contactor separator (CCS, Fig. 3).[41,42]

The MSc degree program in Life Sciences with a specialization in Chemical Development and Production (MLS HES-SO CDP) goes much deeper into flow chemistry.[43] Several modules

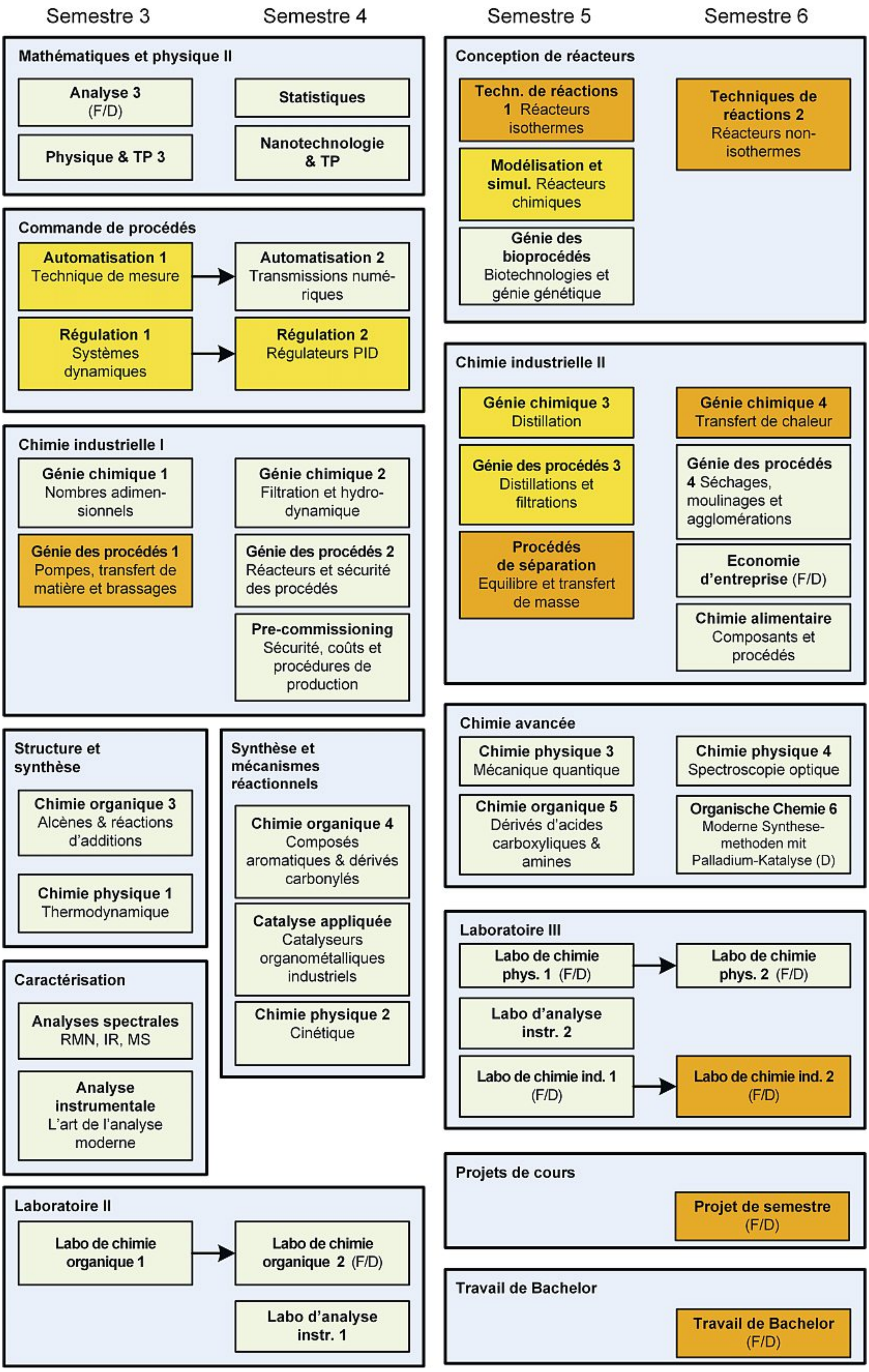


Fig. 1. Chemistry major study plan at HEIA-FR. Only the last four semesters are shown. The first two semesters are not presented, as there are no courses linked to flow chemistry. Yellow: only a few aspects linked to flow are taught. Orange: many flow chemistry aspects addressed.

deal with this theme: S01 (Process Chemistry and Development), S03 (Process Design and Optimization) and, in particular, the S04 module (Chemical Engineering and Process Intensification). For instance, in the S01 module courses, students receive an introduction to synthesis in flow chemistry covering topics like the clever use of reaction mechanism in flow, very fast reactions, working with highly toxic & reactive reagents, and learning how to adapt the chemistry to a flow process. During the S04 module, students learn the flow chemistry nomenclature, the differences, advantages and drawbacks of flow and batch technologies, the specific equipment used in flow, scale-up aspects, and process intensification. Chemical engineering aspects are also addressed in detail: students learn how to design a tubular reactor using heat and mass balances, as well as pressure variation. Concepts like residence

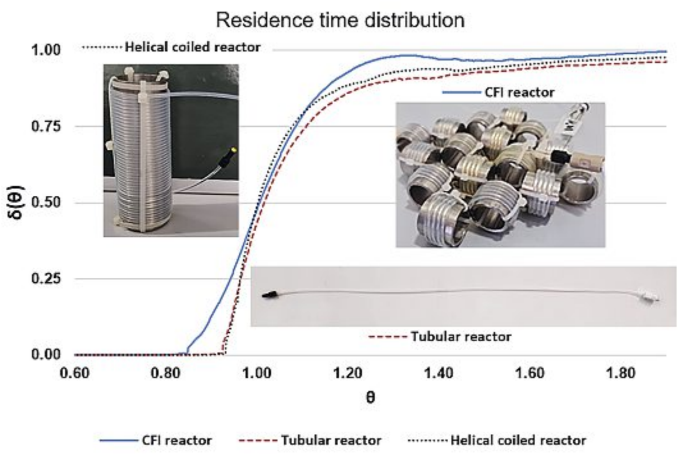


Fig. 2. Residence time distribution investigation with several reactors: straight tubular reactor, helicoidal reactor, and coiled flow inverter reactor.[40]

Fig. 3. CCS used to perform biphasic alkylations in the Bachelor thesis of Weber.[41]

time distributions in reactors and mass transfer problems, especially in a catalytic context, are also addressed.

Simulations of reactor behaviour are performed with Python,[44] while hydrodynamic and thermal aspects, such as flow regime, pressure drop and heat exchange, are studied theoretically and simulated *via* Computational Fluid Dynamics (CFD). Moreover, students, in groups of two, study one scientific article on a specific topic related to either a chemical reaction performed in flow, a special technology in flow, or scale-up. Then, during the oral presentations of the papers, students can exchange and learn from each other. The ultimate goal is to provide them with a good overview of what is possible with flow chemistry. This course ends with a written exam where questions on flow aspects (chemistry, process intensification, flow properties, chemical engineering) are thoroughly examined.

Several Master theses have been completed on topics related to flow chemistry. The Master thesis is an opportunity for students to mobilize the theory learned during their studies and to apply flow chemistry intensively in practice. For example, the aim of an ongoing Master thesis is to find the most productive and sustainable photochemical technology to produce pinocarvone at the multigram scale. This photochemical reaction is investigated in flow, as shown in Fig. 4.[45]

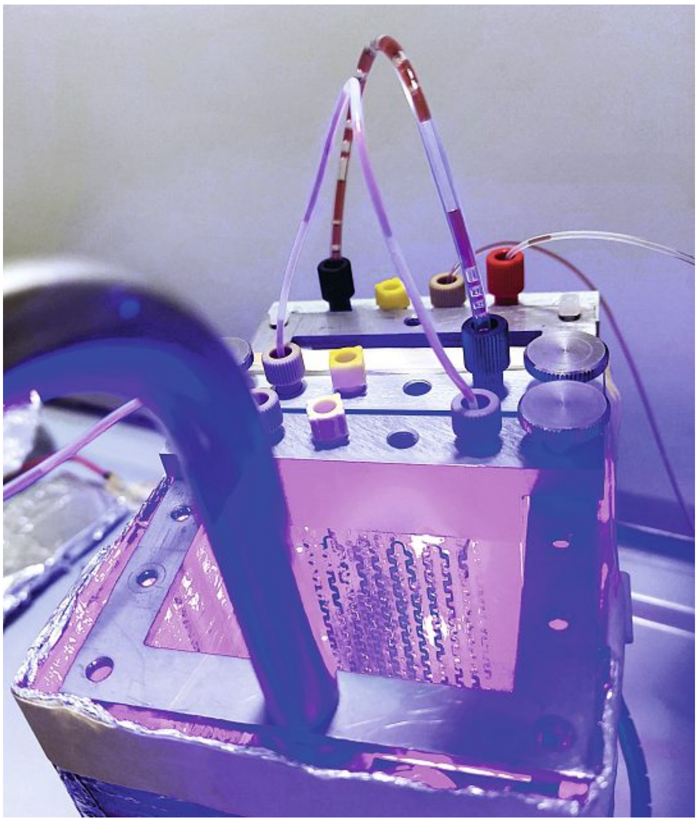

Fig. 4. LTF plates used for the photochemical synthesis of pinocarvone. Ongoing Master thesis at HES-SO.[45]

In other projects, miniaturized CSTRs were designed, constructed and tested with various reactions.[46,47] These novel mini CSTRs, fabricated by 3D printing in stainless steel, have an integrated heating/cooling unit, boast active stirring with a magnetically coupled stirrer, and work with gases (*e.g.* oxygen) *via* a glass frit (Fig. 5).

Our teaching activities in flow chemistry overlap with one of the research areas of the Institute of Chemical Technologies (ChemTech),[48] one of the ten research institutes at the HEIA-FR. The institute has three main areas of activity: chemical process development, characterization technologies, and flow chemistry.[49]


Fig. 5. Mini-CSTRs developed in Master projects by Albergati and Gnädinger.[46,47]

As the primary innovation theme investigated at ChemTech is the intensification of chemical processes, flow chemistry plays a central role in the Institute's R&D portfolio (Fig. 6). Process intensification is an approach initially described as a strategy to reduce the footprint of manufacturing plants.[50] Microreactors are equipment that achieve this intensification. With their excellent space-time yield, their use leads to a reduction in the plant footprint while increasing productivity. In addition to microreactors, ChemTech has other tools to achieve process intensification, including CCS, agitator bead mills for mechanochemistry, and several other continuous technologies.

Several industries collaborate with ChemTech in the field of flow chemistry, either to develop new flow processes/chemistries[51] or to transfer an existing batch process to flow, for example biphasic PTC-catalyzed alkylations.[38] The students at HEIA-FR also benefit from these projects as there is a symbiotic relationship between ChemTech and the chemistry department. Indeed, BSc and MSc students in chemistry very often participate directly or indirectly in industrial projects related to flow.

## 3. Alumni Testimony

A survey among the alumni of the chemistry major (BSc and MSc) of the HEIA-FR shows that 39% of them are using flow chemistry in their job (Fig. 7A), although the majority of the companies (61%,Fig. 7B) that employ our former students already have activities in flow chemistry either in R&D, or in production. To answer the question why companies do not use continuous chemistry, the poll participants mention that, either the batch equipment that is in place is difficult to change for a flow technology (CAPEX and amortization), especially when the batch process gives satisfaction, or that the mentality for this change is not present.

The students who are using flow chemistry in their jobs think that flow will gain in importance within their companies in the future (Fig. 7C). This is driven by the benefits of this technology: cost and energy savings, safety enhancements, more sustainable technology than the batch approach, and a more efficient approach for high tonnage production. Those who do not think that flow chemistry will increase in importance in their company propose three explanations: i) some processes work better in batch than in flow, ii) investment is not seen as necessary, iii) no ressources available to redesign an existing batch process to a flow one.

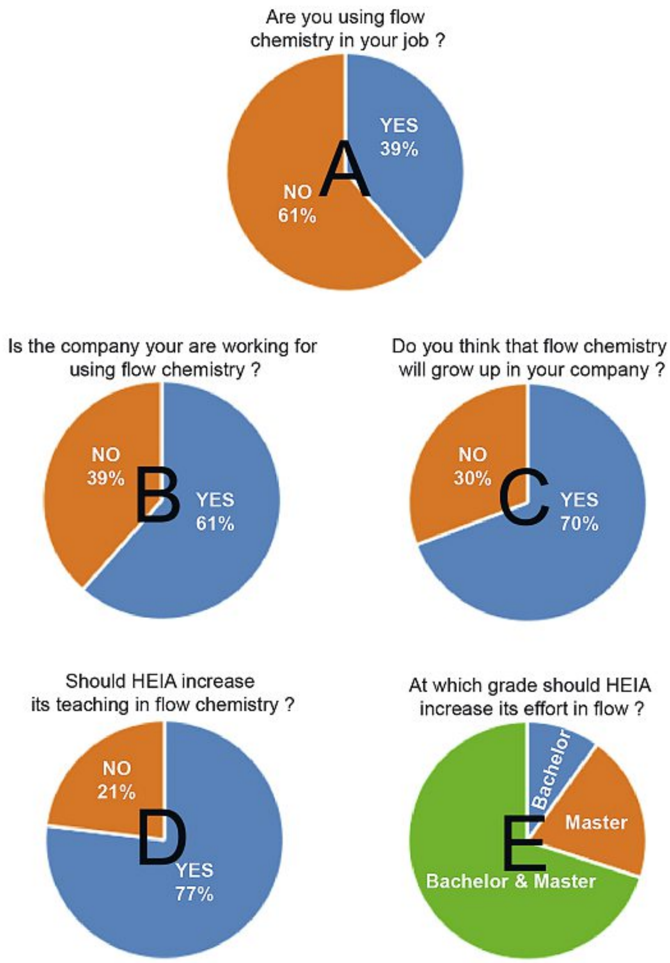


Fig. 7. HEIA-FR Alumni 2022 survey on flow chemistry.

The survey participants see flow chemistry as a very useful technique for large production or for processes that would be unsafe if performed batchwise. Nonetheless, this technology will not completely replace the batch approach. It still faces obstacles acting against its implementation at production scale (*e.g.* more complex to commission, difficult with solids, batch assets to amortize). Finally, the participants see flow chemistry as an advantage from the point of view of Industry 4.0 and sustainability.

All the concepts to understand flow chemistry and the sizing of equipment are taught in various courses (Fig. 1). However, there is not a specific course about flow chemistry. As a consequence, a majority of alumni (77%) think that teaching of flow chemistry at HEIA-FR should be enhanced and reinforced at both the Bachelor and Master degree levels (Fig. 7D and 7E). Indeed, flow technologies are nowadays increasingly being used in industry. Therefore, having a specialized education in the field is seen as an advantage on the job market. For the moment there are no dedicated laboratories for training in flow chemistry, and some alumni think that it would be worthwhile to dedicate some laboratory experiments to flow in the Bachelor and Master programs.

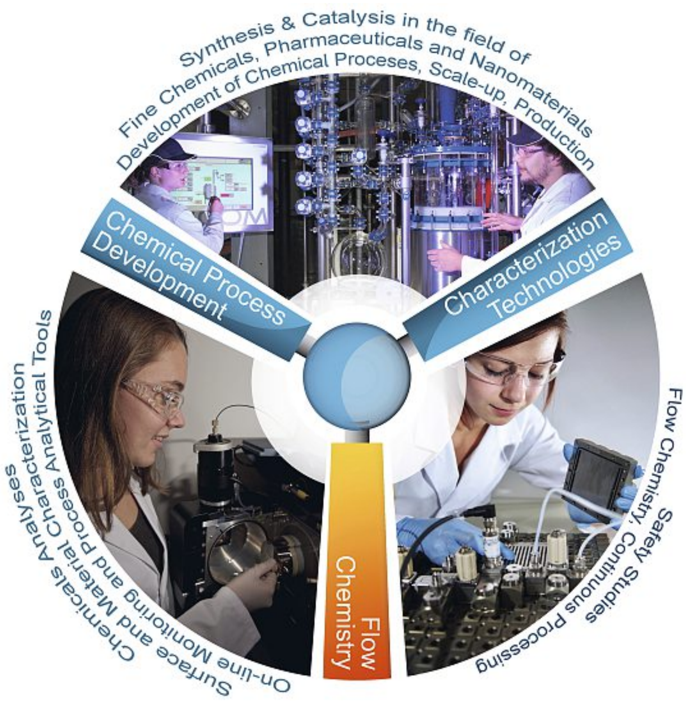


Fig. 6. Flow chemistry is one of the main focus research areas of the ChemTech Institute.

## 4. Conclusion

There is no longer any doubt about the growing importance of flow chemistry. For this reason, this technology should be intensively taught in universities. Indeed, a survey among alumni students of HEIA-FR shows that flow chemistry is not only currently used in industry, but also that it will become more important in the future. As a consequence, the demand for well-trained staff in flow chemistry will grow accordingly. We foresee that flow chemistry teaching will be intensified in the future, though without replacing traditional batch technology. Furthermore, it will induce the cultural change needed by the industry to embrace this new technology with strong and well-informed managerial support. Although the chemistry major at HEIA-FR does not offer a tailored course on flow chemistry at present, all the concepts necessary to understand the technology, to design the relevant equipment, and to apply flow chemistry, are covered in several courses at the Bachelor and Master levels. The dual education in chemistry and chemical engineering is further deepened by exposing the students to flow through laboratory projects (semester, Bachelor and/or Master thesis), as well as research projects within the ChemTech Institute.


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