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# Process Intensification with Microprocess Engineering

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Microreactors and other microdevices have proven to be very efficient tools for process intensification in chemical production due to high mass and heat transfer, low temperature gradient, fast and efficient mixing, and short residence times. Microreactor technology is becoming an increasingly important concept, already successfully used at laboratory scale and in some cases even at pilot and production scale. However, there are still some issues that need to be explored for this technology to be used more widely, such as automation and integration, synthesis of the optimal configurations of microprocess units, process optimization, and cost analysis. The aim of this work is considering process intensification based on microprocess engineering, to identify the challenges involved and to provide a basis for the development of a computer-aided framework for design, optimization, and synthesis of integrated microprocess systems. At the Faculty of Chemistry and Chemical Engineering in Maribor, the acquisition of microprocesses equipment is planned as part of the ongoing Upgrading national research infrastructures – RIUM project. The main vision for the future is to combine mathematical optimization and synthesis of microprocessing systems with experimental testing of various configurations of microreactors and other devices. Based on experimental data, a library of process models for microdevices would be created as part of the MIPSYN-Global process synthesizer, a new successor to the earlier MIPSYN synthesizer. The goal is to create synergies between laboratory microdevices and mathematical programming for the efficient design and optimization of various process applications based on microtechnology.

## 1. Introduction

In the last two decades, conventional batch production of fine chemicals and active pharmaceutical ingredients (APIs) has been replaced by continuous flow chemistry with microreactors in some applications. This is one of the methods that improve conventional processes and allow the use of new, unprecedented synthesis conditions, such as high pressure and high temperatures, within Novel Process Windows (Illg et al., 2010).

The applications of continuous flow chemistry in microdevices have a fundamental impact in both academia and industry. This is due to the advantages of flow over conventional methods. The main advantage is attributed to the design of microstructured devices with a high surface-to-volume ratio (typically 30,000 $m^2/m^3$), which leads to many improved properties of microreactors over batch reactors. For example, high heat and mass transfer, efficient mixing, short residence times. Higher pressures and temperatures can be safely achieved with microprocess flow systems. Process safety is improved and reaction parameters are easier to control (Hughes, 2020).

A review of the literature (Suryawanshi et al., 2018) has shown that applications of laboratory-scale microreactors in chemical engineering are developing rapidly. Most applications are related to the synthesis of organic compounds, fine chemicals and pharmaceuticals. The advantages of microscale synthesis over batch reactors are significant. For example, nitration in batch reactors is often problematic due to the extremely exothermic reaction. In microreactors, the heat generated is efficiently dissipated due to the high heat transfer coefficient (Bojang et al., 2020). Another example is the synthesis of nanoparticles, which is relatively complex and expensive using conventional methods, while efficient synthesis of inorganic and metallic nanoparticles has been reported for flow systems (Gioria et al., 2019). The use of microreactors has also been extended to biosynthesis and biochemical processes (Thompson et al., 2018) and polymerization reactions (Fukuyama et al., 2012). Performing flow chemistry in microreactors can provide us with green and sustainable processes that

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have environmental, economic, and safety benefits. In this field, the synthesis of biofuels, mainly biodiesel from vegetable oils, has been carried out in microreactors (Tiwari et al., 2018).

Like all new technologies, advances in flow chemistry face challenges: solid reactant handling, high viscosity, separation systems, optimization, control, cost, scale-up, education, etc. (Jensen, 2017). Increasing production is challenging because there is no universally accepted method for moving from the laboratory to the pilot and larger production facility. The problem of missing or unpublished publications on a production scale should also be mentioned (Pollington, 2019). The transition from batch to continuous flow production requires a major change in mindset, which can be achieved through training. Knowledge and education on continuous flow microreactor technology need to be improved. A stronger emphasis on interdisciplinarity and multidisciplinarity in operational practice is required.

Despite some successful practical applications of microreactors, the microprocesses are not yet widespread in industry. Therefore, systematic approaches to microprocess production systems need to be developed in terms of microprocess design, control, optimization, and configuration synthesis, as well as economic analysis. The optimization of continuous variables in microreactors, such as temperature, residence time, molar ratio of reactants, has been reported previously (Pereira et al., 2021), but optimization over discrete variables, e.g., structural connections between microdevices, choice of catalyst, ligand, or solvent, is still a challenge.

In this paper, an overview of the applications of microreactors and the challenges associated with them is presented. The vision and conceptual basis for creating an integrated framework for the design and optimization of microprocess systems by combining laboratory experiments and mixed-integer nonlinear programming (MINLP) is presented. This framework would create the synergy between laboratory microdevices and mathematical programming for efficient design and optimization of various microprocess applications.

## 2. Recent advances in flow chemistry

The growing number of publications in the field of microprocess engineering shows the increasing development of applications and production in microreactor systems (Gambacorta et al., 2021). In particular, the field of organic synthesis is well developed. More and more efforts are being made to pursue green and sustainable chemistry using microprocesses. Flow production on a larger scale is being developed mainly in China. Some research has also been done on their economic and environmental performance.

### 2.1 Organic synthesis

The production of fine chemicals and active pharmaceutical ingredients are the areas where flow chemistry is most widely explored. Alkylation reactions, Wittig reactions, Grignard reactions, organolithium exchange, bio-oxidation, DNA ligation, esterification, nitration and so on are all already established chemical syntheses of active ingredients at laboratory scale. Organic synthesis, production of fine chemicals and active pharmaceutical ingredients in microreactors are the most researched areas (Hughes, 2020). Flow microreactors have thus become an important new technology for the chemical and pharmaceutical industries.

Different types of reactions are discovered in microdevices: gas-liquid, liquid-liquid, solid-liquid, gas-liquid-solid, and liquid-liquid-solid reactions. The advantage of gas-liquid reactions under flow conditions is the ability to perform reactions at higher pressures where the solubility of the gas in the reaction medium increases.

Emerging sustainable technologies for chemical synthesis include also photochemistry and electrochemistry under flow conditions. Photochemistry uses photons instead of reagents, and since this is done in flow, irradiation is more efficient and uniform. Due to the small size of the microdevices in electrochemical reactions, no supporting electrolytes are needed (Plutschack et al., 2017).

### 2.2 Microprocesses as a green and sustainable chemistry

Flow chemistry offers great opportunities for the transition to green and sustainable production. Microreactors enable chemical syntheses to be carried out in an environmentally friendly and sustainable way by improving product selectivity, consuming less energy, and enabling syntheses with minimal consumption of auxiliary materials. Higher product selectivity in microreactors is achieved through the rapid and efficient transfer of mass and heat (Yoshida et al., 2011). Reactions in the microreactor system require fewer chemical reagents, making the reactions more environmentally friendly, less expensive, and safer. If the microreactor explodes, the consequences are far less than if a batch reactor of several litters or cubic meters explodes. This approach also avoids hazardous intermediates.

To achieve sustainability, there is a tendency to use alternative solvents such as water, subcritical and supercritical fluids, or ionic liquids. Abad-Fernández et al. (2019) presented a depolymerization of lignin with supercritical water in a microreactor. The main advantage of this process is the direct treatment of black liquors, which allows a high yield of lignin in a very short time.

Another example are chemical syntheses that produce unstable intermediates and organometallic reactions in batch reactors and must be carried out under cryogenic conditions. These conditions require cooling to very low temperatures (e.g. - 78 °C), which results in high energy cost. An alternative to perform such reactions is to use microreactors, in which intermediates do not have time to form due to very short residence times (Yoshida et al., 2011). In addition, reactions can be carried out at higher temperatures than cryogenic temperatures The combination of rapid mixing and shorter residence time in microreactors means that these reactions can proceed at higher temperatures. This leads to lower energy consumption and consequently lower energy costs.

### 2.3 Scale-up and operating issues

Increasing the volume of batch production is a lengthy process and also problematic for some reaction types such as oxidation/reduction reactions, cryogenic reactions, exothermic reactions, reactions with unstable intermediates, etc. (Hughes, 2020). Easier scale-up using microreactor technology is the promise of many researchers and manufacturers in the field of microprocess engineering. There are already some examples of commercial production in flow, which is more evident in China than in Europe (Pollington, 2019).

The parallel combination of multiple microreactors, known as the numbering-up concept, is considered the most common method for increasing production (Togashi et al., 2009). Merck has successfully increased the production of organometallic reactions with five miniature mixers (Krummradt et al., 2000). Clariant presented one of the first transfers of microreactors to the azo pigment industry (Wille et al., 2004). In addition, the production of biodiesel from used cooking oil in a semi-industrial pilot of microreactor was developed (Mohadesi et al., 2019). However, improvements to the numbering-up concept are still needed, as a large number of parallel microreactors may not be economical in terms of equipment costs (Pollington, 2019).

Another scaling-up concept is to increase the channel dimensions of microreactors from 100 μm to 1-5 mm while maintaining key properties such as efficient mixing, fast and high heat transfer and better thermal control (Pollington, 2019). Ehrfeld Mikrotechnik has developed a Miprowa® production reactor with dimensions of 7 m long and 400 mm wide with a product capacity of up to 10,000 t/y for a highly exothermic alkoxylation reaction. The plant has been in continuous operation in China since September 2016 and has replaced a batch process (approx. 20 batch reactors with a volume of 50 $m^3$).

Some issues related to continuous flow chemistry are still challenging. Reactions involving solid reagents in continuous flow microreactors have been a challenge since the beginning of the development of microreactor technology, because handling of solids can clog a flow system (Neyt et al., 2021). The problem may also occur when using different solvents for multistep reactions (Gambacorta et al., 2021). The extension of microprocesses to other applications such as personal care, food technology, home care, surface coating and transportation still needs to be explored.

### 2.4 Economic analysis

Production with microreactor technology brings advantages not only in terms of selectivity, higher product efficiency, green processes and easier scale-up, but also from an economic point of view. The economic advantages result primarily from the high yield and the low proportion of by-products, but also from sustainable plant safety, lower energy consumption and a smaller carbon footprint. On the other hand, changing process methodology from batch to continuous production brings costs. It would be useful to do an upfront analysis of the capital and operating costs for continuous production and compare them to the costs for batch production.

The economic analysis of the fine chemical (4-cyanophenylboronic acid) produced in the microreactor was the first published cost analysis in the field of microreactor technology (Krtschil et al., 2006). The variable and fixed costs were analyzed. The results showed that annualized investment costs amounted to 4 % of the total annual cost. The high variable costs (63 %) were due to the high raw material costs. 33 % of the costs were other fixed costs such as administrative and sales costs. From this economic analysis, it is clear that capital costs are not a critical factor for performing synthesis in the flow microreactor.

In one of the studies, the synthesis of adipic acid in a milli-packed bed reactor was discovered (Wang et al., 2013). The main objective of this study was to demonstrate the performance of acid synthesis directly by oxidation using microreactor technology. What is more, a cost analysis of adipic acid synthesis was performed. The costs of direct and conventional synthesis of adipic acid were compared using an ASPEN economic analyzer. The cost of equipment for the synthesis of adipic acid by the conventional method was 40 M$. With microreactor technology, the cost was reduced to about 18 M$ because in this case the compressors, which represent the highest cost in the conventional method, were not needed. The distribution of the cost of synthesis with microreactors showed that 40 % of the cost of the equipment was the purchase of microreactors.

### 2.5 Life Cycle Assessment

In addition to cost analysis, life cycle assessment (LCA) is an important approach to evaluate how microreactor technology contributes to sustainability and environmental protection. Some LCA analyses for the synthesis of certain substances using microprocesses have already been performed. For example, LCA of rufinamide (Ott et al., 2016), LCA of direct micro-flow synthesis of adipic acid (Wang et al., 2013), LCA of vitamin $D_3$ production (Morales-Gonzalez et al., 2019). The method LCA was used to determine the environmental impact of the whole life cycle for the direct synthesis of adipic acid, which was already mentioned in section 2.2 (Wang et al., 2013). Based on that, they compared the conventional process of acid synthesis and direct microreactor synthesis. It was found that the direct process of acid production in microreactor is more environmentally friendly than the conventional one. Moreover, LCA of the environmental impact in the batch vs. continuous flow process was also performed for the photo-flow chemical synthesis of vitamin $D_3$ from 7-dehydrocholesterol in continuous flow in microreactors (Morales-Gonzalez et al., 2019). It was found, that continuous microflow synthesis of vitamin $D_3$ is a good alternative to the batch process. In a continuous process less solvents are needed, the process is faster and consists of fewer steps.

## 3. Future challenges for systematic design and optimization of microprocesses

In the previous section, it was shown that the foundations for the development of industrial microprocessing systems are in place, including production scale and economics. However, visible examples at production scale are still lacking, and tools need to be developed to evaluate at least indicative investment and operating costs for continuous flow operations. In the following, we present the basis and conceptual framework of an integrated approach to the design and optimization of microprocess systems by combining laboratory experiments and mixed-integer nonlinear programming (MINLP).

### 3.1 The basis for systematic design of microprocesses

Over the decades, chemical engineers have developed many efficient computer-aided tools for the design, optimization, and synthesis of conventional continuous and batch processes. Process optimization and synthesis using mathematical programming is one of the most advanced approaches. It is based on generating a superstructure of alternatives and creating a mathematical model of this superstructure in the form of a MINLP problem that determines the optimal values of the discrete and continuous variables (Sitter et al., 2019). Mixed-integer process synthesizer (MIPSYN-Global) is a unique computer-based tool for automated MINLP synthesis of chemical processes (Kravanja, 2010).

Considering that powerful microprocess laboratory equipment will soon be acquired at the faculty, the main goal would be to identify and test synergies between performing lab experiments with the microprocess equipment and mathematical optimization with the MIPSYN-Global process synthesizer. This program would be upgraded to synthesize microprocesses and use the best of both approaches (laboratory and mathematical programming) in designing and optimizing various process applications based on microtechnology. The parallel and sequential interconnection of a large number of microprocess devices entails a huge number of possible combinations, not all of which can be tested in the laboratory. Therefore, the MINLP approach would be used to predict the optimal microprocess configurations and operating conditions to achieve the desired performance. Then, a smaller and more manageable number of the obtained microprocess solutions would be tested in the laboratory. It is expected that combination of experimental laboratory microflow system and mathematical programming within MIPSYN-Global would reduce the drawbacks and increase the advantages of both approaches.

### 3.2 Conceptual framework for systematic design of microprocesses

Figure 1 shows a preliminary conceptual framework to be created by combining laboratory experiments and the MINLP synthesizer MIPSYN-Global for the synthesis and optimization of microprocess systems. A library of basic models for various microscale operations would be created in MIPSYN-Global, including performance, sizing, and costing. The superstructure containing various possible configurations of microdevices would be modeled in MIPSYN-Global to predict optimal configurations and operating parameters. Based on known chemical kinetics, an initial reactor-separator network would be synthesized using MIPSYN-Global and then laboratory experiments would be conducted with the microflow system for the obtained optimal network topology and under different reaction conditions at different scales. Based on this, the basic models would be tunned or empiric surrogate models for a specific application of microdevices would be derived that include variables having a significant impact on the performance of the device. If necessary, the models could be further corrected, and the cycle repeated. This method of microprocess design would take advantage of a mathematical approach that can process many alternatives and select some of the most promising, as well as the advantage of a laboratory approach to verify the accuracy of the results obtained.

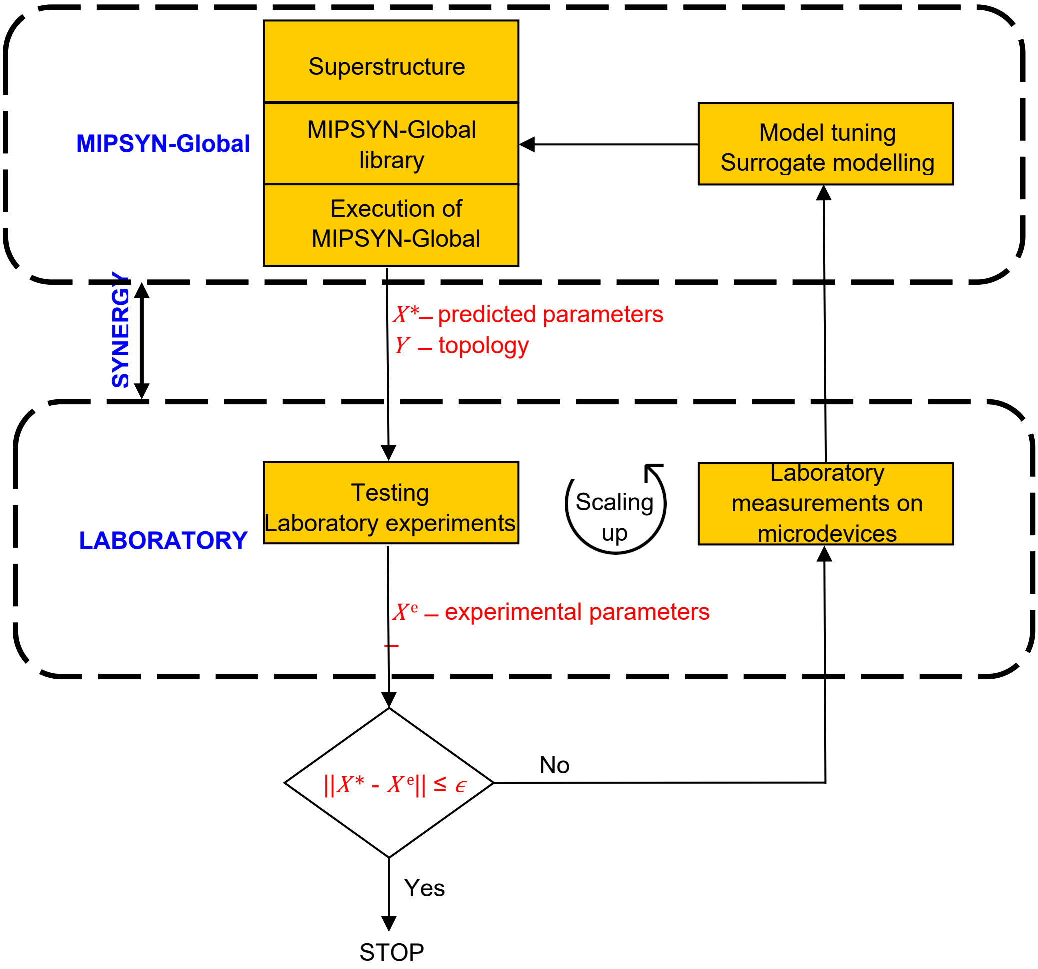

*Figure 1: A conceptual framework for microprocess design and synthesis by combined laboratory approach (microdevices) and mathematical programming (MIPSYN-Global)*

## 4. Conclusions

Flow chemistry is at a stage where many smaller laboratory setups are being studied to test in which areas microreactor technology can be used on a large scale. In the long term, microreactor technology will gain acceptance due to the economic advantages in terms of raw material and energy savings, efficiency, and reduced space requirements.

A review of the literature has shown that the recent focus of microprocess engineering has been on organic syntheses. However, there is a lack of conceptual and systematic approaches to rapidly evaluate the feasibility and viability of upgrading chemical syntheses from laboratory micro-scale to production scale. For microprocess breakthroughs in industry, computer-based tools need to be developed that incorporate process design, optimization, synthesis, and control, as well as economics and the environment. In our future work, models for microdevices will be developed as part of the MIPSYN-Global process synthesizer. On this basis, a framework will be created that would combine microprocess laboratory experiments with the synthesis of microprocesses based on the mathematical programming approach.

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