Chapter 1

Modern Chemical Industry at a Glance

Companies in developed countries are leading the world in base, pharmaceutical and specialty chemicals. For the year 2022, Statista reports an accumulated turnover of more than USD 200 billion for the three market leaders only (BASF SE: USD 93.1 billion, DOW Chemical: USD 56.9 Billion, Bayer AG: USD 54.1 billion), with the top 10 chemical companies comprising 10 % of the global market volume [Sta23, CEF23]. In energy-intensive processes, large quantities of bulk chemicals are produced each year (e.g., 1.76 Million tons/yr of ammonia by BASF SE in 2022 [BAS23a]) while production technology and equipment have barely changed in the last century. Figure 1.1 merely shows the scale-up of the production capacity from 1922 to 2022; however, processes and equipment remain almost unchanged. Compared to developments in other industries, such as automotive, energy, and information technology, changes towards renewable resources and energy efficiency are slow.

Large chemical companies struggle to modernize or replace existing plants because of the high investment and development costs for new and modern processes on a large scale. Especially in light of cost-effective production in emerging markets, where new-built production plants benefit from recent know-how and research, cheap labor, and less restrictive regulation, these high-throughput plants are profitable simply due to past amortization. Instead, R&D investments in developed countries (e.g., 2.3 billion EUR by BASF SE in 2022 [BAS23b]) are aimed at diversifying the

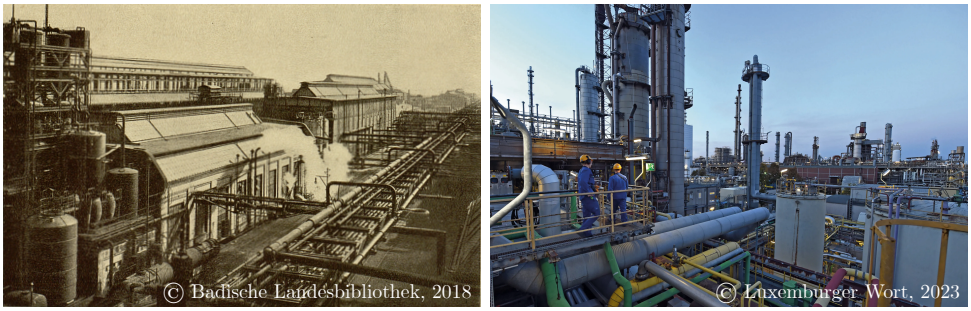

Figure 1.1 Comparison of the BASF production plants for ammonia (Haber-Bosch process) around 1922 (left) and in 2022 (right), photographs from [Ste22, Men23].

product portfolio and specialty chemistry. Since such products require much smaller production capacities, the existing batch process equipment requires long turnover intervals between product lines.

A recent trend towards more sustainability, efficiency and versatility of equipment is found in modular continuous-flow equipment, which sets the general topic of this thesis.

1.1 Importance of Continuous Flow Chemistry

The transformation of batch processes into continuous flow processes is increasingly gaining more attention in research and industry because of several reasons.

Firstly, the field of micro technology entered the realm of industrial applications in chemistry in the 2000s, with general design rules and guidelines emerging in several handbooks [Ehr00, Koc08, Hes09, Mew10]. These advances in micro fluidics and micro reaction technology enable the use of new operating windows. The advantages of large surface-to-volume ratios, i.e., precise control of temperature and reproducible residence time, mixing, and reaction conditions, are exploited in several branches of the chemical engineering field.

Secondly, continuous-flow platforms (lab-on-a-chip) enable end-to-end manufacturing through modular equipment. Modular system components are versatile and interchangeable, and plants can be quickly adjusted to accommodate process conditions for newly developed products.

Lastly, continuous plants are often associated with "green chemistry" [Rog19]. As derivatives of precise operating windows, increased efficiencies in terms of product quality (selectivity) reduce raw material input as well as the need for energy-intensive downstream processing. New process conditions, which are not achievable with batch plants, furthermore enable the development of new (sustainable) process routes. Due to its versatility and predictability, continuous-flow equipment opens the door to accelerated process development, reducing time-to-market, and enabling a never-before seen opportunity of transforming the chemical industry.

1.1.1 Accelerating Diversification and Process Development

Continuous-flow micro fluidic devices are well-known in research for their benefits. In polymer chemistry, for example, several groups demonstrate the customization of intricate block and copolymer molecules with precise polymer chain lengths and molecular weight distributions in micro reactors [Cha08, Wil08, Nag12, Sau17, Yos17]. The technology enables the continuously operated production of computer-designed products with specific properties through the precise control of reaction conditions [Aud17, Wal20]. Scale-up is typically achieved by means of the numbering-up method (i.e., increasing the number of units in parallel) to maintain the advantages of micro fluidics, as shown for the continuous production of polymers by the group of Yoshida [Iwa06, Nag16, Nak19]. The continuous polymerization process development in an industrial context is further addressed in section 1.1.4.

Continuous-flow chemistry is also exploited in pharmaceutical chemistry [Ste17]. The company GSK plc operates several production scale plants for active pharmaceutical ingredients (API) with modular continuous-flow configurations [Pal13]. Another excellent example of the use of modular continuous flow equipment is found in the accelerated development and production of vaccines. During the COVID-19 pandemic, impingement jet micro mixers (Knauer Wissenschaftliche Geräte GmbH) have been used on the laboratory, pilot and production scale to test, trial, and mass produce lipid nanoparticles as mRNA carriers for vaccine production in bio reactors [Meh23, KNA24].

1.1.2 A Sustainable, Decentral, and Enabling Technology

In the wealthy developed world with big players in the chemical industry, sustainable process routes in continuous-flow equipment, such as photochemical reactors, lower the entry barriers into competitive markets [Kay20]. Furthermore, continuous-flow applications enable the development of alternative process routes for patented drugs, e.g., vital diabetes medication [Sag21a, Sag22] or HIV medication [Nqe23] developed in the group of Paul Watts in Gqeberha (South Africa), giving developing countries access to treatment and improving standard of living. The decentralization of API production through these continuous processes allows to create value in local developing markets with local resources instead of relying on charity and funding from the developed world [Sag21b]. Independence from global market forces is desirable, especially when considering that the annual turnover of BASF SE (USD 93.1 billion in 2022) is in the range of a quarter of the total South African GDP (USD 381 billion in 2023) [Urm24, BAS23b].

The preceding reasons emphasize the importance of continuous-flow equipment in the future of the chemical industry. The subsequent sections 1.1.3 and 1.1.4 present the challenges of operating continuous-flow equipment and the context of the research question linked to this thesis.

1.1.3 Challenges of Modular Flow Chemistry

The opportunities of modular continuous-flow chemistry are well-known in the German chemical industry. The reduced cycle time of product development, process development and plant engineering poses certain challenges to the chemical industry and suppliers with well-established and set processes [Ste13].

The manufacturing of continuous-flow equipment requires new technology and materials to meet industry requirements, such as temperature and pressure ratings, GMP, or production capacity [Hun18, Mos20]. Despite many advantages, small dimensions present a major drawback compared to large-scale batch processes. Industrial continuous-flow equipment, such as tubular reactors, is typically built on milli (instead of micro) scale, and when operated in laminar flow regimes shows wide residence time distribution characteristics. Processes involving competitive reactions, especially polymerization reactions, are therefore prone to issues with product quality

or fouling. The mechanisms of homogeneous and heterogeneous fouling in polymer systems are illustrated in figure 1.2.

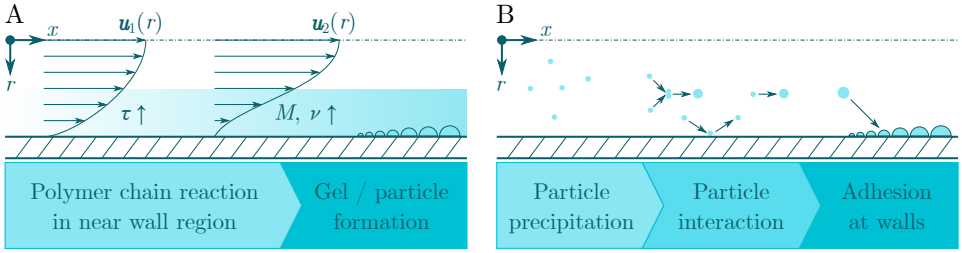

Figure 1.2 Fouling mechanisms in continuously operated polymer reactors. (A) Homogeneous fouling occurs due to larger residence times τ (i.e., molecular weight M and viscosity ν increase due to larger reaction time) in laminar boundary layer regions, and (B) heterogeneous fouling occurs due to polymer particle precipitation and deposition on reactor walls.

To overcome the limitations of inhomogeneous reaction progress, static mixing elements can be used to generate additional radial dispersion. To further ensure the homogeneity of the reagents in milli systems, upstream micro mixers can be used. Bayer et al. [Bay00] demonstrate the reduction of fouling in a milli scale process by implementing an upstream micro mixer, and today micro mixers are well-established in the chemical industry [Mor16, Son18].

However, the design of modular process equipment on industry-relevant scales is intricate and, to this day, does not follow specific standards. Such developments are crucial for the competitiveness of the German chemical industry and are favored by politics and research associations. As an example, the German Ministry of Economic Affairs and Energy (BMWE) funds an initiative for energy efficiency and process acceleration (ENPRO).

1.1.4 ENPRO Initiative and KoPPonA 2.0

The ENPRO initiative (ENergy efficiency and PROcess acceleration) is a publicly funded research initiative. The initiative aims to develop intelligent modular components coupled with smart sensors and model data integration, pushing Industry 4.0 in the German chemical industry. The initiative tackles the entire value chain of the development processes, from product development in the laboratory, process development, to plant construction, and operation.

One key project within the initiative is the joint research project KoPPonA 2.0 (continuous polymerization in modular, intelligent, and fouling-resistant reactors) from 2019 to 2022. A conglomerate of 16 plant operators, plant and measurement equipment suppliers, and academic partners attempts to demonstrate the accelerated development of fouling-resistant polymerization processes toward the pilot plant scale. Three different specialty polymer products (i.e., representing solution polymerization, catalytic polymerization, and emulsion polymerization processes) are chosen to establish a stable engineering foundation to transform existing polymerization batch processes into continuous processes. The project goals include the integration of intelligent modular measurement systems to predict, detect, and reduce fouling. In the course of the project, more than 50 pieces of work are published, 14 of which are research articles in peer-reviewed journals [Zan20, Ari21a, Ari21b, Ari21c, Fre21, Fre22b, Rus22, Hun22, Neß22, Neß23, Sch23, Wel, Wel23a, Wel23b]. However, the lack of understanding of the complex chemistry prevented the scale-up to a fouling-free pilot scale.

The project identified insufficient mixing as one of the main causes of fouling, although upstream micro mixers are able to increase standing times and cleaning interval lengths [Höp23]. To predict the initial triggering mechanism of fouling, mechanistic models reflecting the complex competitive chemistry involved in polymer reactions are required.

1.2 Overview and Systematic of this Thesis

In the course of this thesis, different models are developed to predict micro mixing and the appearance of fouling in the form of selectivity of competitive reactions. This includes phenomenological simulations of heat and mass transport phenomena together with the complex reaction networks that also make up polymerization reactions. These networks typically consist of two types of reaction schemes. Competitive-consecutive reactions compete for the monomer over the growth of the polymer chain length. Competitive-parallel reactions compete for the monomer over the formation of side-products and branching. Since the initial seed of fouling is a highly local phenomenon, predictive simulations and validating experiments require the capability of local interpretation with sufficient spatial and temporal accuracy.

In this thesis, experiments, CFD simulations and micro mixing models are utilized to investigate the influence of fluid dynamic transport mechanisms in laminar flow on the selectivity of chemical reactions. The main focus is put on the *Cascade Mixer 15*, a modular split-and-recombine (SAR) mixer unit which is used in the KoPPonA setup as a premixing stage. The following four steps are taken to illuminate the research questions.

1. To establish a benchmark for CFD simulations, steady-state direct numerical simulations (DNS) are carried out. In chapter 3, the **mesh independence** of the **physical transport of a non-reactive tracer**, **quasi-instantaneous reactions**, and **competitive-parallel reaction schemes** is thoroughly investigated. To effectively exploit the available computational resources, a much smaller geometry of a T-shaped micro mixer is used (d_h = 300 µm). The geometry is simple and the dynamical characteristics of the fluid are well described in the literature. The required mesh element size is derived from the literature depending on the fluid dynamics characteristics (Reynolds number, Re), the molecular transport characteristics (Schmidt number, Sc) and the kinetic characteristics of competitive reactions (Damkoehler number, Da). The gained knowledge is transferred to an industrially significant SAR mixer unit (i.e., the *Cascade Mixer 15* by Ehrfeld Mikrotechnik GmbH, d_h = 1.1 mm) in the form of local mesh refinement based on gradients described in sections 3.2.2, 3.2.3 and appendix A.2. Validation is achieved by different experimental approaches presented in the next steps.

2. The statistics of the physical mixing process (e.g., mixing quality) are described and validated by experiments with **non-reactive tracers** in chapter 4. Furthermore, a **quasi-instantaneous reactive mixing process** in the SAR mixer is used to locally identify areas of completed micro mixing. Micro mixing is assumed to be the precondition for chemical reactions on molecular scale. The experiments include CLSM-LIF of an acid-base reaction (fluorescein), see section 4.4.2.1, and the novel imaging UV-Vis spectroscopy of an acid-base reaction (bromothymol blue), see section 4.4.2.2.

The models of non-reactive and quasi-instantaneous reactive transport in laminar flow are well-investigated in the literature. However, three-dimensional validation by means of CLSM-LIF has only been attempted on micro scale and confirms the

model assumptions on the milli scale investigated in this thesis. Nonetheless, a single reaction is unable to yield insights into the time scales of the mixing process and the selectivity of competitive reaction networks. Therefore, competitive test reactions are used to evaluate micro mixing time scales and their selectivities.

Although competitive test reactions have been modeled with steady-state CFD simulations in laminar flow without the use of micro models in literature, often neither mesh independence is proven nor local validation is given. Most works in literature are satisfied with global validation only. This is due to two main challenges. Firstly, mesh independence is computationally expensive, and the literature has yet to provide a required mesh element size that is dependent on the reaction characteristics (Damkoehler number, Da). Secondly, local validation techniques are only capable of detecting a single chemical species or pH-values. In this thesis, the above challenges are tackled in the following steps.

3. Chapter 5 deals with the introduction of **micro mixing time** as a micro mixing characteristic. First, a one-dimensional **micro mixing model** (i.e., the incorporation model) is used together with the Villermaux-Dushman protocol to determine the global micro mixing times of the continuously operated mixing process in the SAR mixer. The Villermaux-Dushman protocol is thoroughly investigated in literature, the model is well parameterized, and therefore gives a valuable benchmark for this thesis. A novel optical analysis method, (i.e., the imaging UV-Vis spectroscopy) is used to locally investigate the competitive reaction product, see section 5.3, and helps to validate the results from steady-state CFD simulations.

4. The gained knowledge is transferred to a novel **competitive-consecutive reaction scheme** in the *Cascade Mixer 15* (nitrosyl iron complex reactions, NIC reactions) in chapter 6. Although the NIC reactions are sparsely described in the literature, they enable optical concentration measurements of both competitive products. First, micro mixing model is adjusted to suit the NIC system in section 6.3.2. Following up, the model and reaction kinetics are validated by the micro mixing times obtained from the well-known Villermaux-Dushman protocol. Second, the imaging UV-Vis spectroscopy is able to locally resolve the selectivity within the mixer unit, see section 6.3.3.

The methodology mentioned above helps to understand the influence of laminar transport phenomena on the selectivity of competitive reactions. In this work, a length scale is suggested for full resolution of competitive reactions in steady-state laminar flow CFD simulations. Furthermore, the incorporation model is adapted for use in continuous-flow applications and different reaction systems to give micro mixing time scales of the mixing processes. Lastly, a new measurement technique (imaging UV-Vis spectroscopy) is further developed to locally record concentration profiles of multiple species and selectivities of competitive reaction networks.

In the subsequent chapter 2, the theoretical basis required for this thesis is laid out, followed by the detailed methodology and results of the simulation and experimental work, as described above.